Narrative Review
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Peanut Allergy – No Longer a Life Sentence

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Abstract

In this review we provide an overview on the latest knowledge in the prevention and active management of peanut allergy. The rise in incidence of food allergy has generated new challenges in the management of affected individuals. Strategies to counteract the increase in prevalence of peanut allergy can be considered as a pyramid, beginning with primary prevention of those at risk through earlier introduction of peanut into the infant diet, to secondary prevention of peanut-sensitised children through improvements in the correct diagnosis of peanut allergy and finally to the treatment of children with proven peanut allergy. Conclusion: With the paradigm shift towards an active management, peanut allergy should no longer be seen as a life sentence.

Key Words: Immunotherapy ▪ Peanut Allergy ▪ Prevention.

Introduction

The rise in incidence of food allergy worldwide has generated new challenges in the management of affected individuals. However, at the same time, we are learning more about the development of food allergies and strategies to both reduce the risk and offer active management of affected patients.

In this review we provide an overview on the latest knowledge in the prevention and management of peanut allergy.

Epidemiology

Peanut allergy was uncommon before the 1990s, where reports were limited to case series or small cohorts (1, 2). The prevalence of peanut allergy has risen significantly over the last 3 decades (3-5), although this is likely to be, at least in part, due to increased knowledge and recognition of the condition. In both the United Kingdom and Australia, there is evidence that while peanut allergy increased prior to 2000, this increase has now plateaued (4, 6). A systematic review conducted in Europe between 2000 and 2012 reported the point prevalence of challenge-confirmed peanut allergy to be 0.22% (95% confidence interval (CI), 0.16–0.28), with overall pooled estimates for self-reported lifetime prevalence of peanut allergy as 1.3% (95% CI, 1.2–1.5) (7). In Australia, the prevalence of peanut allergy at 12 months was 3.0% (95% CI, 2.4–3.8) and at 4 years 1.9% (95% CI, 1.6–2.3) (8). Even though evidence for the rise in prevalence of food allergy appears to preferentially affect industrialised nations, there is growing evidence of similar trends in rapidly developing countries such as Thailand (9) and China (10).

Peanut is not only a leading cause of food-induced anaphylaxis (11), but is also a major trigger for fatal food-related anaphylaxis. A systematic review and meta-analysis estimated the incidence of fatal peanut anaphylaxis to be between 0.73 and 4.25 per million person years (12).

Risk Factors

Eczema and egg allergy are 2 known independent risk factors for peanut sensitisation and/or subsequent allergy (13-15), although egg allergy may simply be a surrogate for food allergies, given the use of egg as a weaning food in many cultures. The dual-allergen-exposure hypothesis was first described a decade ago and is now widely accepted as explaining, as least in part, the link between infant eczema and risk of subsequent food allergy (16). According to this hypothesis, the transcutaneous exposure of peanut (present in the environment) is accentuated in eczema, while the lack of oral exposure promoting oral tolerance act together to increase the risk of food allergy. Indeed, high levels of household peanut consumption by family members of infants with eczema was found to be a risk factor for peanut allergy (17). Also supporting this hypothesis was evidence showing peanut sensitisation occurring in children through the application of peanut oil to inflamed skin (13). There is a molecular basis for the increased skin permeability in eczema: loss-of-function variants of the epidermal barrier protein, filaggrin, and missense mutations in the serine peptidase inhibitor Kazal type 5 (SPINK5) skin barrier gene are both predisposing factors for eczema (16, 18) and have been associated with an increased risk for food allergy (19, 20).

In a recent US observational study, key clinical factors associated with peanut allergy in a high risk infant cohort (defined as infants between 3 to 15 months having likely egg and/ or milk allergy, and/or moderate to severe eczema with a positive skin prick test (SPT) to egg/ milk) are younger age at initial presentation, lack of breastfeeding, and greater sensitisation to peanut-specific IgE and IgE to the peanut component Ara h 2 (21).

Natural History

Peanut allergy is persistent in around 80% of children (22-24), with low rates of spontaneous resolution from adolescence onwards. A decreasing SPT wheal size predicted tolerance, while an increasing wheal size predicted persistence (22-24). Spontaneous resolution of early-onset (younger than 18 months) peanut allergy mostly occurred by 6 years of age and occurs much less frequently after 10 years old (25).

What Can We Do about This Rising Trend?

Strategies to counteract the increase in prevalence of peanut allergy can be considered as a pyramid, beginning with primary prevention of those at risk of peanut allergy through earlier introduction of age-appropriate forms of peanut into the infant diet, to secondary prevention of peanut-sensitised children, improvements in the correct diagnosis of peanut allergy and finally the treatment of children with proven peanut allergy (Figure 1).

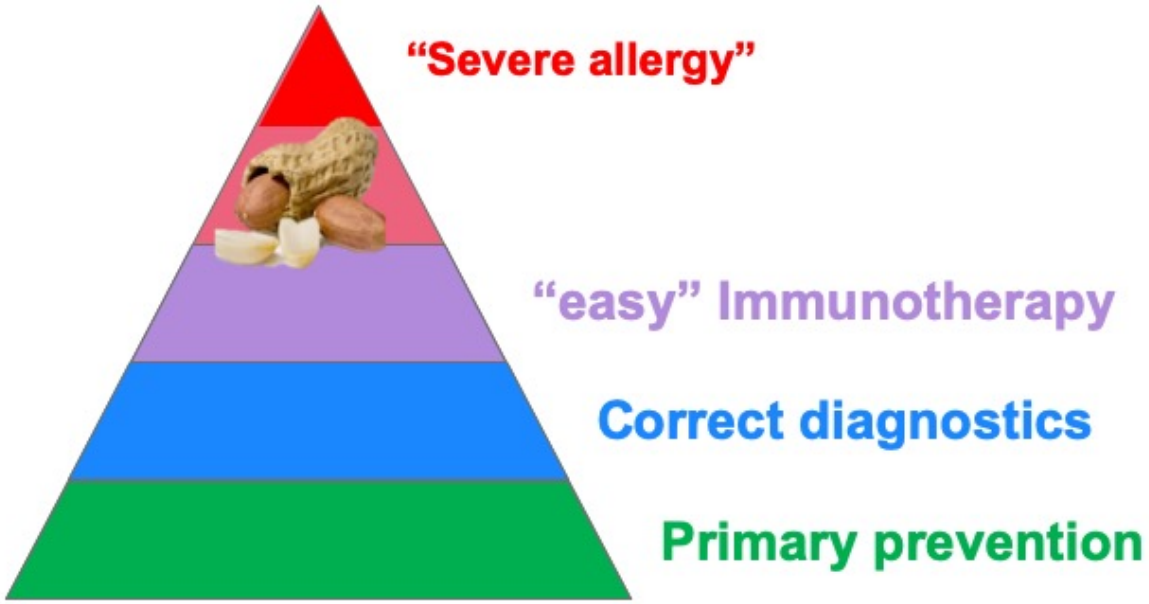

Figure 1. Strategies to counteract the rise in prevalence of peanut allergy. Primary prevention strategies can be applied at a population level to reduce the incidence of peanut allergy, while improved diagnostics can avoid false positive diagnostic tests which might also increase risk of peanut allergy when dietary avoidance is recommended in peanut-sensitised but tolerant children. For those with peanut allergy, immunotherapy can be instituted but there remains around 20-40% of individuals whom experience frequent adverse events with immunotherapy, many of whom will not tolerate the treatment.

Primary Prevention

Primary prevention targets children who are have yet to develop any manifestation of the disease – which, according to the World Health Organisation definition, would include sensitisation in the absence of clinical reactivity. The Learning Early About Peanut (LEAP) study (15) in the UK demonstrated for the first time that introduction of peanut into the infant diet prior to 12 months of age reduces the risk of developing peanut allergy, in contrast to peanut avoidance until age 5 years. The effect was more marked in children with existing egg allergy or significant eczema, with a relative risk reduction of 70% to 86% when compared to strict peanut avoidance until age 5 years. The benefit of earlier peanut introduction persisted when peanut intake was ceased for 12 months (26). However, the LEAP study excluded children with SPT wheals greater than 5mm at baseline. In addition, whether there is a "window of opportunity" by which peanut must be introduced is controversial. Of note, the intervention

did not prevent *all* peanut allergy: 1.9% of those with negative SPT and 10.6% of those with SPT of 1-4mm developed peanut allergy despite earlier introduction (15).

The Enquiring About Tolerance (EAT) Study evaluated whether a more pragmatic approach to early introduction of 6 allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat) in breast-fed infants without specific risk factors for food allergy would protect against the development of food allergy (27). Overall, the study did not find significant reduction in food allergy rates between the early and standard introduction groups by intention-to-treat analysis, however there was a significant reduction in risk by per-protocol analysis. A subsequent secondary analysis reported a significant reduction in food allergy in infants at higher risk of food allergy (for example, those with more severe eczema at enrolment, or with polysensitisation) (28). Many infants in the study struggled to adhere to the earlier introduction of allergens – particularly egg – and where introduction was successful, a lower risk of food allergy was identified, at least for peanut and egg. This highlights the challenges faced when counselling families about primary prevention – adequate intake of foods containing the allergen (which are currently undefined) may only be feasible and achievable by the most determined and motivated families.

Some guidelines advocate for screening of infants at higher risk of developing food allergy (29), however the benefits of this have not been proven (30). Lack of access to screening may result in a delay in introduction, which could increase the risk of the infant developing a food allergy. Screening is not generally offered in countries such as Israel, where peanut is introduced in infancy, and to date, this has not caused major public health concerns. However, some infants will already be allergic to some of these foods when introduced into the diet (Figure 2). Infants with moderate-severe eczema and/or eczema which began in the first 3 months of life seem to be at greatest risk of reacting to egg and peanut when these are introduced into the diet – but where tolerated, these infants will benefit most from earlier introduction.

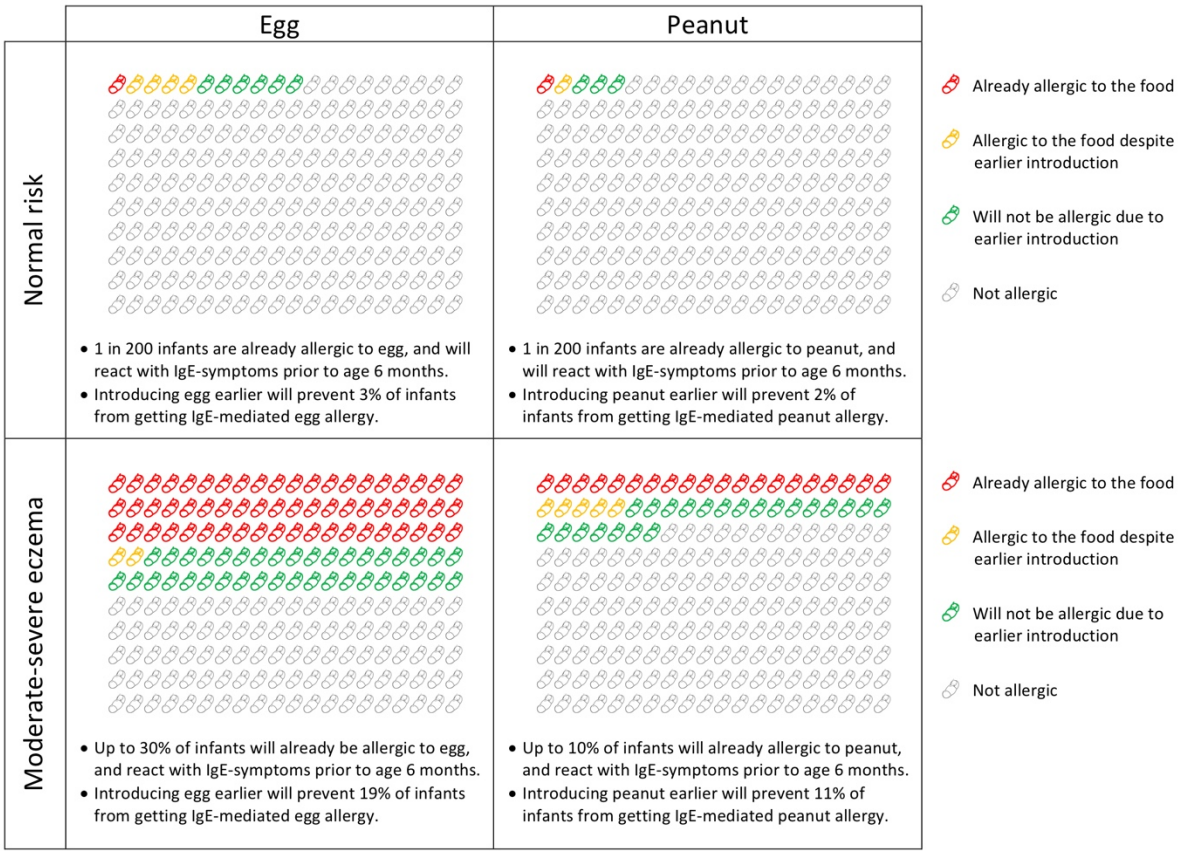

Figure 2. Impact of earlier introduction of egg and peanut into the infant diet before 12 months of age. A proportion of infants (shown in red) will already be allergic to the food when introduced, but to date, no life-threatening reactions have been reported in this context. Those infants shown in green represent those children who will avoid developing food allergy due to earlier introduction. Data from J Allergy Clin Immunol Pract. 2018;6:367-75. doi: 10.1016/j.jaip.2017.12.015. Image reproduced with permission from British Society for Allergy and Clinical Immunology (BSACI).

Improving Diagnostics

The diagnosis of peanut allergy is best made on the basis of a typical history of IgE-mediated reaction i.e. cutaneous hives, angioedema, gastrointestinal symptoms such as abdominal pain and vomiting, or anaphylaxis involving the cardiorespiratory system. However, diagnosis is often based on the presence of IgE-sensitisation without clinical history – particularly in the current context of 'screening' for potential peanut allergy in very young children. Unfortunately, IgE-testing – both skin prick testing and serum-specific IgE in the blood, are associated with a high false positive rate of up to 50%, particularly in infants (8). This highlights the need to distinguish correctly between sensitisation – where an individual has peanut-specific IgE (either in the blood or attached to skin-resident mast cells) but does not react to oral exposure and clinical allergy.

The magnitude of skin prick test wheal size and/or food-specific IgE result does correlate with the *likelihood* of an allergic reaction, but not the *severity* of reaction (31). Clinically useful decision points which are often based on 95% Positive Prediction Values (PPV) have been reported for both tests. For example, a skin prick wheal size to peanut of ≥8mm has been found

in most studies to yield a PPV of ≥95% (i.e. there is at least 95% chance that a child with peanut wheal size of ≥8mm will react during a peanut food challenge) (32-35) and high specificity (36). However, these endpoints – particularly for peanut-specific IgE in blood – have not been defined for infants and very young children, despite their use being recommended in guidelines from USA (29). It is for this reason that the oral food challenge remains the gold standard for a food allergy diagnosis, to avoid unnecessary dietary limitations.

Components Specific IgE Testing

IgE testing to individual components of the peanut protein, rather than then whole protein, has been shown to discriminate better between peanut sensitisation and peanut allergy. In particular, IgE against Ara h 2, a major seed storage protein that is resistant to both heat and digestion, has been shown to have better discrimination when compared to crude peanut-specific IgE (37-39). This is clinically useful, especially when the SPT and/or peanut-specific IgE fall within the equivocal range (≥3mm and/or ≥0.35kU/L, but lower than their respective cut-offs for 95% PPV) (40, 41). The diagnostic utility of other peanut components, in particular Ara h 1, 3, 6 have been less consistent than Ara h 2 (40-42). However, even when using component-resolved diagnostics, there will be 5% of cases where there is a degree of diagnostic uncertainty, and so the need to undertake food challenges to clarify the diagnosis. Furthermore, component testing for peanut allergy only confers a small diagnostic advantage over SPT (39). Despite many advances into the management of peanut allergy, diagnosis and the detection of resolution remains an imperfect science, and clinicians should have a low threshold for undertaking food challenges under safe and appropriate medical supervision to clarify diagnosis.

Active Management

Until recently, the mainstay of management was strict peanut avoidance and the provision of rescue medication for the treatment of accidental allergic reactions. However, even with appropriate dietary avoidance, accidental allergic reactions are common, with 1 in 8 peanut-allergic children experiencing an accidental reaction annually (43).

Food immunotherapy as a form of *active* management for patients with food allergies, has recently generated significant interest amongst all stakeholders. Although the first case of food allergy desensitisation was described in 1908 (44), it has taken over a century for this to evolve into large, multi-centre phase 3 trials. Whether immunotherapy for food allergy is ready for routine clinical practice is still a subject of ongoing heated debate (45, 46). A systematic review and meta-analysis demonstrated that allergen immunotherapy offers a substantial benefit (risk ratio (RR) = 0.16, 95%CI 0.10 to 0.26) in raising the threshold of reactivity to the specific food allergen while receiving immunotherapy – desensitisation (47). It is worth noting however that there was significant heterogeneity in the meta-analysis, across different populations, interventions and outcomes**.** Desensitisation outcomes, ranging from achieving a pre-specified clinical threshold or a certain-fold increase in individual threshold at exit food challenge, to a lack of symptoms to a daily maintenance dose, were all grouped together for this meta-analysis. A more recent meta-analysis specific to peanut oral immunotherapy (OIT) confirmed efficacy of desensitisation (RR in passing exit food challenge = 12·4, 95%CI 6·8 to 22·6) (48). However, the meta-analysis also highlighted the safety concerns: the risk of anaphylaxis in patients undergoing peanut OIT was 3-fold greater in those undergoing OIT, compared to peanut

avoidance (RR=3.12, 95%CI 1.76 to 5.55). This estimation of risk is likely to be an underestimate, given the heterogeneity of the reporting of adverse outcomes (46).

Though the risks involved in OIT is not unexpected, trading treatment-related allergic reactions at home or in hospital (arguably a more controlled setting) for unpredictable, accidental exposures in the community appears to be a risk many patients and their families are willing to take (47). This may well result from a 'resetting' of the expectation of a severe reaction that occurs during OIT: the experience of controlled reactions under medical supervision itself has a significant impact on health-related quality of life (HRQL) measures, and one group has reported that around one third of the overall improvement in HRQL with OIT is linked to the screening challenge that is usually undertaken prior to starting treatment (49). As yet, there is a paucity of efficacy and safety data relating to longer term follow-up, which needs to be urgently addressed.

Alternative to OIT exist. Epicutaneous immunotherapy (EPIT) to peanut is a novel method which involves transdermal administration of peanut allergen using a patch device with the objective to induce tolerance. The recently completed clinical trials for the peanut EPIT device has shown excellent safety profile with low withdrawal rates, albeit only a modest increase in cumulative reactive dose after 12 months of treatment (50). Longer treatment durations may have greater efficacy, but this needs to be confirmed.

Sublingual immunotherapy (SLIT) is a well-studied method of immunotherapy in individuals with allergic rhinitis. There are far fewer trials of SLIT to peanut (51-53), with only one head-to-head comparison of SLIT to OIT (54). Given the log-fold lower treatment dose in SLIT compared to OIT, it is not surprising to find that SLIT is able to induce modest levels of desensitisation (SLIT patients reaching lower eliciting dose thresholds than OIT), but with an excellent safety profile – adverse events mainly involving oropharyngeal symptoms usually not requiring treatment, with rare systemic symptoms or need for adrenaline (55). Longer durations of treatment appear to be associated with a greater treatment effect (52).

Irrespective of route of administration, the desensitisation is, in most cases, temporary. The majority of the published data relates to OIT: when peanut-OIT is stopped for 4–6 weeks, over half of patients lose their levels of desensitisation (46) i.e. patients do not demonstrate tolerance (prolonged immune unresponsiveness that persists after withdrawal of the allergen). This loss of desensitisation appears to increase where avoidance occurs for a longer duration post treatment (56). Given the lack of data in this area, the term sustained unresponsiveness has been introduced as an outcome in immunotherapy trials to describe the state of unresponsiveness after a period of allergen avoidance following food immunotherapy. Sustained unresponsiveness is more likely in patients with initial lower levels of sensitisation (56), but baseline markers of sensitisation do not currently predict sustained unresponsiveness in a clinically-predictive manner. Longer term efficacy is clearly important to patients; the lack of data to inform longer-term efficacy (beyond 1 year of treatment) and safety is a major gap in evaluating OIT for clinical practice.

Eosinophilic oesophagitis (EoE) is a chronic, immune-mediated disease characterized by eosinophil infiltration of the oesophagus. Symptoms of EoE include abdominal pain, vomiting, reflux, anorexia, dysphagia, food impaction and chest pain. There is evidence suggesting an increased risk of EoE in patients undergoing OIT/ SLIT (57). As most trials do not routinely use endoscopy to confirm the diagnosis of EoE in suspected cases, estimates for the rate of EoE in patients undergoing OIT range from 5.1% based on biopsy-proven cases to as high as 34% based on symptoms only (58).

The role of adjuvants with food immunotherapy has been studied in several small trials, with the hope of improving on the two current major drawbacks of conventional immunotherapy – high rates of adverse events and poor efficacy in sustained unresponsiveness. Adjuvants such as anti–immunoglobulin E monoclonal antibody (omalizumab) and probiotics have shown some promise in mitigating the above two issues respectively (59). Omalizumab used as an adjunct to OIT seems to be effective in reducing reactions during OIT dose escalation but reactions may resume once omalizumab is discontinued. Omalizumab added to OIT has not been found to increase the likelihood of OIT-induced desensitisation or sustained unresponsiveness (59). One study evaluated peanut OIT with co-administration of a probiotic (Lactobacillus rhamnosus); the authors report high rates of desensitisation (90%) and notably high rates of sustained unresponsiveness (82.1%), however the latter was assessed at varying timepoints, from as little as just 2 weeks off OIT (60). This, combined with a lack of a intervention arm in which participants received OIT without the probiotic unfortunately limit comparisons to conventional peanut OIT, and the interpretation of study efficacy and longer-term outcome data which have been published (60, 61).

Finally, at the top of the pyramid are those with "severe peanut allergy" – patients with a history of severe or refractory anaphylaxis to peanut (and whom are considered at too high risk for conventional OIT), or those who have failed peanut OIT due to the frequency or severity of adverse reactions. In general, about 20% of patients undergoing OIT fall into this category (62). It is possible that SLIT or EPIT may be a more pragmatic option for these patients, perhaps allowing them to then undergo OIT at a later stage, but this group of patients have to date been excluded from clinical trials (62). There remains a need to provide better education for both patients/their families but also the food industry, to improve the awareness of food allergies, and the optimal recognition and management of reactions.

In the meantime, clear and transparent information about the risks and benefits of allergen immunotherapy must be communicated to patients and caregivers; we would contend that allergen immunotherapy should only be carried out in centres with experience in managing anaphylaxis and undertaking desensitisation.

Future Directions

With the widespread change in allergy prevention guidelines across the world following findings from the LEAP study (15), the paradigm in managing peanut allergy has changed. Pragmatic clinical studies are needed to explore the longer-term feasibility and cost-effectiveness of primary prevention in both high risk infants and the wider population. For those with peanut allergy, more data are needed to improve safety and longer-term outcomes (such as sustained unresponsiveness), before allergen immunotherapy can be considered the standard of care for peanut-allergic children.

Conclusion

The management of peanut allergy in children is gradually shifting from one of passive allergen avoidance and treatment of reactions to one of prevention, active desensitisation and tolerance induction. With this shift, the diagnosis of peanut allergy should no longer be seen as a life sentence. More data is needed to improve the new treatment strategies available, so that we are able to offer personalised immunotherapy to optimise safety and longer term efficacy.

Conflict of interest: The authors declare that they have no relevant conflicts of interest.

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