Review

Recent advances in the management of food allergy

Katherine Anagnostou[1] & Adam Fox*,[1]
[1]Department of Paediatric Allergy, Guy's and St Thomas' Hospitals NHS Foundation Trust, Westminster Bridge Road, London, UK
*Author for correspondence:
Tel.: +44 (0) 20 7188 9525/6
adam.fox@gstt.nhs.uk

Practice points

- Food allergies are a common problem in childhood. Lately, there has been a shift in the management of food allergies towards a more active approach.
- Allergy testing, not only to the index food, but also to related allergens in high risk patients, allows a more precise and prompt diagnosis and at the same time reduces the risk of unnecessary dietary restrictions.
- Early introduction of potentially allergenic foods may help reduce the risk of food allergy and may play a role in tolerance induction.
- Recent evidence suggests that probiotics, as well as the introduction of baked milk and baked egg into the diet of carefully selected children allergic to milk and egg respectively, may hasten the development of tolerance.
- Food immunotherapy is an emerging area of considerable interest, which has shown promise as a form of active treatment for food allergies.
- This more active approach to managing food allergy significantly increases complexity, as well as having a potentially large resource implication, particularly with regard to increased number of food challenges. The health economics of this requires further evaluation.

Food allergies are common in children and they can be severe. They result in dietary restrictions and significantly affect quality of life. There is currently no cure for food allergies and the mainstream approach to management consists of food avoidance and provision of emergency medication. Recently, a more active approach to management is being adopted, which includes anticipatory testing, early introduction of potential food allergens, active tolerance induction and active risk management, all of which are discussed at length in this review.

Keywords: advisory labels • components • food allergy • oral immunotherapy • probiotics • tolerance induction

Introduction

Food allergy is common, affecting 6–8% of children, and is potentially severe. Its prevalence is increasing, a phenomena noted in other atopic disorders in the western world over the past few decades [1,2]. The prevalence of food allergy is highest in infants and toddlers, with 2.5% of infants suffering from milk allergy and up to 10% of 1-year olds suffering from food allergies, including cow's milk, egg, nuts, soya, wheat and fish/shellfish [3–5].

Food allergies have a significant effect on the quality of life of sufferers and their family. Anxiety stems from fear of accidental ingestion and allergic children face various social restrictions and school issues [6].

Certain food allergies, such as cow's milk, soya, egg and wheat, are usually outgrown after a few years and a period of dietary exclusion. Fish, shellfish, peanut and tree nut allergy, on the other hand, tend to be lifelong and rarely resolve [7].

Future Medicine part of fsg

There is no cure for food allergy. The traditional approach is based on strict avoidance of the offending food (elimination diet) and prompt treatment of adverse reactions, resulting from accidental exposure. Children and families are provided with emergency medication and a management plan on how to treat allergic reactions [8].

Recently, based on numerous strands of research, a more active approach towards the management of food allergy is being adopted. This approach has many facets including: actively testing for related allergens in high risk patients once a specific food allergy has been identified (anticipatory testing); early dietary introduction of potentially allergenic foods that are tolerated, as a means to prevent the development of allergy; active induction of tolerance to known allergens; and active risk management. These numerous approaches, rely on an emerging evidence base and may significantly increase the complexity of managing children with food allergy. As our understanding of these new approaches develops, we will be able to better identify the children who are likely to benefit the most. In the interim, these management strategies remain restricted to specialist practice with limited applicability to primary care. However, as they have the potential to significantly improve quality of life and reduce the development of further allergies, they warrant further study as to their precise place in future practice. This article looks at each of these areas, in turn, focusing exclusively on IgE-mediated food allergy.

Anticipatory testing

Children with allergy to one food are at risk of having more food allergies [9]. Therefore, the initial presentation with one food allergy in high risk patients should be used as a clear indicator that further assessment is required. Failure to adopt this approach, will mean that further food allergies will only be discovered when the child unexpectedly reacts on exposure, with potentially severe consequences. Alternatively, the child may be unnecessarily restricted from consuming foods considered as 'high risk', for example, nuts, simply due to fear of reaction, further adding to the burden of anxiety and food avoidance. The diagnostic process in food allergy involves taking an allergy-focused history, followed by targeted allergy testing (either skin prick or specific IgE testing), with cases where diagnostic doubt remains being subject to oral provocation challenge [8].

However, recent food allergy diagnostic guidance recommend allergy testing not only to the allergen suspected of causing the index reaction, but also known co-allergens i.e. allergens known to occur with increased frequency in those with certain other allergies [10,11]. Examples include, testing for peanut allergy in children with egg allergy, where the estimated rate of co-allergy in approximately 20–30% or sesame allergy, in those with known peanut allergy (estimated prevalence of 25%) [12,13]. Some common avoidance patterns occur where there is no evidence of co-allergy, for example, avoidance of shellfish, such as crustaceae in children with fish allergy and hence appropriate testing could provide reassurance for safe introduction.

This anticipatory approach could be taken a step further, given the extensive evidence that the presence of eczema in infancy is an important risk factor for the development of IgE-mediated food allergy. Hill *et al.* showed that increasing severity of eczema during infancy as well as earlier age of onset, are both risk factors for development of allergy [14–18].

A recent study by Mailhol *et al.*, investigated the point prevalence and risk factors for food allergy in a cohort of 386 children with eczema. The authors conclude that children below 2 years old, with early onset or severe eczema, are at higher risk of food allergy and may be candidates for food allergy evaluation [18]. Evaluation would include careful history and allergy testing, ideally around the time of weaning, when allergenic foods are to be encountered and would focus on the common allergens known to be relevant for the child's ethnic background and household diet. For example, while allergy to milk and egg are common around the world, allergy to legumes such as chickpea or lentil is more common in families where a south Asian diet is consumed [19].

Central to this anticipatory approach, however, is the ability to differentiate between allergy and sensitization, especially in children with no clinical history of consuming the suspect allergen. The ongoing improvement in allergy diagnostics makes this approach more practicable. Component testing is a recent development that may have the potential to better differentiate between clinical reactivity and sensitization, effectively reducing the need for food challenges. Dang *et al.* have shown that the use of Ara h 2 in the diagnosis of peanut allergy has the potential to reduce the number of patients requiring referral to specialist services for confirmation of food allergy by using OFCs [20]. Proof of principle has been demonstrated for milk, egg, peanut and various other allergens [21–27]. Dang *et al.* have demonstrated that the increased diagnostic value of Ara h 2 over peanut specific IgE may decrease the need for provocation challenges in clinical practice [20]. More studies are needed to confirm this, as it has been noted that correlations are not fully established yet and may differ, depending on the populations studied and different geographical regions. For peanut allergy, for example, a recent study reported different patterns of immunological reactivity to peanut components, in

three different geographical regions. American patients showed higher levels of IgE antibodies to Ara h 1, Ara h 2 and Ara h 3, whereas patients from Spain, had higher rates of sensitization to Ara h 9 and Swedish patients, had higher levels of IgE antibodies to Ara h 8 (the Bet v 1 homolog) [28].

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, when there is evidence of sensitization with no clinical history to help interpret this. As a result, the more broadly testing is done, the more supervised oral provocation challenges will be required, and hence, there is a requirement for clinical capacity to carry this out, if this approach is to be adopted. Further evaluation to better understand the health economics of this is required.

Another component of anticipatory testing is the ongoing follow-up of known allergies. Food allergy may resolve over time (except in most cases of nut and seafood allergy). Milk allergy has been shown to resolve in 79% by the age of 16 years [29], whereas 68–82% of children outgrow their egg allergy by 16 years [30]. There is, therefore, a role for monitoring food-specific IgE antibodies (decreasing levels are associated with an increased chance of allergy resolution) to determine when a food challenge should be repeated [31]. Repeating food challenges at regular intervals to check for resolution can have important benefits for the allergic child and the family [32]. Re-introduction of the food would not only have nutritional benefits, but also the potential to significantly improve quality of life if results are favorable [33,34]. However, it is important to note that food challenges are not without risk and have a significant resource implication [8,35]. This approach will inevitably increase the number of food challenges and if these are not performed rapidly, any delay may increase the family's anxiety with regards to food allergy diagnosis and potentially, as discussed below, result in a missed opportunity for tolerance induction.

In summary, anticipatory testing for related co-allergens, in carefully selected patients, would allow more precise and prompt diagnosis and reduce the risk of unnecessary avoidance of safe foods. However, this approach increases the need for diagnostic food challenges and the economic impact of this requires further study.

Early food introduction

In June 1998, the UK Department of Health published recommendations aimed at halting the rising incidence of peanut allergy. These stated that 'Pregnant women who are atopic or have an atopic partner may wish to avoid eating peanuts during pregnancy and lactation. Infants with a family history of atopy, should be exclusively breastfed for 4–6 months and should avoid peanuts until 3 years' [36]. This, and broadly similar advice from the American Academy of Paediatrics, were based on the conclusion that peanut sensitization, occurring as a result of exposure *in utero* or via lactation, was mechanistically possible. This advice was withdrawn in 2009, as there was not sufficient evidence to support that maternal avoidance has any benefits in preventing the development of food allergy in infants [37,38]. A recent prospective study examined the association between peri-pregnancy consumption of peanuts and tree nuts by non-allergic mothers. The authors reported that higher consumption of peanuts and tree nuts by the mothers during pregnancy was, in fact, associated with a lower risk of peanut and tree nut allergy in the offspring, while other studies report no significant association [39,40].

For infants at increased risk of atopy, as a result of their family history, the advice to delay introduction of solid foods until 6 months of age and the introduction of major food allergens until after 3 years of age has also being challenged [37]. Prolonged, exclusive breastfeeding after the age of 4 months has not been shown to have any effect in reducing atopy. In fact, it has been associated with the development of asthma and eczema [41,42].

It is now suggested that early introduction of an allergic food may actually play an important role in tolerance induction.

Katz *et al.* have 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 those 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 [43].

In a cross sectional study by Koplin *et al.*, it has been suggested that early introduction of egg might have a protective effect against egg allergy. The study included 2589 infants and examined the relationship between timing of infant feeding and subsequent risk of food allergy. Infants introduced to cooked egg at 4–6 months had a lower risk of egg allergy than those introduced to cooked egg after that time [44]. A birth cohort of 3781 children in Finland was studied by Nwaru *et al.* Egg introduction before the age of 11 months was inversely associated with the development of asthma, allergic rhinitis and atopic sensitization. By contrast, introduction of a limited number of foods at the age of 3 months was associated with an increase in atopic sensitization later in life [45,46].

Du Toit *et al.* studied the prevalence of peanut allergy among Jewish children in the UK and Israel, in relation to timing and amount of peanut consumption. They found a tenfold higher prevalence of peanut allergy in the UK compared with Israel (1.85 vs 0.17%). Since the participating children shared a similar genetic background, the effect of genetics was unlikely to account for the difference in prevalence. Following assessment of peanut consumption in both countries, results showed that peanut is introduced earlier and is eaten more frequently in Israel than in the UK. Israeli infants start consuming peanut-containing foods during early weaning, whereas UK infants mostly avoid peanuts for the first 3 years of life. The investigators concluded that early consumption of peanuts in infancy, as well as consumption of frequent and high doses of peanut protein is associated with a low prevalence of peanut allergy, possibly due to induction of oral tolerance [13].

In practice, this evidence supports the view that even in children with known food allergy, allergenic foods should not be delayed and where there is an increased risk of co-allergy, for example, for peanut among egg allergic children, the use of anticipatory testing can help support the early introduction of peanut into the diet. This also helps broaden the dietary repertoire of the infant and reduces the number of foods being avoided. The above approach is particularly useful as increasing number of food avoidance has been shown to increase the risk of nutritional compromise and abnormal feeding patterns [47,48].

However, further data from ongoing interventional studies such as LEAP are required, to better understand if early food introduction can actively help reduce the risk of food allergy [12].

Active tolerance induction

Recent studies investigating the natural history of cow's milk and egg allergy have shown that resolution rates are not as high as considered previously, with the majority of milk and egg allergic children developing tolerance in late childhood [29,30]. Persistence of both allergies into late childhood years can affect not only nutritional status but also quality of life. It would, therefore, be beneficial to find ways that would accelerate tolerance development. Once a food allergy has been diagnosed, the traditional approach has been careful avoidance, yet more recently, evidence has started to emerge relating to new strategies to help tolerance develop more quickly [8,49]. Three areas have been of particular interest – the use of probiotics in infants with milk allergy, the role of baked egg and milk introduction in children with milk or egg allergies and the role of desensitization to food.

There has been long-standing interest in the potential role of probiotics in modulating the allergic response in food allergy [50]. There is recent evidence that maternal probiotic supplementation during pregnancy and breastfeeding has been shown to reduce the risk of eczema in high-risk infants [51]. Canani *et al.* investigated the role of Lactobacillus GG (LGG) on acquisition of tolerance in infants with cow's milk allergy. A total of 80 infants (age 1–12 months) were randomly assigned to receive either an extensively hydrolysed casein formula (EHCF) or EHCF with LGG. Participants were challenged to milk at 6 months and 12 months in both groups and the authors showed that the infants receiving EHCF with LGG had a higher probability of acquiring tolerance to cow's milk than those receiving ECHF alone. In conclusion, supplementation of ECHF with LGG was shown to accelerate the development of tolerance in infants with cow's milk allergy [52].

Further evidence of an effect has come from a multicenter study observing the development of tolerance in milk allergic children who had been started on a number of different hypoallergenic formulas [53]. Among the 260 children with IgE (111 children) or non-IgE mediated milk allergy, the rate of acquiring oral tolerance after 12 months, was significantly higher in the groups receiving EHCF (43.6%) or EHCF + LGG (78.9%) compared with the other groups: rice hydrosylate (32.6%), soy formula (23.6%) and amino acid formula (18.2%). Logistic regression analysis revealed that tolerance induction was influenced by the mechanism of allergy (IgE vs non-IgE) and also formula choice. The authors concluded that EHCF appeared to accelerate tolerance acquisition compared with other formula choices and that this effect is augmented by LGG [53]. However, the study was neither randomized nor interventional and hence open to selection bias, with more severe cases of milk allergy, most likely to run a prolonged course, more likely to have been prescribed amino acid formula. Interventional studies, which are underway, are required to clarify this effect of probiotics on tolerance induction.

Many parents had recognized that despite a diagnosis of milk or egg allergy, their children could tolerate the allergen when extensively heated, such as baked in cakes, waffles or muffins. Studies revealed that 70–75% of milk and egg allergic children can tolerate the allergen when extensively heated [54,55]. This can make dietary restriction much easier, but potentially also help develop tolerance more quickly.

Kim *et al.* reported on the outcome of a group of children who incorporated baked milk products into their diet. In total, 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 milk than the comparison group. The investigators concluded that the addition of baked milk into the diet of milk allergic children appears to accelerate resolution of cow's milk allergy [56].

Peters *et al.* recently investigated 140 infants with challenge-confirmed egg allergy at age 1 year. A year later, egg allergy had resolved in 66 (47%) infants. Resolution was found to be lower in children with baked egg allergy at age 1 year compared with baked egg tolerance (13 and 56%, respectively) Also, frequent ingestion of baked egg (≥5 times per month) compared with infrequent ingestion (0–4 times per month) increased the likelihood of tolerance [57]. A similar study evaluated the role of baked egg in the development of tolerance to regular egg. Of the 70 subjects who regularly consumed baked egg, 53% were tolerant of regular egg by the end of the 37-month study period, compared with only 28% (of the 47 subjects) in the comparison group (strict avoidance of all forms of egg). Subjects who were consuming baked egg products were 14 times more likely to develop tolerance to regular egg compared with the comparison group. It was also noted that subjects in the group that regularly consumed baked egg developed tolerance to regular egg earlier. The median time to regular egg tolerance was 50 months in the baked egg-consuming group versus 78.7 months in the comparison group [58]. 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, including using components tests, is relatively unhelpful [59]. Given that reactions to baked egg or milk may be severe, it remains necessary to use oral food challenges under medical supervision to definitively delineate the allergic status of each child [44,60].

Another area of intense research interest is food oral immunotherapy (OIT) and has shown promise as a form of active treatment for food allergies. The administration of small, but increasing doses of an allergenic food to children that are allergic to the food, has been shown to increase their threshold of reactivity (desensitization), induce clinical tolerance and enable them to eat varying amounts of the allergenic food without reactions. Food oral immunotherapy studies have been conducted for various allergens, but mostly concentrated on milk, egg and peanut.

Skripak *et al.* conducted a double-blind placebo-controlled study of OIT for cow's milk allergy in 20 subjects 6–19 years of age. After OIT, the median cumulative dose inducing a reaction in the active treatment group was 5140 mg compared with 40 mg pre-OIT. There was no change in the median threshold in the placebo group. Although reactions were common during the study, nearly 90% were transient and did not require treatment [61].

A recent double-blind placebo-controlled, randomized egg oral immunotherapy study of 55 children, 5–18 years old, with egg allergy, resulted in a 55% rate of desensitization in the active group after 10 months of therapy. No subjects in the placebo group were desensitized. Once maintenance was discontinued for 6–8 weeks, however, only 28% of children were desensitized at 24 months [62].

A two-step, Phase II, randomized-controlled crossover trial of peanut OIT in 99 children aged 7–16 years, investigated the role of peanut oral immunotherapy in peanut allergic children inclusive of all severities of peanut allergy. Among OIT participants, 84% were desensitized to 800 mg, the equivalent of five peanuts. In the active group, 24 of 39 (62%) OIT participants were desensitized to 1.4 g of peanut protein, compared with zero of 46 participants in the control group. When compared with control participants, those successfully completing the study's OIT protocol, had a significant 25-fold increase of their threshold level of reactivity to peanut over baseline. A significant improvement in the quality of life was reported for both participants and their caregivers. Despite most of OIT participants reporting adverse events, reactions were mild and mostly treated with oral antihistamines and b2-agonists [63].

Oral desensitization to foods appears to require regular consumption of the relevant allergen in order to maintain clinical tolerance. Discontinuation of oral immunotherapy even for short periods of time (a few weeks) has so far resulted in loss of desensitization [62,64]. Families contemplating such therapy will need to balance the benefit of increased clinical tolerance with the risk of allergic reactions, compared with a strategy of complete avoidance. Phase III studies are required to further investigate long-term effects of this intervention. Future research will further improve safety and efficacy of this form of treatment.

Overall, we can conclude that there is evidence to suggest that probiotics, as well as introduction of baked milk and baked egg into the diet of children allergic to cow's milk and egg, respectively, may have a role in active induction of tolerance. Furthermore, for those who do not naturally outgrow their allergies in early childhood, OIT is being seen as an increasingly realistic option, albeit still not in widespread clinical practice. Over time, management of food allergy has thus become a balancing act between avoiding allergens and promoting acquisition of tolerance [65].

Active risk management (advisory labels)

In many countries around the world (including in 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 [66,67]. It is important to note however, that there are different legal requirements and significant variations between countries regarding mandatory labeling of food allergens. A recent review suggests that a globally agreed framework on food labeling would ensure that foods produced around the world can be safely ingested by consumers irrespective of allergy status. Legislation would be required to introduce uniformity among manufacturers in conducting a risk assessment for allergen content and then communicating that risk in an easily understandable way to the allergic consumer [68].

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 [66]. On the other hand, since advisory statements are voluntary and thus not present on all at-risk products, there is also a risk that unlabelled foods could be contaminated with allergen, thus it is difficult for a consumer with food allergy to know which foods may contain 'traces' of allergen with the current labeling systems [69–71].

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 [67]. Avoidance of foods with advisory labels, places an additional burden on the allergic consumer, with a survey reporting that shoppers avoiding products with advisory labels, spending 39% more time identifying suitable foods, and paying on average 11% more than their non-allergic counterparts [67]. 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 [72]. When questioned, labels including 'this product does not contain any nuts but is made in a factory that uses nuts', 'cannot guarantee is nut free' and 'may contain traces of nuts' were avoided by only approximately 50% of parents of nut-allergic children. Previous allergic reaction to nut products had no bearing on outcome [72]. A recent survey of 239 British healthcare professionals revealed that only 38% of health professionals 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 didn't have their emergency medication. A history of asthma or anaphylaxis increased the likelihood that complete avoidance was recommended [73].

While there remains no clear evidence base to inform how patients should be advised, an individual approach remains best practice whilst more data is required to better understand what, if any, additional risk results from less stringent avoidance. It is important to note that allergen dose thresholds for reactions vary between individuals and that this might affect their likelihood of reaction to products containing 'trace' amounts of allergen.

Conclusion

For many years, management of food allergy consisted of allergen avoidance and emergency treatment while waiting for allergies to be outgrown. However, a more active approach to management, drawing on the emerging evidence base, is helping to improve quality of life, prevent development of new allergies and actively attempt to induce tolerance. The health economic impact of these new approaches remains largely undefined.

Future perspective

An active approach to the management of food allergies has many advantages for food allergic children, including the possibility of tolerance induction and a significant improvement in their quality of life. We believe, that in the next few years, this approach will be adopted by the majority of clinician allergists and allergy centres around the world.

Food immunotherapy is an emerging area of considerable interest, which is showing considerable promise as a form of active treatment and is also expected to evolve in the near future.

Financial disclosure/conflict of interest

A Fox has received grant funding from Danone and ALK-Abello, conference fees from Meda, GSK, ALK-Abello and consultantcy/lecture fees from Danone, Nestle, Mead Johnson, Abbott, Lactofree, Meda, Thermofisher Scientific. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest.

1 Pereira B, Venter C, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers. *J. Allergy Clin. Immunol.* 116(4), 884–892 (2005).

2 Venter C, Hasan Arshad S, Grundy J *et al.* Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. *Allergy* 65,(1) 103–108 (2010).

3 Sampson HA. Update on food allergy. *J. Allergy Clin. Immunol.* 113(5), 805–819; quiz 820 (2004).

4 Sicherer SH, Sampson HA. Food allergy. *J. Allergy Clin. Immunol.* 125, S116–25 (2010).

5 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.* 127(3), 668–676.e1–2 (2011).

6 Avery NJ, King RM, Knight S, Hourihane JOB. Assessment of quality of life in children with peanut allergy. *Pediatr. Allergy Immunol.* 14(5), 378–382 (2003).

7 Burks AW, Tang M, Sicherer S *et al.* ICON: food allergy. *J. Allergy Clin. Immunol.* 129(4), 906–920 (2012).

8 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 Acknowledgments Primary Authors Office of Food Additive Safety. *J. Allergy Clin. Immunol.* 126(Suppl 6), S1–S58 (2010).

9 Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J. Allergy Clin. Immunol.* 133(2), 291–307.e5 (2013).

10 Practice C. NICE clinical guideline 116 – Food allergy in children and young people: Diagnosis and assessment of food allergy in children and young people in primary care and community settings. National Institute for Health and Clinical Excellence. London, UK (2011).

11 Sherwood E, Boyd A. Food allergy in children and young people. *InnovAiT* 5(2), 76-82 (2012).

12 Du Toit G, Roberts G, Sayre PH *et al.* Identifying infants at high risk of peanut allergy: The Learning Early About Peanut Allergy (LEAP) screening study. *J. Allergy Clin. Immunol.* 131(1), 135–143 (2012).

13 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.* 122(5), 984–991 (2008).

14 Sporik R, Hill D, Hosking C. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin. Exp. Allergy* 30(11), 1540–1546 (2000).

15 Hill DJ, Heine RG, Hosking CS *et al.* IgE food sensitization in infants with eczema attending a dermatology department. *J. Pediatr.* 151(4), 359–363 (2007).

16 Hill DJ, Sporik R, Thorburn J, Hosking CS. The association of atopic dermatitis in infancy with immunoglobulin E food sensitization. *J. Pediatr.* 137(4), 475–479 (2000).

17 Hill DJ, Hosking CS, de Benedictis FM *et al.* Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. *Clin. Exp. Allergy* 38(1), 161–168 (2008).

18 Mailhol C, Giordano-Labadie F, Lauwers-Cances V, Ammoury A, Paul C, Rance F. Point prevalence and risk factors for food allergy in a cohort of 386 children with atopic dermatitis attending a multidisciplinary dermatology/ paediatric allergy clinic. *Eur. J. Dermatol.* 24(1), 63–69 (2001).

19 Dias RP, Summerfield A, Khakoo GA. Food hypersensitivity among Caucasian and non-Caucasian children. *Pediatr. Allergy Immunol.* 19(1), 86–89 (2008).

20 Dang TD, Tang M, Choo S *et al.* Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. *J. Allergy Clin. Immunol.* 129(4), 1056–1063 (2012).

21 Fiocchi A, Bouygue GR, Albarini M, Restani P. Molecular diagnosis of cow's milk allergy. *Curr. Opin. Allergy Clin. Immunol.* 11(3), 216–221 (2011).

22 Caubet JC, Nowak-Węgrzyn A, Moshier E, Godbold J, Wang J, Sampson HA. Utility of casein-specific IgE levels in predicting reactivity to baked milk. *J. Allergy Clin. Immunol.* 131(1), 222–224.e1–4 (2013).

23 Caubet JC, Kondo Y, Urisu A, Nowak-Węgrzyn A. Molecular diagnosis of egg allergy. *Curr. Opin. Allergy Clin. Immunol.* 11(3), 210–215 (2011).

24 Bartnikas L, Sheehan W, Larabee K. Ovomucoid is not superior to egg white testing in predicting tolerance to baked egg. *J. Allergy Clin. Immunol. Pract.* 1(4), 354–360 (2013).

25 Nicolaou N, Poorafshar M, Murray C *et al.* Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J. Allergy Clin. Immunol.* 125(1), 191–197.e1–13 (2010).

26 Sicherer SH, Wood RA. Advances in diagnosing peanut allergy. *J. Allergy Clin. Immunol. Pract.* 1(1), 1–13 (2013).

27 Lieberman JA, Glaumann S, Batelson S, Borres MP, Sampson HA, Nilsson C. The utility of peanut components in the diagnosis of IgE-mediated peanut allergy among distinct populations. *J. Allergy Clin. Immunol. Pract.* 1(1), 75–82 (2013).

28 Vereda A, van Hage M, Ahlstedt S *et al.* Peanut allergy: clinical and immunologic differences among patients from 3 different geographic regions. *J. Allergy Clin. Immunol.* 127(3), 603–607 (2011).

29 Skripak JM, Matsui EC Mudd K Wood R. The natural history of IgE-mediated cow's milk allergy. *J. Allergy Clin. Immunol.* 120(5), 1172–1177 (2007).

30 Savage JH, Matsui EC Skripak JM, Wood RA. The natural history of egg allergy. *J. Allergy Clin. Immunol.* 120(6), 1413–1417 (2007).

31 Thong BY, Hourihane JO. Monitoring of IgE-mediated food allergy in childhood. *Acta Paediatr.* 93(6), 759–764 (2004).

32 Shek LP, Soderstrom L, Ahlstedt S, Beyer K, Sampson HA Determination of food specific IgE levels over time can

predict the development of tolerance in cow's milk and hen's egg allergy. *J. Allergy Clin. Immunol.* 114(2), 387–391 (2004).

33 DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire – Parent form in children 0–12 years following positive and negative food challenges. *Clin. Exp. Allergy* 40(3), 476–485 (2010).

34 Van der Velde JL, Flokstra-de Blok BM, de Groot H *et al.* Food allergy-related quality of life after double-blind, placebo-controlled food challenges in adults, adolescents, and children. *J. Allergy Clin. Immunol.* 130(5), 1136–1143. e2 (2012).

35 Pongracic JA, Bock SA, Sicherer SH. Oral food challenge practices among allergists in the United States. *J. Allergy Clin. Immunol.* 129(2), 564–566 (2012).

36 Committee on Toxicity. COT report on peanut allergy (1998). http://cot.food.gov.uk

37 Greer FR, Sicherer SH, Burks AW *et al.* Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 121(1), 183–191 (2008).

38 Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. *J. Allergy Clin. Immunol. Pract.* 1(1), 29–36 (2013).

39 Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J. Allergy Clin. Immunol.* 123(2), 417–423 (2009).

40 Frazier AL, Camargo CA Jr, Malspeis S, Willett WC, Young MC. Prospective study of peripregnancy consumption of peanuts or tree nuts by mothers and the risk of peanut or tree nut allergy in their offspring. *JAMA Pediatr.* 168(2), 156–162 (2013).

41 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* 360(9337), 901–907 (2002).

42 Bergmann RL, Diepgen TL, Kuss O *et al.* Breastfeeding duration is a risk factor for atopic eczema. *Clin. Exp. Allergy* 32(2), 205–209 (2002).

43 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.* 126(1), 77–82. e1 (2010).

44 Koplin JJ, Osborne NJ, Wake M *et al.* Can early introduction of egg prevent egg allergy in infants? A population-based study. *J. Allergy Clin. Immunol.* 126(4), 807–813 (2010).

45 Nwaru BI, Takkinen HM, Niemelä O *et al.* Introduction of complementary foods in infancy and atopic sensitization at the age of 5 years: timing and food diversity in a Finnish birth cohort. *Allergy* 68(4), 507–516 (2013).

46 Nwaru BI, Takkinen HM, Niemelä O *et al.* Timing of infant feeding in relation to childhood asthma and allergic diseases. *J. Allergy Clin. Immunol.* 131(1), 78–86 (2013).

47 Flammarion S, Santos C, Guimber D *et al.* Diet and nutritional status of children with food allergies. *Pediatr. Allergy Immunol.* 22(2), 161–165 (2011).

48 Meyer R, De Koker C, Dziubak R *et al.* Malnutrition in children with food allergies in the UK. *J. Hum. Nutr. Diet.* 27(3), 227–235 (2014).

49 Fiocchi A, Brozek J, Schünemann H *et al.* World allergy organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines. *Pediatr. Allergy Immunol.* 21 (Suppl. 2), 1–125 (2010).

50 Nermes M, Salminen S, Isolauri E. Is there a role for probiotics in the prevention or treatment of food allergy? *Curr. Allergy Asthma Rep.* 13(6), 622–630 (2013).

51 Rautava S, Kainonen E, Salminen S, Isolauri E. Maternal probiotic supplementation during pregnancy and breast-feeding reduces the risk of eczema in the infant. *J. Allergy Clin. Immunol.* 130(6), 1355–1360 (2012).

52 Berni Canani R, Nocerino R, Terrin G *et al.* Effect of lactobacillus GG on tolerance acquisition in infants with cow's milk allergy: a randomized trial. *J. Allergy Clin. Immunol.* 129(2), 580–582, 582.e1–5 (2012).

53 Berni Canani, R *et al.* Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: a prospective multicenter study. *J. Pediatr.* 163, 771–777.e1 (2013).

- **This prospective study demonstrates that infants with IgE-mediated milk allergy who received extensively hydrolysed casein-based formula with LGG outgrew their milk allergy significantly quicker than children who received other formulas.**

54 Nowak-Wegrzyn A, Fiocchi A. Rare, medium, or well done? The effect of heating and food matrix on food protein allergenicity. *Curr. Opin. Allergy Clin. Immunol.* 9(3), 234–237 (2009).

55 Lemon-Mulé H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J. Allergy Clin. Immunol.* 122(5), 977–983.e1 (2008).

56 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.* 128(1), 125–131.e2 (2011).

- **Demonstrates that consumption of baked milk by children with IgE-mediated milk allergy were able to tolerate it and this led to an increase in their speed of tolerance development, compared to similar children who strictly avoided all milk.**

57 Peters RL, Dharmage SC, Gurrin LC *et al.* The natural history and clinical predictors of egg allergy in the first 2 years of life: a prospective, population-based cohort study. *J. Allergy Clin. Immunol.* 133(2), 485–491 (2014).

58 Leonard SA, Sampson HA, Sicherer SH *et al.* Dietary baked egg accelerates resolution of egg allergy in children. *J. Allergy Clin. Immunol.* 130(2), 473–480.e1 (2012).

59 Lemon-Mulé H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J. Allergy Clin. Immunol.* 122(5), 977–983.e1 (2008).

60 Tan JW, Campbell DE, Turner PJ *et al.* Baked egg food challenges – clinical utility of skin test to baked egg and ovomucoid in children with egg allergy. *Clin. Exp. Allergy* 43(10), 1189–1195 (2013).

61 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.* 122(6), 1154–1160 (2008).

62 Burks AW, Jones SM, Wood RA *et al.* Oral immunotherapy for treatment of egg allergy in children. *N. Engl. J. Med.* 367(3), 233–243 (2012).

63 Anagnostou K Islam S1, King Y *et al.* Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a Phase 2 randomised controlled trial. *Lancet* 383(9925), 1297–1304 (2014).

•• **In this randomized controlled trial of OIT, 62% of the participants in the active group were successfully desensitized to 1.4 g of peanut protein, whereas 84% were desensitized to 800 mg of peanut protein. Quality of life was shown to improve significantly following successful immunotherapy.**

64 Vickery BP, Scurlock AM, Kulis M *et al.* Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J. Allergy Clin. Immunol.* 133(2), 468–475 (2014).

65 Katz A, Virk Hundal N, Yuan Q, Shreffler W. Cow's milk allergy: a new approach needed? *J. Pediatr.* 163(3), 620–622 (2013).

66 Turner PJ, Kemp AS, Campbell DE. Advisory food labels: consumers with allergies need more than "traces" of information. *BMJ* 343, d6180 (2011).

67 Aware B. May contain "labelling – the consumer's perspective. The Food Standards Agency. www.food.gov.uk/multimedia/pdfs/maycontainreport.pdf

68 Allen KJ, Turner PJ, Pawankar R *et al.* Precautionary labelling of foods for allergen content: are we ready for a global framework? *World Allergy Organ. J.* 7(1), 10 (2014).

69 Pele M, Brohée M, Anklam E, Van Hengel AJ. Peanut and hazelnut traces in cookies and chocolates: relationship between analytical results and declaration of food allergens on product labels. *Food Addit. Contam.* 24(12), 1334–1344 (2007).

70 Ford LS Taylor SL, Pacenza R, Niemann LM, Lambrecht DM, Sicherer SH. Food allergen advisory labeling and product contamination with egg, milk, and peanut. *J. Allergy Clin. Immunol.* 126(2), 384–385 (2010).

71 Hefle SL Furlong TJ, Niemann L, Lemon-Mule H, Sicherer S, Taylor SL. Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts. *J. Allergy Clin. Immunol.* 120(1), 171–176 (2007).

72 Noimark L, Gardner J, Warner JO. Parents' attitudes when purchasing products for children with nut allergy: A UK perspective. *Pediatr. Allergy Immunol.* 20(5), 500–504 (2009).

73 Turner PJ, Skypala IJ, Fox AT. Advice provided by Health Professionals regarding precautionary allergen labelling. *Pediatr. Allergy Immunol.* 25(3), 290–292 (2014).