



IgE-mediated food allergy in children

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Food allergy is a serious health issue affecting roughly 4% of children, with a substantial effect on quality of life. Prognosis is good for the most frequent allergens with almost all children outgrowing their allergy. However, the long-term implications for disease burden are substantial for children with persistent allergies (eg, peanuts, tree nuts, fish, and shellfish) and for those with high concentrations of milk, egg, and wheat IgE. Antigen avoidance has been the time-honoured approach both for prevention and treatment. However, findings from studies done in the past 5 years show that early contact with food can induce tolerance and desensitisation to foods. We review the epidemiology, natural history, and management of food allergy, and discuss the areas of controversy and future directions in research and clinical practice.

Introduction

Food allergy in children is a serious and often life-threatening health issue affecting roughly 4% of children and their families worldwide, and requiring changes in dietary habits and social interactions.¹ Food allergy is caused by an immunological reaction that results in non-tolerance to a specific food or foods. In most children, this disorder is mainly mediated by IgE, but some children have non-IgE-mediated cell-mediated allergy presenting with gastrointestinal symptoms.² The two most common food allergens are milk and egg, and the third varies between countries:¹ peanuts in the USA and Switzerland, wheat in Germany and Japan, tree nuts in Spain, and sesame in Israel.² The burden of disease is difficult to accurately estimate; however, a prospective survey³ of hospital admissions for food-allergic reactions by the British Paediatric Surveillance Unit that included 13 million children older than 10 years reported 0·89 hospital admissions per 100 000 children per year. Peanut was the most common allergenic trigger (21%), followed by tree nuts (16%), and milk (10%).³ During this survey, eight children died from anaphylaxis (0·006 deaths per 100 000 children aged 0–15 years per year) and milk caused 50% of fatalities.⁴ We review the epidemiology, natural history, prevention, and management of food allergy in children; look at controversies in the specialty; and consider future directions for research and clinical practice.

Epidemiology

The exact incidence of food allergy is yet to be established. Large discrepancies between reported and diagnosed food allergy and self-reported food allergy exist, which vastly overestimate the prevalence of food allergy.^{1,2,5} In developed countries the prevalence of true food allergy diagnosed by oral food challenge is roughly 3–8% in children and 1–3% in adults.^{1,2,5,6} These rates vary between countries and have increased in recent years.^{7–9} Nevertheless, in comparison with a study done more than 20 years earlier in the USA, a UK study done between 2001 and 2002 that looked at the incidence of food allergy in 969 children showed no significant differences in cumulative incidence.⁵ Conversely, in 2007, 3·9% of children in the USA younger than 18 years reported food allergy, with an increase in prevalence of 18% from 1997 to 2007.¹⁰ Studies from the UK, Australia, and the USA showed a marked increase in hospitalisations for anaphylaxis, urticaria, and angioedema between 1990 and 2005.^{11–13} These large increases in hospital admissions are probably caused by an increase in either incidence or severity.¹³ This evidence prompted some investigators to define food allergy as an evolving public health issue, emerging over the past 10–15 years as a second-wave allergy epidemic—ie, two peaks of increased incidence, the first peak relates to respiratory allergy, the second peak to food allergy.¹⁴ In regions such as Australia, which led the first-wave respiratory epidemic (eg, asthma and seasonal rhinitis), IgE-mediated food allergy confirmed by food challenge now affects up to 10% of infants,¹⁵ suggesting that the increased prevalence of allergic disease might be related to modifiable environmental factors. Although the parents of these children were among the first generation to experience the large-scale rise in allergic diseases, disorders of oral tolerance were less common. This new generation seems less likely to outgrow food allergy than their predecessors, which will have long-term implications for disease burden.¹⁴

Search strategy and selection criteria

We searched the Cochrane Library, Medline, and relevant specialty journals (from Jan 1, 1980, to July 31, 2012). We used the search terms “food allergy” or “atopic dermatitis” or “anaphylaxis” or “immunotherapy”. We selected publications in the past 12 years with an emphasis on the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We searched only articles in English or those translated into English. We also searched the reference list of articles identified by this strategy and selected those we judged relevant. We included randomised controlled trials, observational studies, retrospective studies, meta-analyses, review articles, editorials, and case reports.

Natural history

The prognosis for food allergy in children has traditionally been regarded as good for the most frequent allergens, with almost all children outgrowing their food allergy. In 1994, the reported resolution rates for cow's milk allergy

were roughly 45–50% at age 1 year, 60–75% at age 2 years, and 85–90% at age 3 years.¹⁶ However, a 2007 study reported 21% non-tolerance in children aged 16 years; these children had increased concentrations of cow's milk IgE at all ages.¹⁷ As a result, the prognosis for cow's milk allergy in this population is thought to be worse than previously reported, and the increased potential for persistent allergy to cow's milk and the effect of specific IgE concentrations on prognosis should be considered in the counselling of families on expected clinical course. Some children develop tolerance during adolescence, showing that follow up and re-evaluation of children who are allergic to cow's milk is an important part of their continuing care.

The same pattern of tolerance has been recorded in children with egg allergy. Resolution was reported in 4% of children by 4 years of age, 12% by 6 years of age, 37% by 10 years of age, and 68% by 16 years of age.¹⁸ Children with increased concentrations of egg IgE at all ages, and those with egg IgE greater than 50 kU/L were unlikely to develop egg tolerance.¹⁸ Similarly, about 50% of children with soy allergy outgrew their allergy by 7 years of age, with a peak IgE concentration greater than 50 kU/L predictive of an 18% rate of resolution.¹⁹

Wheat allergy follows the same pattern of tolerance as egg allergy in children with rates of resolution of 29% by 4 years of age, 56% by 8 years of age, and 65% by 12 years of age.²⁰ In this population, the median age of resolution was about 6·5 years, with wheat allergy persisting into adolescence in a few children. Increased concentrations of wheat IgE were associated with poor outcomes, although many children with high concentrations of wheat IgE outgrew their allergy. A more positive outcome was reported in a small Finnish study,²¹ with a resolution rate of 84% in children aged 10 years and 96% in children aged 16 years. Allergy to sesame is increasingly detected in many countries, tends to appear early in life (median age of onset of allergy in these patients was 1 year, the follow up was done for an average of 6·7 years), is characterised by immediate reactions to a minimum amount of allergen, and has an 80% rate of persistence.²²

Allergies to peanuts and tree nuts are usually associated with fatal episodes of anaphylaxis. These episodes are especially concerning in adolescents and young adults, in whom life-threatening and fatal food allergy-related reactions are most common. About 20% of children with peanut allergy, and less than 10% of those with tree nut allergy acquire tolerance.²³ Additionally, peanut allergy can recur, with a reported recurrence rate of 8%.²³ Fish and shellfish allergy are also regarded as persistent with a high risk of anaphylaxis.²⁴ The long-term implications for disease burden might not be as promising as believed, especially for children with persistent allergies (eg, peanuts, tree nuts, fish, and shellfish) and for those with high concentrations of specific milk, egg, and wheat IgE.

Diagnosis and management

Diagnosis of IgE-mediated food allergy is indicated through medical history and physical examination and is confirmed by the presence of antigen-specific IgE and positive food challenge when necessary. Medical history should ascertain the possible causal food or foods, the form in which the allergen is ingested (eg, raw, semi-cooked, cooked, or baked), quantity of allergen ingested, time course of reactions, nature of reactions, and cofactors such as exercise or ingestion of aspirin or alcohol.²⁵ Individuals who consistently develop any of the following symptoms within minutes to 1–2 h after ingestion of a specific food should be assessed for possible food allergy: urticaria, angioedema, erythema, pruritus, vomiting, abdominal pain, persistent cough, hoarse voice, wheeze, stridor, respiratory distress, or nasal congestion.²⁶ Cardiovascular symptoms such as hypotension, extreme lethargy, or syncope, are less common but also warrant investigation for food allergy, especially if they occur in combination with one of the above symptoms.

The presence of antigen-specific IgE can be detected by skin prick test or by immunoassay of serum antigen-specific IgE. Increased concentrations of serum antigen-specific IgE and size of the skin prick test wheal are generally associated with increased likelihood of a clinical reaction, but neither is predictive of reaction severity.^{27–32} If results of antigen-specific IgE testing do not correspond with the clinical and food history, a food challenge is indicated. The double-blind, placebo-controlled food challenge is the most specific test for diagnosis of food allergy, and reliably distinguishes sensitisation from clinical allergy. However, because these tests are time and labour intensive, single-blind or open food challenges are usually more practical in the clinical setting and can be used to diagnose allergy in some cases—eg, in young children or patients with evident objective symptoms of reaction. Food challenges have to be done in a facility with on-site medical supervision and resources for the management of acute reactions. Children who have had a previous severe reaction to a known food should not undergo a challenge with that food for at least 2 years after the reaction. If the reaction is believed to be post-prandial and induced by exercise, food challenge should be followed by exercise.³³

Although children with a parent or sibling with allergic disease are more likely to develop food allergy, such infants or children should not undergo routine testing before consumption of highly allergenic foods, such as milk, egg, or peanut.³⁴ However, testing can be considered in infants with eczema that started in the first months of life and in individual cases as established by clinical judgment. Up to now, no cures for food allergy exist. Treatment involves avoidance of trigger foods and management of symptoms as they arise. Strict avoidance of the causal food or foods is the main treatment for food allergy. Although avoidance is regarded as the safest approach, efficacy of this approach is unproven in

randomised controlled trials. Complete avoidance of food allergens is difficult,^{35,36} and the risk of accidental and severe reactions can create anxiety and diminish quality of life among children and caregivers.^{37–39} Treatment should include patient education on specific tactics for avoidance of food allergens. Children should understand how to recognise their allergens in ingredient labels of packaged food and should be aware of situations in which risk for accidental exposure is increased—eg, at restaurants or a friend's home. Prevention of cross contact of foods with allergen during food preparation and serving is also important.

Generally, children should avoid only foods that they are allergic to. For some allergies, foods that might be cross reactive should also be avoided. For example, children with an allergy to a particular shellfish (eg, shrimp, crab, or lobster) should avoid all shellfish, and those with a particular tree nut allergy (eg, walnut, almond, hazelnut, cashew, pistachio, and Brazil nuts) should avoid all tree nuts unless sensitivity is ruled out by food challenge. However, generally, children allergic to peanuts do not have to avoid other legumes—eg, soybean. Because food allergy might put children at risk for inadequate nutrition,^{40–42} children and their caregivers can consult with a dietitian to create a nutritionally adequate, allergen-free diet.

Management of symptoms

No drugs are available to prevent IgE-mediated food-induced allergic reactions. Antihistamines are used to manage non-severe allergic reactions, and epinephrine serves as a foundation for management of acute, severe systemic allergic reactions—ie, anaphylaxis.³⁴ If antihistamines alone are given for acute reactions, children should be monitored. If symptoms become more severe, epinephrine should be given immediately. Children with a history of severe allergic reactions can be given epinephrine in response to mild symptoms.

The decision to prescribe an epinephrine autoinjector depends on the presence of risk factors for anaphylaxis or death from anaphylaxis.⁴³ US guidelines recommend the prescription of an epinephrine autoinjector to

children with a food allergy who have asthma, a history of a previous systemic allergic reaction, or a known allergy to peanut, tree nuts, fish, or crustacean shellfish.³⁴ US guidelines also recommend that any patient with IgE-mediated food allergy be considered for an epinephrine autoinjector. Most guidelines in the UK and Australia do not recommend an epinephrine autoinjector for children with positive antigen-specific IgE or a skin prick test for children who have not had a clinical allergic reaction.⁴³ Children who are prescribed epinephrine autoinjectors should be counselled on when and how to use them, because the use of injectors by parents and children is not intuitive.⁴⁴

Children with symptoms of anaphylaxis should be placed in a recumbent position with their legs elevated. Because cases of sudden death have been reported in children who stood up during a severe reaction, the recumbent position should be maintained.⁴⁵ If symptoms persist or progress, epinephrine dosing can be repeated after 5–15 min. In up to 20% of cases of anaphylaxis, biphasic reactions occur.⁴⁶ Therefore, children who undergo food-induced anaphylaxis and receive epinephrine should be transported by ambulance to an emergency facility for observation and additional treatment if needed. Observation is usually 4–6 h, although children with severe or refractory symptoms might need to be observed for longer.⁴⁷ Systemic corticosteroids are commonly given to prevent biphasic or protracted reactions, but no randomised controlled trials have been done to assess their effectiveness in the management of anaphylaxis.⁴⁸ Children with persistent asthma are at increased risk of severe anaphylaxis. An inhaled β_2 -agonist via a spacer device or nebuliser is a useful adjuvant in the treatment of bronchospasm associated with anaphylaxis.⁴⁹ The table shows the grading of anaphylactic reactions and the panel shows indications for the prescription of self-injectable epinephrine.

Persistent management

Physicians should see children with food allergy at least once a year, and especially children in the first few years of life (first 5 years of life). In later childhood (5–14 years of

	Skin	Gastrointestinal tract	Respiratory	Cardiovascular	Neurological
1 Mild	Itchy eyes or nose, cutaneous pruritus, urticaria, flushing	Oral tingling or pruritus, abdominal pain, nausea, vomiting	Runny nose, sneezing, throat tightness or tingling, mild wheezing	Tachycardia higher than 15 beats per min	Irritability in young children, reduced activity, increased anxiety
2 Moderate	Diffuse urticaria and angioedema	Severe abdominal pain, repeated vomiting, diarrhoea, dysphagia	Hoarseness, cough, moderate dyspnoea, moderate wheezing	Tachycardia higher than 15 beats per min	Light-headedness, feeling of pending life-threatening event
3 Severe		Profuse diarrhoea, loss of bowel control	Severe wheezing, cyanosis, or SaO ₂ <92%, respiratory arrest	Hypotension*, bradycardia, collapse, cardiac arrest	Confusion, loss of consciousness

Severity score is based on the most affected organ system. *Hypotension defined as systolic blood pressure at 1 month to 1 year less than 70 mm Hg, at 1–10 years more than 70 mm Hg plus (age times two), at more than 10 years less than 90 mm Hg. SaO₂=percentage of available haemoglobin that is saturated with oxygen. Modified from Muraro and colleagues,⁴⁹ by permission of John Wiley and Sons.

Table: Grading of severity of anaphylactic reactions

age), visits every 2–3 years might be best. Annual visits should include a review of any accidental ingestion or reactions, nutritional status, approaches for allergen avoidance, steps for management of anaphylaxis, and the need for a new epinephrine autoinjector. Children without asthma should be assessed for its presence, and children with coexisting asthma should be queried to establish whether the disease is adequately controlled. Annual reviews and re-education are especially important for children approaching adolescence because this is a time for increased risk of death from anaphylaxis.³⁴

Retesting

Because sensitisation to foods can change over time, children should be monitored for evidence of tolerance to previously allergenic foods or development of novel food allergies. Continuing clinical histories show whether assessment with skin prick tests or serum antigen-specific IgE is warranted. The optimum interval for follow-up testing is not known and could depend on the allergenic food. Milk and egg allergy are often outgrown in the first 4–6 years of life, but allergy to peanuts or tree nuts is usually not outgrown. For allergy to milk, egg, soy, or wheat, testing every 12–18 months is standard practice in the first 5 years of life. If the food allergy has not resolved by age 5 years, the interval for follow-up testing is extended to every 2–3 years.²⁶ Although the likelihood of resolution of peanut allergy is low, resolution occurs most commonly by 5 years of age.⁵⁰ Therefore, retesting for peanut allergy could follow a similar course as for allergy to milk, egg, soy, or wheat.²⁶ Retesting can be done every 2–4 years for allergies to tree nuts, fish, and crustacean shellfish.

Oral immunotherapy

Many small, mostly uncontrolled trials have confirmed the efficacy of induction of desensitisation by oral or sublingual progressive doses of the offending food,^{51–56} and the immunological changes induced by oral immunotherapy are now better understood. Findings from a recent study of children with egg allergies showed oral immunotherapy can result in sustained unresponsiveness to egg.⁵⁷ These data suggest that a child with an egg allergy can consume egg without pronounced symptoms 4–6 months after discontinuation of egg ingestion if given oral immunotherapy.⁵⁷

Open questions and areas of controversy

Antigen avoidance as prevention

The prevailing framework for prevention of food allergy has been to restrict maternal diet during pregnancy and lactation and the infant's diet in the first 3 years of life.⁵⁸ This basic theory led to the production of several guidelines for high-risk infants (defined as children with a sibling or parent affected by any atopic disease) that recommended a delayed introduction of cow's milk and other dairy products during the first year of life, egg

Panel: Indications for prescription of self-injectable epinephrine

Absolute indications

- Previous cardiovascular or respiratory reaction to a food, insect sting, or latex
- Exercise-induced anaphylaxis
- Idiopathic anaphylaxis
- Food allergy and coexisting persistent asthma

Relative indications

- Any reaction to small amounts of a food (eg, airborne food allergen or contact only via skin)
- History of a previous mild reaction to peanut or a tree nut
- Distance of home from medical facilities
- Food allergy reaction in a teenager

Modified from Muraro and colleagues,⁴⁹ by permission of John Wiley and Sons.

during the second year, and fish and nuts during the third year.^{25,59} In view of the prevalence of atopic disease in the general population, these guidelines affected many children. However, delayed introduction of food allergens in the infant's diet was ineffective in the prevention of allergy and can in fact increase the risk of allergy.^{59,60} Therefore, the traditional avoidance strategy has been reconsidered in the past decade. In fact, the present thinking for proper development of food tolerance postulates that avoidance can be deleterious and prevent the development of normal regulatory mechanisms, and that early repeated exposure to an antigen can lead to tolerance.^{60–63} Data supporting early introduction of allergenic foods in at-risk children are in contrast with WHO guidelines recommending exclusive breastfeeding for the first 6 months of life.^{64,65} Researchers are investigating the strategy of exposure to allergenic foods in primary prevention and treatment of food allergy.^{66,67}

Breastfeeding as prevention

Although some findings from studies in the late 1980s showed a protective effect of breast milk and food-allergen avoidance,⁶⁸ data from more recent observational studies suggest an association between increased risk for allergic symptoms and prolonged breastfeeding.^{69,70} However, these later studies should be interpreted with caution because the wide prescription in at-risk atopic families of extended breastfeeding and delayed introduction of complementary foods could have caused reverse causality bias. No evidence of reduced atopic disease as a result of exclusive breastfeeding beyond 4 months of age exists. Findings from a recent meta-analysis⁶⁵ suggest decreased morbidity and mortality from gastrointestinal infections in infants who are exclusively breastfed for 6 months in comparison with infants who receive both breastmilk and formula from age 4 months. However, no significant reduction in the development of atopic disease and an increased risk of

allergy with prolonged breastfeeding was seen in children exclusively breastfed for 6 months. In high-risk infants who are unable to be completely breastfed, little evidence exists of an association between prolonged feeding with hydrolysed formula (compared with cow's milk formula) and a reduction in infant and childhood allergy and infant cow's milk allergy.⁷¹

Timing of solid food introduction

The negative effect of delayed introduction of food allergens in the first year of life has been well documented.^{72–75} Israeli children receiving peanut butter at 6 months of age were ten times less likely to develop IgE-mediated peanut allergy than were Jewish children in the UK who were not given peanuts according to a preventive public health campaign.⁷² In view of the same genetic background of the two populations, the only difference between groups was the timing of peanut introduction in the diet, showing that avoidance is not protective and can promote IgE-mediated food allergy in children.

Development of tolerance might be helped by exposure to food proteins during a crucial early window between 3–4 months and 6–7 months of age.⁶⁰ However, in a large-scale population-based prospective study, infants fed regularly with cow's milk protein formula 14 days after birth were less likely to develop IgE sensitisation,⁷⁶ and delayed intermittent or low-dose exposure was an additional risk.⁷⁷ Although early-feeding practices remain controversial, insufficient evidence is available for deliberate early exposure to common allergenic foods in clinical practice.^{66,67,78}

Two randomised controlled trials, Learning Early About Peanut Allergy (LEAP; NCT00329784) and Enquiring About Tolerance (EAT; ISRCTN14254740), are assessing whether the early introduction of allergenic foods leads to tolerance and protection against IgE-mediated food allergy. The LEAP study is examining the preventive effect of early introduction of peanuts in children. The EAT study is investigating the effect of the introduction of six foods (peanut, cow's milk, hen egg, fish, wheat, and sesame) during breastfeeding from age 3 months compared with the standard food introduction at around 6 months of age. Until the results of these studies are available, the issue of early feeding practice will remain controversial.

Eczema and diet

Delayed introduction of solid foods has been recommended to improve the control of eczema and prevent allergic sensitisation. However, the effectiveness of elimination diets has not been proven, and despite dietary restrictions, allergic sensitisation still takes place through an impaired skin barrier. Percutaneous sensitisation is an especially active process in atopic dermatitis because of the increased permeability of the skin^{68,70} associated with a local abnormal T-helper-2-mediated skin inflammation.^{79,80} Findings from murine studies show that allergic sensitisation happens

after cutaneous exposure^{81,82} and that food-specific T cells can be isolated from the damaged skin of patients with eczema.⁸³ These reports explain the close link between eczema and the development of food allergies; the more impaired the skin barrier, the earlier and stronger the food sensitisation.⁸⁴ Ingestion of food proteins is essential for the development of tolerance because the interaction between the proteins and gut-associated lymphoid tissue is necessary for the activation of T-helper-1 response, and transcutaneous exposure to low-dose food proteins leads to T-helper-2 response and production of IgE by B cells.^{82–84} Therefore, the timing and balance of cutaneous and oral exposure establish whether a child will develop allergy or tolerance.⁸

In some children with atopic dermatitis, ingestion of a known food allergen exacerbates the symptoms of atopic dermatitis. If the child avoids the food, the symptoms of atopic dermatitis improve, but the disease remains. Because food allergy is not a common causal factor of atopic dermatitis exacerbation,⁸⁵ an avoidance diet should be discouraged. The notion that atopic dermatitis is caused by food allergy no longer seems valid because food sensitisation can happen through the skin, and children can develop sensitisation without exposure to the antigenic food—eg, a baby who is exclusively breastfed.⁸⁶ Despite this finding, and the limited number and weak methods of the randomised clinical trials showing the efficacy of dietary restriction in atopic dermatitis, the practice of avoidance diets was supported in the most recent guidelines.^{87–90} Because of its high prevalence, atopic dermatitis is the main discrepancy in the management of food allergies and continues to affect many children.

Diet and allergic risk

In children who test positive for food-specific IgE (with or without atopic dermatitis), avoidance of foods regularly eaten without allergic symptoms can be detrimental because this practice disrupts oral tolerance and increases the risk of anaphylaxis upon re-exposure.^{91–94} Further, a high frequency of acute reactions has been reported in patients with atopic dermatitis at diagnostic re-exposure.⁹⁵ Therefore, the recommended practice of temporary elimination diet before food challenge is questionable.

Testing in high-risk children

Guidelines on infant feeding and available evidence do not support routine testing for specific IgE in breastfed children with atopic dermatitis before the introduction of common food allergens. Nevertheless, in some infants who are very likely to have a food allergy or atopic dermatitis or both (that started in the first months of life), testing can be considered.²⁶ According to this recommendation, children with very high antigen-specific IgE are very likely to be allergic and children with lower antigen-specific IgE should be tested by means of an oral food challenge. However, avoidance diets are still

commonly recommended. In view of recent data, children with high allergic risk could be tested with the intent to introduce any positive food early and in a safe setting.

Oral food challenge

According to existing guidelines,⁹⁶ after a positive challenge, food avoidance should be recommended and a follow-up visit and assessment within 12 months should be provided. This approach does not consider that tolerance is likely to develop gradually, and that long before the child tolerates normal amounts, he or she can tolerate small amounts of the offending food. It is a relief for families when children can tolerate small amounts of basic foods such as milk, eggs, or wheat, even if larger doses can cause symptoms.⁹⁷ Data from several observational studies suggest low-dose challenge protocols suited to young children outgrowing their food allergy to prove that a child can eat small amounts of the food without an allergic reaction.^{98,99} Because of insufficient high-quality evidence, this approach cannot be recommended in clinical practice.

Oral immunotherapy

The use of oral immunotherapy has been studied for almost 15 years.¹⁰⁰ Oral immunotherapy protocols for the most common foods (ie, milk, egg, wheat, and peanuts) have been published by the USA, UK, France, Germany, Japan, Finland, Spain, Netherlands, South Korea, and Italy. Protocols varying from rapid induction in hospital to slowly increasing home protocols have been tested. Oral immunotherapy is often effective in desensitisation (ie, tolerance of a large amount of food that was possible before treatment) in a large percentage of cases, even in children with severe reactions and high concentrations of specific IgE.^{52,54,56,101–106}

An important point to consider in the assessment of costs and benefits of oral immunotherapy for individual patients is that without treatment, children older than 6 years with severe allergies and high concentrations of IgE are very unlikely to outgrow their allergy¹⁷ and are at high risk of anaphylaxis.^{49,107} Further, with antigen-avoidance treatment, nearly half of children with a peanut allergy have allergic reactions as a result of accidental ingestion of peanuts within 2–5 years of treatment initiation.^{35,36} Adverse events during oral immunotherapy are common but easy to manage in most cases.^{52,55,107–109} Oral immunotherapy is still experimental and large, multicentre randomised controlled trials are needed; however, whether sufficient data for long-term efficacy, safety, and cost-effectiveness exist to warrant introduction into clinical practice is controversial.^{26,51,110–112}

Future directions and conclusions

Alternative immunotherapeutic strategies to treat allergies are being investigated including diets containing extensively heated (baked) milk and egg, sublingual immunotherapy, treatments with modified antigens, and

epicutaneous allergen immunotherapy.^{113–115} Additionally, immunotherapy combined with anti-IgE monoclonal antibodies has safely caused desensitisation in a small population of children with peanut allergies.¹¹⁶ Studies with more consistent and appropriate diagnostic criteria are needed to better understand the incidence, prevalence, natural history, and temporal trends of food allergy and associated disorders. The natural history of food allergy needs further delineation including making clearer the differences between children and adults who develop food allergy, other associated disorders such as atopic dermatitis, the effect on the natural history of food allergy, and the development of biomarkers to better classify chronic patients versus those who will outgrow their disease early in life.

Oral food challenge is the gold standard for diagnosis of food allergy. This test is accurate and sensitive but also presents the greatest risk to the patient and should be done in hospital settings where trained personnel, drugs, and equipment are readily available for the management of anaphylaxis. The use of skin prick tests or in-vitro allergen-specific IgE tests are now widespread and, if negative, are a good predictor of a negative food challenge. Basophil assays to establish whether individuals are allergic to foods are being developed and have not yet been introduced into clinical practice. Biomarkers need to be developed to diagnose patients with individual allergen component assays or epitope assays.

Further research is needed to understand food avoidance and the effect of specific food allergies on rates of remission. The timing of follow-up testing on the basis of specific allergenic foods will be important to establish. Additional studies are also needed to examine the importance of avoidance of potentially allergenic foods in the management of atopy and atopic dermatitis, and in patients without documented food allergy. The exclusive use of extensively or partly hydrolysed infant formulas in infants who are not exclusively breastfed and at risk of atopic disease should be more thoroughly investigated.³⁴ Finally, studies of the treatment of food-induced anaphylaxis and assessments of the most effective methods for education of patients, families, and health-care professionals are needed to most effectively protect patients at risk of anaphylaxis related to food proteins.

Conflicts of interest

GL, IB, EB, and BK have no conflicts of interest to declare. WB is a minority stockholder for Allertein (USA), MastCell, Inc. (USA), and is a consultant for Merck and Co (USA). He has received grants for research projects from the National Institutes of Health. He is on the Medical Board of Directors of Food Allergy and Anaphylaxis Network (USA), Board Member of the American Academy of Allergy, Asthma and Immunology (USA), Dermatological Allergy Committee Member of the American College of Allergy, Asthma and Immunology (USA), Study Section Member of NIH Hypersensitivity, Autoimmune, and Immune-mediated Diseases Study (USA), and is on the Reviewer Board of the *Journal of Allergy and Clinical Immunology* (USA).

References

- 1 Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007; **120**: 638–46.

- 2 Fiocchi A, Brozek J, Schunemann H, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines. *Pediatr Allergy Immunol* 2010; **21**: 1–125.
- 3 Colver AF, Nevantaus H, Macdougall CF, Cant AJ. Severe food-allergic reactions in children across the UK and Ireland, 1998–2000. *Acta Paediatr* 2005; **94**: 689–95.
- 4 Macdougall CF, Cant AJ, Colver AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. *Arch Dis Child* 2002; **86**: 236–39.
- 5 Venter C, Pereira B, Voigt K, et al. Prevalence and cumulative incidence of food hypersensitivity in the first 3 years of life. *Allergy* 2008; **63**: 354–59.
- 6 Osterballe M, Hansen TK, Mortz CG, Host A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005; **16**: 567–73.
- 7 Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002; **110**: 784–89.
- 8 Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008; **121**: 1331–36.
- 9 Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003; **112**: 1203–07.
- 10 Kagan RS, Joseph L, Dufresne C, et al. Prevalence of peanut allergy in primary-school children in Montreal, Canada. *J Allergy Clin Immunol* 2003; **112**: 1223–28.
- 11 Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. *Thorax* 2007; **62**: 91–96.
- 12 Lin RY, Cannon AG, Teitel AD. Pattern of hospitalizations for angioedema in New York between 1990 and 2003. *Ann Allergy Asthma Immunol* 2005; **95**: 159–66.
- 13 Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993–1994 to 2004–2005. *J Allergy Clin Immunol* 2007; **120**: 878–84.
- 14 Prescott S, Allen KJ. Food allergy: riding the second wave of the allergy epidemic. *Pediatr Allergy Immunol* 2011; **22**: 155–60.
- 15 Osborne NJ, Koplin JJ, Martin PE, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011; **127**: 668–76.
- 16 Host A. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. *Pediatr Allergy Immunol* 1994; **5** (suppl 5):1–36.
- 17 Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007; **120**: 1172–77.
- 18 Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol* 2007; **120**: 1413–17.
- 19 Savage JH, Kaeding AJ, Matsui EC, Wood RA. The natural history of soy allergy. *J Allergy Clin Immunol* 2010; **125**: 683–86.
- 20 Keet CA, Matsui EC, Dhillon G, Lenehan P, Paterakis M, Wood RA. The natural history of wheat allergy. *Ann Allergy Asthma Immunol* 2009; **102**: 410–15.
- 21 Kotaniemi-Syrjänen A, Palosuo K, Jartti T, Kuitunen M, Pelkonen AS, Makela MJ. The prognosis of wheat hypersensitivity in children. *Pediatr Allergy Immunol* 2010; **21**: 421–28.
- 22 Cohen A, Goldberg M, Levy B, Leshno M, Katz Y. Sesame food allergy and sensitization in children: the natural history and long-term follow-up. *Pediatr Allergy Immunol* 2007; **18**: 217–23.
- 23 Skripak JM, Wood RA. Peanut and tree nut allergy in childhood. *Pediatr Allergy Immunol* 2008; **19**: 368–73.
- 24 Tsaouri S, Triga M, Makris M, Kalogeromitros D, Church MK, Piftis KN. Fish and shellfish allergy in children: Review of a persistent food allergy. *Pediatr Allergy Immunol* 2012; **23**: 608–15.
- 25 American College of Allergy, Asthma, and Immunology. Food allergy: a practice parameter. *Ann Allergy Asthma Immunol* 2006; **96** (suppl 2): 1–68.
- 26 Burks AW, Tang M, Sicherer S, et al. ICON: food allergy. *J Allergy Clin Immunol* 2012; **129**: 906–20.
- 27 Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001; **107**: 891–96.
- 28 Boyano-Martinez T, Garcia-Ara C, Diaz-Pena JM, Martin-Esteban M. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. *J Allergy Clin Immunol* 2002; **110**: 304–09.
- 29 Garcia-Ara C, Boyano-Martinez T, Diaz-Pena JM, Martin-Munoz F, Reche-Frutos M, Martin-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. *J Allergy Clin Immunol* 2001; **107**: 185–90.
- 30 Osterballe M, Bindslev-Jensen C. Threshold levels in food challenge and specific IgE in patients with egg allergy: is there a relationship? *J Allergy Clin Immunol* 2003; **112**: 196–201.
- 31 Celik-Bilgili S, Mehl A, Verstege A, et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy* 2005; **35**: 268–73.
- 32 Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. *J Allergy Clin Immunol* 2004; **114**: 144–49.
- 33 Romano A, Di Fonso M, Giuffreda F, et al. Food-dependent exercise-induced anaphylaxis: clinical and laboratory findings in 54 subjects. *Int Arch Allergy Immunol* 2001; **125**: 264–72.
- 34 Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010; **126** (suppl 6): 1–58.
- 35 Bock SA, Atkins FM. The natural history of peanut allergy. *J Allergy Clin Immunol* 1989; **83**: 900–04.
- 36 Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *J Pediatr* 2000; **137**: 749–55.
- 37 Wassenberg J, Cochard MM, Dunngalvin A, et al. Parent perceived quality of life is age-dependent in children with food allergy. *Pediatr Allergy Immunol* 2012; **12**: 412–19.
- 38 Rouf K, White L, Evans K. A qualitative investigation into the maternal experience of having a young child with severe food allergy. *Clin Child Psychol Psychiatry* 2012; **17**: 49–64.
- 39 Klennert MD, Robinson JL. Addressing the psychological needs of families of food-allergic children. *Curr Allergy Asthma Rep* 2008; **8**: 195–200.
- 40 Tiainen JM, Nuutinen OM, Kalavainen MP. Diet and nutritional status in children with cow's milk allergy. *Eur J Clin Nutr* 1995; **49**: 605–12.
- 41 Christie L, Hine RJ, Parker JG, Burks W. Food allergies in children affect nutrient intake and growth. *J Am Diet Assoc* 2002; **102**: 1648–51.
- 42 Agostoni C, Fiocchi A, Riva E, et al. Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period. *Pediatr Allergy Immunol* 2007; **18**: 599–606.
- 43 Tang MLK, Kang LW. Prevention and treatment of anaphylaxis. *Paediatr Child Health* 2008; **18**: 809–16.
- 44 Mehr S, Robinson M, Tang M. Doctor: how do I use my EpiPen? *Pediatr Allergy Immunol* 2007; **18**: 448–52.
- 45 Pumphrey RS. Fatal posture in anaphylactic shock. *J Allergy Clin Immunol* 2003; **112**: 451–52.
- 46 Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. *Immunol Allergy Clin North Am* 2007; **27**: 309–26.
- 47 Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; **117**: 391–97.
- 48 Choo KJ, Simons FE, Sheikh A. Glucocorticoids for the treatment of anaphylaxis. *Cochrane Database Syst Rev* 2010; **3**: CD007596.
- 49 Muraro A, Roberts G, Clark A, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy* 2007; **62**: 857–71.
- 50 Ho MH, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. *J Allergy Clin Immunol* 2008; **121**: 731–36.
- 51 Fisher HR, du Toit G, Lack G. Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance?: a meta-analysis of published RCTs. *Arch Dis Child* 2011; **96**: 259–64.

- 52 Longo G, Barbi E, Berti I, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol* 2008; **121**: 343–47.
- 53 Buchanan AD, Green TD, Jones SM, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007; **119**: 199–205.
- 54 Staden U, Rolinck-Werninghaus C, Brewé F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 2007; **62**: 1261–69.
- 55 Skripak JM, Nash SD, Rowley H, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2008; **122**: 1154–60.
- 56 Keet CA, Frischmeyer-Guerrero PA, Thyagarajan A, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol* 2012; **129**: 448–55.
- 57 Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med* 2012; **367**: 233–43.
- 58 American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics* 2000; **106**: 346–49.
- 59 Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol* 2012; **129**: 1187–97.
- 60 Prescott SL, Smith P, Tang M, et al. The importance of early complementary feeding in the development of oral tolerance: concerns and controversies. *Pediatr Allergy Immunol* 2008; **19**: 375–80.
- 61 Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2010; **125** (suppl 2): 116–25.
- 62 Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2006; **3**: CD000133.
- 63 von Hertzen LC, Savolainen J, Hannuksela M, et al. Scientific rationale for the Finnish Allergy Programme 2008–2018: emphasis on prevention and endorsing tolerance. *Allergy* 2009; **64**: 678–701.
- 64 American academy of paediatrics. Breastfeeding and the use of human milk. *Pediatrics* 2012; **129**: 827–41.
- 65 Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev* 2012; **8**: CD003517.
- 66 Kim JS, Sicherer S. Should avoidance of foods be strict in prevention and treatment of food allergy? *Curr Opin Allergy Clin Immunol* 2010; **10**: 252–57.
- 67 Prescott SL, Bouygue GR, Videky D, Fiochi A. Avoidance or exposure to foods in prevention and treatment of food allergy? *Curr Opin Allergy Clin Immunol* 2010; **10**: 258–66.
- 68 Zeiger RS, Heller S, Mellon MH, et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol* 1989; **84**: 72–89.
- 69 Sears MR, Greene JM, Willan AR, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002; **360**: 901–07.
- 70 Pesonen M, Kallio MJ, Ranki A, Siimes MA. Prolonged exclusive breastfeeding is associated with increased atopic dermatitis: a prospective follow-up study of unselected healthy newborns from birth to age 20 years. *Clin Exp Allergy* 2006; **36**: 1011–18.
- 71 Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006; **4**: CD003664.
- 72 Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008; **122**: 984–91.
- 73 Poole JA, Barriga K, Leung DY, et al. Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics* 2006; **117**: 2175–82.
- 74 Nwaru BI, Erkkola M, Ahonen S, et al. Age at the introduction of solid foods during the first year and allergic sensitization at age 5 years. *Pediatrics* 2010; **125**: 50–59.
- 75 Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. *Pediatrics* 2008; **121**: 44–52.
- 76 Katz Y, Rajuan N, Goldberg MR, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 2010; **126**: 77–82.
- 77 Saarinen KM, Savilahti E. Infant feeding patterns affect the subsequent immunological features in cow's milk allergy. *Clin Exp Allergy* 2000; **30**: 400–06.
- 78 Burks AW. Early peanut consumption: postpone or promote? *J Allergy Clin Immunol* 2009; **123**: 424–25.
- 79 Spergel JM, Mizoguchi E, Brewer JP, Martin TR, Bhan AK, Geha RS. Epicutaneous sensitization with protein antigen induces localized allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. *J Clin Invest* 1998; **101**: 1614–22.
- 80 Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003; **348**: 977–85.
- 81 Saloga J, Renz H, Larsen GL, Gelfand EW. Increased airways responsiveness in mice depends on local challenge with antigen. *Am J Respir Crit Care Med* 1994; **149**: 65–70.
- 82 Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Disruption of the stratum corneum allows potent epicutaneous immunization with protein antigens resulting in a dominant systemic Th2 response. *Eur J Immunol* 2004; **34**: 2100–09.
- 83 van Reijssen FC, Feliuss A, Wauters EA, Bruijnzeel-Koomen CA, Koppelman SJ. T-cell reactivity for a peanut-derived epitope in the skin of a young infant with atopic dermatitis. *J Allergy Clin Immunol* 1998; **101**: 207–09.
- 84 Hill DJ, Hosking CS, de Benedictis FM, Oranje AP, Diepgen TL, Bauchau V. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin Exp Allergy* 2008; **38**: 161–68.
- 85 Fleischer DM, Bock SA, Spears GC, et al. Oral food challenges in children with a diagnosis of food allergy. *J Pediatr* 2011; **158**: 578–83.
- 86 García C, El-Qutob D, Martorell A, et al. Sensitization in early age to food allergens in children with atopic dermatitis. *Allergol Immunopathol (Madr)* 2007; **35**: 15–20.
- 87 Greenhawt M. The role of food allergy in atopic dermatitis. *Allergy Asthma Proc* 2010; **31**: 392–97.
- 88 Werfel T, Ballmer-Weber B, Eigenmann PA, et al. Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA2LEN. *Allergy* 2007; **62**: 723–28.
- 89 Darsow U, Wollenberg A, Simon D, et al. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venerol* 2010; **24**: 317–28.
- 90 Werfel T, Erdmann S, Fuchs T, et al. Approach to suspected food allergy in atopic dermatitis. Guideline of the Task Force on Food Allergy of the German Society of Allergy and Clinical Immunology (DGAKI) and the Medical Association of German Allergologists (ADA) and the German Society of Pediatric Allergy (GPA). *J Dtsch Dermatol Ges* 2009; **7**: 265–71.
- 91 David TJ. Anaphylactic shock during elimination diets for severe atopic eczema. *Arch Dis Child* 1984; **59**: 983–86.
- 92 Flinterman AE, Knulst AC, Meijer Y, Bruijnzeel-Koomen CA, Pasmans SG. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. *Allergy* 2006; **61**: 370–74.
- 93 Larramendi CH, Martín Esteban M, Pascual Marcos C, Fiandor A, Díaz Pena JM. Possible consequences of elimination diets in asymptomatic immediate hypersensitivity to fish. *Allergy* 1992; **47**: 490–94.
- 94 Barbi E, Gerarduzzi T, Longo G, Ventura A. Fatal allergy as a possible consequence of long-term elimination diet. *Allergy* 2004; **59**: 668–69.
- 95 Niggemann B, Sielaff B, Beyer K, Binder C, Wahn U. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy* 1999; **29**: 91–96.
- 96 Nowak-Węgrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work Group report: oral food challenge testing. *J Allergy Clin Immunol* 2009; **123** (suppl 6): 365–83.
- 97 Foucard T, Lilja G. Monitoring of IgE-mediated food allergy in childhood. *Acta Paediatr* 2004; **93**: 730–33.
- 98 Devenney I, Norrman G, Oldaeus G, Stromberg L, Falth-Magnusson K. A new model for low-dose food challenge in children with allergy to milk or egg. *Acta Paediatr* 2006; **95**: 1133–39.
- 99 Longo G, Berti I, Barbi E, et al. Diagnosed child, treated child: food challenge as the first step toward tolerance induction in cow's milk protein allergy. *Eur Ann Allergy Clin Immunol* 2012; **44**: 54–60.

- 100 Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. *Hepatogastroenterology* 1998; **45**: 52–58.
- 101 Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol* 2009; **124**: 292–300.
- 102 Alvaro M, Giner MT, Vazquez M, et al. Specific oral desensitization in children with IgE-mediated cow's milk allergy. Evolution in one year. *Eur J Pediatr* 2012; **171**: 1389–95.
- 103 Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy* 2004; **59**: 980–87.
- 104 Martorell A, De la Hoz B, Ibanez MD, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. *Clin Exp Allergy* 2011; **41**: 1297–304.
- 105 Patriarca G, Nucera E, Roncallo C, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 2003; **17**: 459–65.
- 106 Fuentes-Aparicio V, Alvarez-Perea A, Infante S, Zapatero L, D'Oleo A, Alonso-Lebrero E. Specific oral tolerance induction in paediatric patients with persistent egg allergy. *Allergol Immunopathol (Madr)* 2012; published online July 24. DOI:10.1016/j.aller.2012.02.007.
- 107 Barbi E, Longo G, Berti I, et al. Adverse effects during specific oral tolerance induction: in-hospital "rush" phase. *Eur Ann Allergy Clin Immunol* 2012; **44**: 18–25.
- 108 Barbi E, Longo G, Berti I, et al. Adverse effects during specific oral tolerance induction: in home phase. *Allergol Immunopathol (Madr)* 2012; **40**: 41–50.
- 109 Calvani M, Miceli Sopo S, Giorgio V. Oral immunotherapy in food allergy: how difficult to weigh its risks and benefits? *J Allergy Clin Immunol* 2011; **128**: 250–51.
- 110 Thyagarajan A, Varshney P, Jones SM, et al. Peanut oral immunotherapy is not ready for clinical use. *J Allergy Clin Immunol* 2010; **126**: 31–32.
- 111 Katz Y, Goldberg MR, Stein M, Levy M. Oral immunotherapy: ready for prime time? *J Allergy Clin Immunol* 2011; **127**: 289–90.
- 112 Wasserman RL, Sugerman RW, Mireku-Akomeah N, Mansfield L, Baker JW. Office-based oral immunotherapy for food allergy is safe and effective. *J Allergy Clin Immunol* 2011; **127**: 290–01.
- 113 Kim JS, Nowak-Wegrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *J Allergy Clin Immunol* 2011; **128**: 125–31.
- 114 Nowak-Wegrzyn A, Sampson HA. Future therapies for food allergies. *J Allergy Clin Immunol* 2011; **127**: 558–73.
- 115 Leonard SA, Sampson HA, Sicherer SH, et al. Dietary baked egg accelerates resolution of egg allergy in children. *J Allergy Clin Immunol* 2012; **130**: 473–80.
- 116 Nadeau KC, Kohli A, Iyengar S, DeKruyff RH, Umetsu DT. Oral immunotherapy and anti-IgE antibody-adjunctive treatment for food allergy. *Immunol Allergy Clin North Am* 2012; **32**: 111–33.