

Active management of food allergy: an emerging concept

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Received 4 August 2014

Revised 9 October 2014

Accepted 15 October 2014

ABSTRACT

IgE-mediated food allergies are common and currently there is no cure. Traditionally, management has relied upon patient education, food avoidance and the provision of an emergency medication plan. Despite this, food allergy can significantly impact on quality of life. Therefore, in recent years, evolving research has explored alternative management strategies. A more active approach to management is being adopted, which includes early introduction of potentially allergenic foods, anticipatory testing, active monitoring, desensitisation to food allergens and active risk management. This review will discuss these areas in turn.

INTRODUCTION

Food allergy is common, affecting 6–8% of children.^{1–2} The prevalence of food allergy is highest in infants and toddlers, with 2.5% of infants suffering from cow's milk allergy, while other allergens such as egg, nuts, soya, wheat and fish/shellfish are also common.^{3–4} Food allergies have a significant effect on the quality of life of allergic children and their caregivers.⁵ Anxiety stems from fear of accidental ingestion with potentially severe reactions, and allergic children face various social restrictions and issues at school.

Certain food allergies, such as cow's milk, soya, egg and wheat, are usually outgrown after a few years of dietary exclusion. Fish, shellfish, sesame, peanut and tree nut allergy tend to be lifelong and rarely resolve.⁶

There is no cure for food allergy. The traditional approach is based on patient education, strict avoidance of the offending food (elimination diet) and prompt treatment of adverse reactions resulting from accidental exposure. Children and families are provided with patient-specific emergency medication and a management plan on how to treat allergic reactions.⁴

Recently, with advances in allergy research, a more active approach to managing food allergy is being adopted. This approach includes early dietary introduction of potentially allergenic foods that are tolerated, as a means to prevent the development of allergy; actively testing for related allergens once a specific food allergy has been identified (anticipatory testing); active monitoring and desensitisation to known food allergens and active risk management. These numerous approaches may significantly increase the complexity of managing children with food allergy. However, they also have the potential to significantly improve quality of life and reduce the development of further allergies. This

What is already known

- ▶ Food allergy is common in childhood and affects quality of life.
- ▶ A reliable clinical history, in combination with positive skin prick tests or specific IgE, is required for the diagnosis of food allergy.
- ▶ There is currently no cure for food allergy.
- ▶ Traditionally, the management of food allergy includes strict food avoidance, patient education and provision of emergency medication.

What this study adds

- ▶ Early introduction of potentially allergenic foods may help reduce the risk of food allergy and may play a role in clinical tolerance induction.
- ▶ Appropriate allergy testing and interpretation, of the index food, and also related allergens in high-risk patients, allows a more precise diagnosis and minimises food exclusions, as long as appropriate facilities are in place to conduct diagnostic food challenges.
- ▶ The introduction of modified allergenic food, such as baked cow's milk and baked egg into the diet of carefully selected children allergic to cow's milk and egg respectively, may hasten the development of clinical tolerance.
- ▶ Food immunotherapy is an emerging area of research, which has shown promise, but is not yet ready for a routine clinical treatment modality.

article looks at each of these areas, in turn, focusing only on IgE-mediated food allergy, with specific reference to cow's milk, egg and peanut allergy.

EARLY FOOD INTRODUCTION IN INFANTS

The ideal scenario in actively managing food allergy would be primary prevention. Over the last two decades, there have been significant changes with respect to infant feeding guidance from the Department of Health in the UK. Complementary feeding was recommended to be delayed until 6 months, with longer delays for specific allergenic foods such as peanuts.⁶ This was based on very limited data and has now been withdrawn. Current

To cite: Anagnostou K, Stiefel G, Brough H, et al. *Arch Dis Child* Published Online First: [please include Day Month Year] doi:10.1136/archdischild-2014-306278

guidelines, written in 2008, recommend exclusive breastfeeding for 6 months and avoidance of potentially allergenic foods (peanuts, other nuts, seeds, milk, eggs, wheat, fish or shellfish) until after 6 months of age with no recommendation for any maternal allergen avoidance during pregnancy or lactation.⁷ However, even these data are starting to be challenged, as evidence is suggesting that early introduction of an allergenic food may actually play an important role in the prevention of the development of food allergy as described below.

Du Toit *et al*⁸ compared the prevalence of peanut allergy among Jewish children in the UK and Israel in relation to the timing and amount of peanut consumption during infancy. They found a 10-fold higher prevalence of peanut allergy in the UK compared with Israel (1.85% vs 0.17%). It was also evident that peanuts were introduced earlier and eaten more frequently by Israeli children compared with the UK. Israeli infants start consuming peanut-containing foods during early weaning, whereas UK infants mostly avoided peanuts for the first 3 years of life (which was the current UK public health advice at the time). The authors concluded that early consumption of peanuts in infancy, and consumption of frequent and high doses of peanut protein were associated with a low prevalence of peanut allergy, possibly due to induction of oral tolerance.

Katz *et al*⁹ reported on a large cohort of over 13 000 infants in a prospective study investigating risk factors for cow's milk allergy. They found that infants with exposure to cow's milk protein in the first 2 weeks of life had a significantly lower incidence of cow's milk allergy compared with infants who introduced cow's milk after the age of 4–6 months. The investigators concluded that early exposure to cow's milk protein may be protective against the development of IgE-mediated cow's milk allergy. Similarly with egg, early introduction might have a protective effect against egg allergy. A cross-sectional study including 2589 infants examined the relationship between timing of infant feeding and subsequent risk of food allergy. Infants introduced to loosely cooked egg (eg, scrambled egg) at 4–6 months had a lower risk of egg allergy than those introduced to loosely cooked egg after that time.¹⁰

Whilst these observations show promise, further data from interventional studies are required. Within the UK there are two ongoing studies, namely the LEAP (Learning Early About Peanut allergy) and EAT (Enquiring About Tolerance) studies. The LEAP Study involves 640 high-risk children, enrolled when aged 4–11 months, examining the effect of early peanut consumption on the risk of developing peanut allergy.¹¹ Each child was randomly assigned to follow either avoidance or consumption of an age-appropriate peanut snack three times a week. The proportion of each group that develops peanut allergy by 5 years of age will be compared to determine which approach works best for preventing peanut allergy.

The EAT Study is testing the hypothesis that the introduction of six allergenic foods (cow's milk, egg, wheat, sesame, fish and peanut) into the diet of infants from 3 months of age, alongside continued breastfeeding, results in a reduced prevalence of food allergies by 3 years of age (<http://www.eatstudy.co.uk>). The EAT study will compare early introduction of the above foods compared with standard UK recommendations described above.

Finally, in Germany, the HEAP (Hen's Egg Allergy Prevention) study will involve 800 children, randomised to receive either hen's egg or a placebo at 4–6 months of age, with the effect on egg allergy measured at 12 months of age (http://www.charite-ppi.de/aktuelles/klinische_studien/huehnereiallergie_praeventionsstudie/).

In summary, there are promising results looking at the early introduction of allergenic foods into the diet of infants,

however more rigorous study outcomes are awaited, suggesting that the window of opportunity may vary depending on the food. There are several ongoing interventional studies, which will provide more definitive guidance on introductory feeding for infants.

ANTICIPATORY TESTING

The diagnostic process for IgE-mediated food allergy involves taking an allergy-focused history, followed by targeted allergy testing (either skin prick test (SPT) or specific IgE testing), and in cases where diagnostic doubt remains, an oral provocation challenge remains the gold standard diagnostic modality. Recent food allergy diagnostic guidance^{11a} recommends allergy testing to the allergen suspected of causing the index reaction, and known co-allergens, that is, allergens commonly found to be present in association with another. Mono-allergic food allergy is rare and the commonest example is testing for tree nut allergy in children with peanut allergy, in whom the estimated rate of co-allergy is 30–40%.¹² Other examples include testing for peanut allergy in children with egg allergy, in whom the estimated rate of co-allergy is approximately 20–30% or sesame allergy, in those with known peanut allergy (estimated prevalence of 25%).^{8 11} However, some common avoidance patterns occur when there is no evidence of co-allergy, for example, avoidance of shellfish, such as crustaceans, in children with fish allergy and hence appropriate testing could provide reassurance for safe introduction. Therefore, this anticipatory approach has the potential advantages of avoiding unwanted allergic reactions in the community, avoiding unnecessary restrictions in the diet, and also, by facilitating early introduction, potentially preventing development of allergy to co-allergens, which requires further investigation.

Anticipatory testing could be taken a step further in relation to eczema. In up to 30% of children with moderate to severe eczema, food allergens may act as triggers to the severity of the disease.¹³ In children less than 3 years of age with moderate/severe eczema, it has been suggested that further testing and evaluation should be performed to hen's egg and cow's milk, as well as the most prevalent food allergens in a given population due to the risk of food allergy.¹⁴ Furthermore, based on evidence from the LEAP study, we suggest that evaluating peanut allergy in infants with moderate to severe eczema should be considered.¹¹ In fact, in the LEAP study, even the group with mild eczema had an increased risk of sensitisation.

Central to this anticipatory approach, however, is the ability to accurately diagnose food allergy and differentiate it from sensitisation (a state when genetically predetermined individuals have circulating specific IgE to a specific allergen, yet exposure to that allergen does not result in clinical reactivity). Therefore, specific IgE and SPTs without a supporting clinical history cannot be used in isolation to definitively diagnose food allergy. An oral food challenge may be required to make a definitive diagnosis. There are exceptions to this, as there have been a significant number of studies identifying the values of specific IgE and SPT that have a positive predictive value (PPV) of 95% for whether a child has an allergy to egg, milk, peanuts or fish using double-blind placebo-controlled food challenges as the gold standard.¹⁵ These 95% PPVs are often used as diagnostics in the absence of a clinical history. It is important to note that these predictive values have generally been established in older children and vary depending on age.

In addition, there are ongoing improvements in allergy diagnostics, which makes this anticipatory approach more practicable. Component resolved diagnostics is a recent development that may have the potential to better differentiate between

clinical reactivity and sensitisation, effectively reducing the need for food challenges. This approach involves the measurement of IgE levels to the individual component proteins that make up the allergenic food, some of which have been identified as more reliable at differentiating between sensitisation without allergy and clinically relevant allergy. The most convincing data come from peanut components.^{16 17} More studies are needed to confirm this, as it has been noted that correlations have not been fully established yet and may vary, depending on the populations studied and different geographical regions.

Despite the ongoing improvements in diagnostics, anticipatory testing in children at risk of allergy to foods they have yet to consume will inevitably lead to diagnostic uncertainty. As a result, numerous food challenges are likely to be required to make a definitive diagnosis, when a child with no history of consumption is identified as having evidence of sensitisation. The economic impact of this will require further study. However, this approach will allow more precise and prompt diagnosis, the prevention of reactions with potential severe consequences and preventing unnecessary avoidance of related foods.

DESENSITISATION TO FOOD ALLERGENS

Once a food allergy has been diagnosed, the traditional approach has been careful avoidance with only intermittent monitoring, yet more recently, evidence has started to emerge relating to new strategies to help tolerance develop more quickly.⁶ Three areas have been of particular interest—the role of baked egg and cow's milk introduction in children with egg or cow's milk allergies, the role of desensitisation to food and the use of probiotics in infants with cow's milk allergy.

Unlike peanut, cow's milk and egg allergy are generally considered childhood allergies with a favourable outcome due to the natural history of the individual food allergy. Although, recent evidence suggests the rate of development of tolerance is slower than initially thought of (particularly in studies from specialist centres), the majority of cow's milk and egg allergic children develop tolerance in late childhood.^{18 19} Persistence of both allergies into late childhood years can affect nutritional status and quality of life. Therefore, it would be beneficial to find ways that would accelerate tolerance development and avoid complete milk and egg dietary avoidance. Studies revealed that 70–75% of milk and egg allergic children can tolerate the allergen when extensively heated.^{20 21} This can make dietary restriction much easier, but potentially also help develop tolerance more quickly. Oral immunotherapy (OIT) can hasten the resolution of allergy to baked milk and egg and lead more rapidly to the acquisition of naturally occurring tolerance as discussed below.

Kim *et al*²⁰ reported on the outcome of a group of children with milk allergy who incorporated baked milk products into their diet. A total of 59% of subjects developed tolerance to milk in the baked milk-consuming group compared with only 22% in the comparison group, who followed strict milk avoidance. Overall, subjects who incorporated baked milk into their diet were 16 times more likely to become tolerant to all forms of cow's milk than the comparison group. Furthermore, the addition of baked milk into the diet appeared to accelerate resolution of cow's milk allergy.

A similar study evaluated the role of baked egg consumption in the development of tolerance to regular loosely cooked egg in egg allergic children. Of the 70 subjects who regularly consumed baked egg, in 3 years 53% were egg tolerant compared with only 28% (of the 47 subjects) in the comparison group. Subjects who were consuming baked egg products were 14

times more likely to develop tolerance to regular egg compared with the comparison group (strict avoidance of all forms of egg). It was also noted that subjects in the group who regularly consumed baked egg developed tolerance to regular egg earlier (median time to resolution 50 vs 78.7 months).²²

Unfortunately, it can be difficult to separate out those children who can and cannot tolerate the allergen in the extensively heated form and allergy testing; even component tests, prove relatively unhelpful.²¹ Given that reactions to baked egg or cow's milk may be severe, many centres recommend oral food challenges under medical supervision to definitively delineate the allergic status of each child.¹⁰ However, the British Society for Allergy and Clinical Immunology guidelines for milk and egg allergy do suggest situations where home introduction of baked milk and baked egg can be considered,^{23 24} although the potential for anaphylaxis, even to baked allergen, means that such home challenges remain contentious.

An area of intense research interest is food OIT. The administration of small but increasing doses of an allergenic food to patients who are allergic to that food has been shown to increase their clinical tolerance and enable them to eat varying amounts of the allergenic food, without reactions. Food OIT studies have been conducted for various allergens, but mostly concentrated on cow's milk, egg and peanut with good efficacy in desensitising allergic patients to the relevant food.^{25–27}

Brożek *et al*²⁸ performed a systematic review to assess the evidence supporting the use of OIT in IgE-mediated cow's milk allergy. They reported that OIT, compared with an elimination diet alone, increased the likelihood of achieving full tolerance to cow's milk.

A recent double-blind placebo-controlled, randomised egg OIT study of 55 children, 5–18 years old, with egg allergy, resulted in a 55% rate of desensitisation in the active group after 10 months of therapy. No subjects in the placebo group achieved tolerance induction. Once maintenance egg consumption was discontinued for 6–8 weeks, only 28% of children remained desensitised at 24 months.²⁶

A two-step, phase II, randomized, controlled crossover trial of peanut OIT in 99 children aged 7–16 years investigated the role of peanut OIT in peanut allergic children inclusive of all severities of peanut allergy. Among OIT participants, 91% were desensitised to 800 mg, the equivalent of five peanuts. In the active group, 24 of 39 (62%) OIT participants were desensitised to 1400 mg of peanut protein compared with none of 46 participants in the control group. Those who completed the study protocol had a significant 25-fold increase of their no observed adverse effect level over baseline, and their caregivers had a significant improvement in quality of life. Adverse effects were mild, although almost of the OIT participants reported adverse events.²⁷

It is apparent that OIT provides a fertile ground for future treatments of food allergies. However, such an intervention in its current form involves long-term treatment, requiring careful supervision, as it can result in serious adverse reactions. In addition, it does not work for all participants. The potential of food immunotherapy in achieving long-term tolerance (when participants are able to consume the food without any restrictions, without any need for ongoing therapy) versus transient desensitisation (an increase in the threshold of reactivity to the allergen that requires regular therapy to be maintained), is still unknown and under investigation. OIT currently requires regular allergen consumption to maintain desensitisation, and cessation of allergen ingestion has resulted in return of symptoms for the majority of patients.^{26 29} It is important to note

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that food OIT presents an exciting, potentially disease-modifying treatment approach to food allergy, but is not yet recommended for routine clinical use and should not be attempted outside specialist practise.

PROBIOTICS

Another area of interest in food allergy management involves the potential role of probiotics in modulating the allergic response. Two separate studies reported that supplementation of extensively hydrolysed casein formula with *Lactobacillus* GG was shown to accelerate the development of tolerance in infants with cow's milk allergy.^{30 31} Currently, further prospective, interventional trials are underway, in order to clarify this effect of probiotics on tolerance induction (PRESTO, Danone, Netherlands Trial Register NTR3725).

ACTIVE RISK MANAGEMENT (ADVISORY LABELS)

In many countries around the world (including European countries), specific food allergens must be disclosed when they are ingredients in pre-packed foods, according to existing law. There are currently 14 food allergens which are part of this legal requirement. In addition, manufacturers can choose to add advisory statements, although these are currently voluntary. Current legislation does not cover cross-contamination of food products.^{32 33}

Despite the fact that most foods with advisory labels do not contain sufficient amounts of allergen to trigger a reaction in an allergic individual, the risk is not trivial, particularly for confectionery items.³² However, foods with no advisory labels may contain levels of allergen sufficient to trigger allergic reactions in susceptible individuals.^{34–36}

The widespread use of advisory labels and the variability in wording employed (such as 'may contain...', 'may contain traces of...' or 'made in a factory...'), causes considerable confusion and anxiety to people with allergies and their carers.³³ Many patient-support groups understandably recommend complete avoidance in an attempt to minimise the risk of reactions, but a large proportion of allergic patients disregard advisory labels without seemingly experiencing adverse effects.³⁷ A recent survey of 239 British health care professionals revealed that only 38% recommended complete avoidance of foods with advisory labels to nuts (but no nut listed in the ingredients), while 22% advised no avoidance was necessary. The majority recommended avoidance only in certain circumstances, such as if they were unwell or did not have their emergency medication. A history of asthma or anaphylaxis increased the likelihood that complete avoidance was recommended.³⁸

Despite this variation in advice, there is no doubt that the provision of accurate information about labelling and risks is required to enable patients and their families to make an informed choice about avoidance measures. However, this process is time consuming and the fact that provision of accurate information from healthcare professionals is variable would need to be evaluated further. Importantly dietetic input as part of a multidisciplinary allergy consultation has been shown to improve patient understanding of allergen avoidance with a resulting reduction in accidental allergen exposures in the community.³⁹ While there remains no clear evidence base to inform how patients should be advised, an individual approach remains best practice, while more data are required to better understand what, if any, additional risk results from less stringent avoidance.

CONCLUSIONS

An active approach to the management of food allergies has many advantages for food allergic children and their families, possibly including the possibility of tolerance induction and a significant improvement in quality of life. Food immunotherapy is an emerging area of considerable interest, which is showing promise as a form of active treatment and is also expected to evolve in the near future. There is a clear need to further refine current protocols to ensure safety, long-term efficacy and acceptability of this intervention. The health economic impact of these new approaches remains largely undefined; a careful assessment of the cost/benefit ratio would be required before they are ready to enter current guidelines.

Practice points

- ▶ Early introduction of potentially allergenic foods may help reduce the risk of food allergy and may play a role in clinical tolerance induction.
- ▶ Appropriate allergy testing and interpretation of the index food and also related allergens in high-risk patients allows a more precise diagnosis and minimises food exclusions, as long as appropriate facilities are in place to conduct diagnostic food challenges.
- ▶ The introduction of modified allergenic food, such as baked cow's milk and baked egg, into the diet of carefully selected children allergic to cow's milk and egg, respectively, may hasten the development of clinical tolerance.
- ▶ Food immunotherapy is an emerging area of research, which has shown promise, but is not yet ready for a routine clinical treatment modality.

Contributors ATF developed the original concept. ATF and KA drafted the initial manuscript. GS, GdT, HB and GL reviewed and amended the original and later drafts.

Competing interests GS has received lecture fees from Danone and Thermofisher Scientific. HB has received grant funding from Action Medical Research Charity, the Food Allergy Research and Education Charity, and the National Institutes of Health (NIH) through the Immune Tolerance Network. HB has received conference fees from Meda, Thermofisher Scientific, Danone, Mead Johnson and consultancy/lecture fees from Meda, Thermofisher Scientific and ALK-Abello. GdT is a voluntary scientific advisor for the Anaphylaxis Campaign. GL has received research support from the ITN/NIAD, the Food Allergy Initiative, the National Peanut Board, the Food Standards Agency, the Food Allergy and Anaphylaxis Network, MRC Asthma UK Centre, and the Department of Health through the National Institute for Health Research Comprehensive Biomedical Research Centre award to the Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust; is on the DBV Technologies advisory board; is a voluntary scientific advisor for the Anaphylaxis Campaign and the National Peanut Board; has received lecture fees from Sodilac, Novartis, Nestle Nutrition, GlaxoSmithKline, and the Sero Symposia International Foundation; and has stock/stock options in DBV Technologies. ATF has received grant funding from Danone and ALK-Abello, conference fees from Meda, GSK, ALK-Abello and consultancy/lecture fees from Danone, Nestle, Mead Johnson, Abbott, Lactofree, Meda, Thermofisher Scientific, is a voluntary scientific advisor for the Anaphylaxis Campaign and Allergy UK.

Provenance and peer review Commissioned; externally peer reviewed.

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Arch Dis Child published online November 5, 2014

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