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REVIEW

How do we know when peanut and tree nut allergy have resolved, and how do we keep it resolved?

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Summary

Over the last two decades, the prevalence of peanut and tree nut allergy has increased throughout the western world. Adverse reactions to these foods account for over 50% of all deaths resulting from food-related anaphylaxis. Until recently, evidence suggested that all peanut and tree nut allergy were permanent. It is now known that about 20% and 10%, respectively, of young patients outgrow peanut and tree nut allergies. Achieving tolerance is associated with increasing circulating T regulatory cells and reduced production of allergen-specific IgE. Reliable predictors of resolution are not yet available. A direct correlation between skin test weal size and allergen-specific IgE, at the time of diagnosis and likelihood of resolution, has been reported. Resolution of peanut or tree nut allergy cannot be determined conclusively by either allergen-specific IgE analysis or by skin prick testing. Oral food challenge is the gold standard for determining resolution of food allergy. Food challenges should only be undertaken in a clinical setting fully equipped to deal with a potential severe adverse reaction. Approximately 8% of patients who outgrow peanut allergy may suffer a recurrence, but recurrent tree nut allergy has not been reported to date. Infrequent ingestion of peanut may be related to the re-emergence of allergy. Induction of tolerance through oral immunotherapy or sublingual immunotherapy is now being actively studied, but remains experimental. Studies have reported short-term desensitization to peanut, but ongoing follow-up will determine whether tolerance is achieved long term.

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Introduction

Peanut and tree nut allergies are an increasing problem in the developed world. Their association with anaphylaxis and anaphylaxis-associated death ensures that they impact heavily on the quality of life of patients and their caregivers [1, 2]. In the past, it was believed that peanut and tree nut allergies were lifetime afflictions. However, it has been demonstrated that peanut and tree nut allergies can resolve, although less commonly compared with other food allergies. This article reviews the diagnosis of peanut and tree nut allergies and their resolution, our understanding of how tolerance develops, and how we are learning to manipulate this phenomenon.

Diagnosis of peanut and tree nut allergy

In light of its significance, it is critical that a diagnosis of peanut and tree nut allergy is correct. The presenting history must always be the starting point in determining whether a particular adverse reaction was related to peanut or tree nut ingestion. Key aspects of the history that point to a reaction being IgE mediated include the time interval between exposure and onset of symptoms, clinical manifestations of a reaction, duration of symptoms, response to emergency treatment, and consistency with which a reaction occurs on exposure to the food in question [3]. There are cases in which a clinical history is clear-cut. In these cases, the role of subsequent testing is primarily to create a quantitative baseline that can be used in ongoing surveillance of the patient's allergy. However, when the history is less clear, testing can serve as an indicator of a possible underlying allergy. The choices offered to the clinician are skin prick testing (SPT) with peanut and tree nut extracts (commercially available or made fresh from peanuts/peanut butter or individual tree nuts) or measurement of peanut-specific IgE (PN-IgE) or tree nut-specific IgE (TN-IgE), or both. The original serum

detection test for specific IgE, the RAST test, has been superseded by newer *in vitro* methods to measure allergen-specific IgE. The ImmunoCAP (Phadia, Uppsala, Sweden), Immulite, and Turbo RAST are all the systems available in the United States to measure IgE antibodies to specific allergens in human serum or plasma. The three techniques have been compared recently, and there are differences in each assay. All are reproducible, but the allergen-specific IgE values in each are not equivalent [4, 5]. The most widely used IgE test, and the one referred to in the following studies, is the ImmunoCAP IgE test.

Interpretation of test results for the diagnosis of peanut and tree nut allergy

As with any laboratory tests, SPTs and PN-IgE and TN-IgE levels have their limitations, and their correct interpretation is essential. It must be remembered that the presence of a positive SPT or allergen-specific IgE does not indicate that one will always have an allergic reaction when eating the food [6, 7], especially in children with atopic dermatitis [6]. If a clinician is faced with a positive SPT, PN-IgE, or TN-IgE without a clear history of reaction after peanut or tree nut ingestion, then it has to be determined whether a future adverse reaction is likely.

The diagnostic value of peanut SPTs has been explored. Sporik and colleagues performed SPT and oral food challenges (OFCs) to peanut on 92 children, 20% of whom were <2 years of age. Among this cohort, an SPT weal diameter ≥ 8 mm in children older than 2 years of age and ≥ 4 mm in children younger than 2 years of age had a positive predictive value (PPV) of 100%. These data emphasize the importance of age when considering the predictive value of tests [7]. Wainstein et al. [8] performed a similar study and showed that no child with an SPT weal diameter of ≥ 15 mm had a negative food challenge. Thus, the PPV was 100% at 15 mm. The PPV of a weal at >8 mm was 78% in this study.

This difference in reported PPVs of similar weal sizes demonstrates an important limitation of predictive values: PPVs vary according to the prevalence of a condition in the population and may be lower in the general population due to the lower prevalence of food allergy [9]. Both Sporik and Wainstein recruited their cohorts from tertiary referral centres. Lack and colleagues performed a study that collected SPT data from both a tertiary centre and a community birth cohort. They also reported that a weal diameter of >8 mm resulted in a 95% PPV of adverse reaction to peanut. Likelihood ratios are a way of circumventing the issue of variable prevalence. They are independent of prevalence and are, in this case, defined as the likelihood of a particular weal size in patients with positive challenges vs. the likelihood of that weal size in subjects with a negative challenge. A value >10 suggests a clinically useful test (for a more detailed explanation of this topic, please refer to Du Toit et al. [9]).

The value of PN-IgE as a method for predicting a reaction to peanut ingestion has also been carefully investigated. Sampson et al. [10, 11] created probability curves showing that PN-IgE values of >14 kilounits of antibody per litre (kU/L) and 6 kU/L carry a $>95\%$ or 90% probability, respectively, of a clinical reaction to peanut if ingested. However, negative predictive values are poor. Thus, patients with serum PN-IgE levels of <6 kU/L may still have adverse reactions to peanut upon ingestion. Once again, absolute values may not be transferable between patient populations due to variable prevalences of disease within these populations.

The combination of SPT and PN-IgE values may also increase the PPV of a given result. Wainstein et al. [8] found that combining an SPT of ≥ 8 mm and a PN-IgE ≥ 0.37 kU/L increased the PPV from 78% of an SPT value alone to 83%. Nolan et al. [12] showed that a weal diameter of ≥ 7 mm, together with a PN-IgE of <10 kU/L, predicted a positive challenge in patients with a PPV of 93%.

With respect to tree nuts, Ho and colleagues performed an analysis of 906 patients who underwent SPTs and OFCs to tree nuts including almond, Brazil nut, cashew, hazelnut, pecan, pistachio, and walnut. The SPTs were analysed against formal food challenges performed within 3 months of the skin testing. The investigators identified 8 mm as the SPT weal diameter that predicted a positive OFC with $\geq 95\%$ accuracy for cashew, hazelnut, and walnut. At the same time, no 95% PPVs could be determined for almond, Brazil nut, pistachio, or pecan [13]. Clark and Ewan [14] performed an observational study of 1000 children and adults allergic to at least one nut (Brazil nut, almond, hazelnut, or walnut). They found that only 3% of subjects tolerating any nut had an SPT weal diameter ≥ 8 mm (≥ 9 mm for Brazil nut).

Less is known regarding the correlation between specific TN-IgE values and the likelihood of reaction. Clark and Ewan [14] found that only 5% of adults and children who tolerated any tree nut had TN-IgE values >15 kU/L. Maloney et al. [11] recently published a walnut-specific IgE >18.5 kU/L with a 95% predicted probability of reaction. They also designed probability curves for almond and pistachio, but state that further validation was needed.

Although peanuts and tree nuts belong to different botanical families, peanut-allergic patients have a significantly high degree of co-allergy to tree nuts with a reported incidence between 23% and 68% [15–19]. It has been demonstrated through *in vitro* assays that PN-IgE antibodies that cross-react with tree nut allergens can cause effector cell activation [19, 20].

Collectively, all of these studies demonstrate that the chance of an adverse reaction to peanuts and tree nuts

increases as the SPT weal size and/or PN-IgE or TN-IgE level increases. Ultimately, but the gold standard for the diagnosis of food allergy is the double-blind, placebo-controlled, food challenge (DBPCFC). In clinical practice, however, an open or single-blind OFC is often all that is necessary. With regard to peanut, 14 kU/L is often referred to as a decision point, a value at which a decision is made that a food challenge to peanut is not appropriate as the chance of adverse reaction is extremely high [21]. As stated above, such decision points are not yet available for tree nuts, with the exception of walnut (>18.5 kU/L).

Commonly, physicians find themselves in a situation when the test results give a less clear answer. They must then weigh all the evidence available to them and decide whether it is more appropriate to advise avoidance or recommend a food challenge. In general, confirmation of peanut and tree nut allergy by OFC is not the norm.

Peanut allergy resolution

A decade ago, it was generally accepted that peanut allergy was life long. Between 1973 and 1985, Bock and Atkins confirmed peanut allergy in 48 children by DBPCFC. Two to 14 years after their original assessment, they succeeded in re-contacting 32 members of the cohort. Half reported reacting adversely to peanut within the year before re-evaluation. All subjects tested continued to have a positive SPT to peanut extract, and all subjects declined a repeat peanut challenge. It was concluded that none of the patients had resolution of their peanut allergy. However, the need for future studies with follow-up food challenges was emphasized [22].

Subsequently, Hourihane and colleagues challenged 120 of a total of 230 children referred to a regional paediatric allergy unit with a previous history of adverse reaction to peanut ingestion. The decision to challenge was based on a clinical need in each case. The patient's last reaction to peanut ranged from 15 to 72 months before their OFC. Those with a previous history of anaphylaxis were not challenged. Twenty-two (18%) passed an open OFC to peanut [23]. Five of the 13 patients who had an SPT at the time of challenge had a positive skin test, showing the importance of food challenge in determining resolution. This was the first study showing evidence that resolution of peanut allergy was possible, although the numbers may be exaggerated, as allergy to peanut was not confirmed by OFC at the time of diagnosis.

Vander Leek and colleagues enroled 83 children diagnosed with peanut allergy before their fourth birthday. The purpose of the study was to evaluate them yearly to track adverse peanut reactions. Four children had negative DBPCFC responses to peanuts during follow-up [24]. However, the original diagnosis of peanut allergy in all four children was based on clinical history without confirmation by OFC.

Rangaraj and colleagues designed a study to evaluate peanut allergy resolution in a general paediatric setting. Children aged between 4 and 16 years with a history of peanut allergy, no history of an adverse reaction to peanut in the previous 2 years, a PN-IgE of <17.5 kU/L, and a SPT weal diameter <8 mm underwent DBPCFCs to peanut. Of a total of 54 children, only eight children were eligible for food challenge, and four challenges were negative. Thus, 15% of the children achieved resolution of their peanut allergy [25].

Skolnick and colleagues enrolled patients aged 4–20 years with a diagnosis of peanut allergy determined retrospectively by reviewing records of adverse reactions, skin testing, and *in vitro* IgE antibody testing. Only two patients were diagnosed by OFC. All recruits were evaluated by a questionnaire, skin testing, and *in vitro* IgE antibody testing. Those who had had no adverse reactions in the previous 12 months and had a PN-IgE level <20 kU/L were offered an OFC to peanut. Eighty-five of the 223 patients underwent DBPCFC to peanut. Forty-eight passed their challenge. Thus, in this study, peanut allergy resolved in approximately 21.5% of patients [18]. As a follow-up to the Skolnick study, Fleischer and colleagues reported on a group of 80 patients between the ages of 4 and 10.9 years who were challenged to peanut on the basis of a PN-IgE of <5 kU/L. Peanut allergy was also determined retrospectively by reviewing records of adverse reactions, skin testing, and *in vitro* IgE antibody testing. Forty-four (55%) of these passed an OFC [26]. Collectively, these studies, despite limitations in original diagnosis, consistently show that a proportion of children achieve resolution of their peanut allergy.

Predictors of peanut allergy resolution

In light of the burden on quality of life associated with peanut allergy [1], reliable predictors of those likely to achieve resolution would be beneficial to clinicians and families. Skolnick's study showed that the PN-IgE level at diagnosis was significant in predicting later tolerance. Only two of 54 (4%) patients with an initial PN-IgE level >10 kU/L outgrew their peanut allergy. However, this study was a retrospective cohort study, and initial PN-IgE levels were only available in 16 of the 48 patients who passed the challenge and in 14 of 37 patients who failed the challenge [18]. In contrast, the study by Fleischer and colleagues did not demonstrate a significant association between the PN-IgE at the time of diagnosis and peanut allergy resolution. In fact, peanut allergy resolution was achieved in two patients with an initial PN-IgE of greater than 70kU/L, as demonstrated by oral challenge [26]. Skolnick and colleagues also found that patients in whom peanut allergy resolved had a lower rate of eczema than those who failed ($P=0.04$), and were significantly more likely to have had only cutaneous reactions as part of their

original presentation. Also, children whose initial reactions involved three organ systems were significantly more likely to have ongoing peanut allergy. Furthermore, they also did not find that the severity of the initial reaction was predictive of allergy resolution [18].

In order to define predictors of resolution more accurately, Ho and colleagues performed a prospective cohort study, recruiting children <2 years old with peanut allergy and following them longitudinally from 1995 through 2000. Food challenges were performed when SPT weal diameters measured ≤ 4 mm for children younger than 2 years old and ≤ 8 mm for older children. Consistent with previous studies, resolution of peanut allergy occurred in 21.4% of study participants. An SPT weal diameter to peanut of >6 mm or PN-IgE level of >3 kU/L before 2 years of age reduced the probability of developing peanut tolerance by half. An increase in weal diameter by 3 mm or greater between ages 1 and 4 years was strongly predictive of failure to develop tolerance, whereas decreasing levels were a good prognostic sign. Factors not related to prognosis included age at diagnosis, mode of presentation, severity of index reaction, total IgE levels, other atopic illnesses or food allergy, or early inhalation allergen sensitization [27]. One potential weakness was that the original diagnosis was based on SPT alone and not OFC. It is possible that some individuals may have merely been sensitized and never actually allergic to peanut.

Tree nut allergy resolution

Tree nut allergy had also long been considered as a lifelong condition. Fleischer and colleagues challenged 39 children out of a total of 278 with a previous history of tree nut allergy. One hundred and one children had clinical reactivity to at least one tree nut based on a history of reaction after exposure to a tree nut and evidence of TN-IgE by SPT or serum IgE testing. Fifty of the 101 patients met established challenge criteria, but only 20 were challenged; the remaining 30 patients declined to undergo food challenge. Of the 20 challenged, nine passed (45%); therefore, the authors concluded that 8.9% acquired oral tolerance (95% CI, 4–16%; nine out of 101 with a history of prior tree nut clinical reactivity). Four of the nine patients who outgrew tree nut allergy were allergic to cashew, three to pecan, and two to walnut. Nineteen other patients who were challenged had never eaten a tree nut, but were given a diagnosis of tree nut allergy solely on the basis of detection of TN-IgE. Fourteen (74%) of them passed, and five failed, showing that even patients who have never ingested tree nuts, but who have evidence of TN-IgE must undergo OFCs to prove or refute true tree nut allergy before allowing the introduction of tree nuts into the diet. The authors concluded that their estimate of 9% could have been an underestimate of the true resolution rate of tree nut allergy. They discussed that if the additional 30 patients with a history of clinical reactivity were challenged, and assuming that those 30 patients had the same passing rate as the 20 who actually underwent the challenge (45%), the resolution rate would then have increased to 21.8% (95% CI, 14–31%). Furthermore, if the analysis was not restricted to only patients with a prior history of reacting to a tree nut, so that all 278 patients were included in the analysis, then at least 23 of the 278 patients (8.3%; 95% CI, 5–12%) outgrew tree nut allergy [17]. However, the most conservative estimate of the three is approximately 9%, as this was the one calculated with the number of patients who passed challenges using only the subgroup of patients who had both prior clinical reactivity and evidence of TN-IgE.

Predictors of tree nut allergy resolution

Fleischer and colleagues showed that the severity of initial reactions to tree nuts was not predictive of resolution of allergy. There was a significantly lower rate of atopic dermatitis in the population that passed challenges to tree nuts than in those with an ongoing tree nut allergy ($P=0.009$). There was no significant difference in rates of other allergic diseases including asthma and allergic rhinitis. Patients who passed tree nut challenges were significantly less likely to have other current food allergies than those who failed challenges ($P=0.03$) and those with ongoing tree nut allergy ($P<0.0001$). It is important to note that none of the patients whose tree nut allergy resolved had a history of reacting to more than two different tree nuts, and hence patients who are allergic to multiple tree nuts may be less likely to outgrow tree nut allergy. Patients who had outgrown peanut allergy were also significantly more likely to outgrow tree nut allergy, compared with patients who had ongoing peanut and tree nut allergies ($P<0.0001$) [17]. This latter finding, while interesting, however, needs further investigation as it may have been affected by bias, including parents being more willing to consent to tree nut OFCs if their children had outgrown peanut allergy.

Mechanisms of resolution

The immunological mechanisms resulting in the resolution of food allergy, either naturally or after immunotherapy, are not well understood. It is hypothesized that food allergy results from a failure to develop oral tolerance to specific food antigens [28], and that resolution of food allergy is a result of achieving that tolerance. Oral tolerance refers to a state of active inhibition of immune responses to an antigen by means of prior exposure to that antigen through the oral route. It is estimated that $<0.01\%$ of the antigenic material that enters the intestinal tract gains access to the circulation [29]. The intestinal barrier consists of a single layer of cells (enterocytes) and

is selectively permeable via surface transporters that only allow non-antigenic amino acids and peptides across the cell membrane after degradation by enzymes that are anchored in the enterocyte microvillus [29]. Any food protein that avoids digestion is taken up by the intestinal epithelium and degraded in lysosomes [30]. It is suggested that presentation of this material in the presence of MHC II by intestinal epithelium acting as non-professional antigen-presenting cells may induce tolerance [31]. Mouse models of food allergy have shown that animals sensitized to a particular antigen have an increased uptake of this antigen across the epithelium [32]. The low-affinity IgE receptor, FcεRII/CD23, which is up-regulated by IL-4, is believed to be important in this process [29].

Movement of antigenic material between enterocytes is prevented by intercellular molecules including desmosomes, adherence junctions, and tight junctions. Th2 mouse models have been shown to have disruption of these junctions allowing increased permeability [33]. Beneath the epithelial layer, there are abundant immunological cells through which food antigens can generate responses. Specialized M cells transport protein antigens to areas of lymphoid tissue called Peyers Patches, which are rich in dendritic cells that in turn present food antigens to resident B and T cells [34]. Murine studies have shown that oral tolerance can be achieved by two mechanisms: (1) active suppression by T regulatory cells or (2) T cell anergy or deletion. Antigen dose determines which form of tolerance occurs; low doses of antigen favour tolerance driven by T regulatory cells, and high doses favour anergy-driven tolerance [35]. Children who outgrow food allergy have been shown to have higher numbers of circulating T regulatory cells than those who do not [36, 37]. It is also hypothesized that achieving tolerance results in a shift from a Th2 lymphocyte phenotype to a Th1 profile with reduced IgE production. This shift may also repair intestinal barrier permeability. Children who achieve natural tolerance through elimination show a decrease of allergen-specific IgE, and a similar response is seen in children successfully treated by OIT [38–40]. Jones et al. [37] saw an increase over time in IFN-γ-producing T cells in their patients receiving peanut OIT.

Confirming resolution

It is essential to confirm that peanut and tree nut allergy resolution have occurred before advising patients that they no longer need to practice complete avoidance. A recent history of incidental ingestion without adverse reaction is helpful, but should never be considered a demonstration of tolerance. The threshold for a reaction can vary considerably between patients and at different times for the same patient [41, 42]. The only way to truly declare a patient tolerant is by having them complete an OFC. This challenge may be open, single, or double-blinded depending on the particular situation. Fleischer and colleagues advise that OFCs should be reserved for children older than 4 years of age. Older children are more inclined to inform parents and physicians of subtle symptoms of an adverse reaction, allowing a challenge to be terminated before large volumes of peanut or tree nut have been ingested. In some situations, a repeat challenge may be indicated for patients who have failed an OFC previously. Fleischer et al. [26] reported four patients who originally failed a peanut OFC but later passed a challenge 1–2 years later. Similarly, in their tree nut study, two patients who passed an OFC had failed a tree nut challenge previously [17]. It is also important to remember that tolerance to peanut does not imply that patients have achieved tolerance to tree nuts. Equally important is the fact that tolerance to one tree nut does not mean that one is tolerant to all tree nuts, even tree nuts that cross-react with each other, such as cashew and pistachio, and walnut and pecan [11]. Therefore, each tree nut should be challenged separately.

Before a decision is made to challenge, it is recommended that SPTs and PN-IgE or TN-IgE levels be performed. However, both tests have limitations in terms of predicting which patients are likely to pass a challenge. There are no absolute cut-off points below which a challenge can be performed without risk. In the Skolnick study [18], patients with a PN-IgE of $\leq$ 20 kU/L were offered a challenge to peanut. Thirty-two percent (41 out of 126) of patients eligible for challenge declined. Among the 85 patients challenged to peanut, the range of PN-IgE levels was comparable between those who did and did not pass the challenge, $<$0.35–20.4 and $<$0.35–18.2 kU/L, respectively. Sixty-seven percent of patients with PN-IgE levels $<$2 kU/L and 61% with levels $<$5 kU/L had negative challenge results.

Similarly, Fleischer and colleagues found that 55% of patients with PN-IgE levels of $\leq$ 5 kU/L and 63% with PN-IgE levels of $\leq$ 2 kU/L passed challenges. Looking at this in reverse, 45% of patients with PN-IgE levels of $\leq$ 5 kU/L or less and 37% with PN-IgE levels of $\leq$ 2 kU/L failed a challenge to peanut [26]. Evidence of patients' PN-IgE levels trending down over time is also an important marker of potential resolution of peanut allergy [27]. It is recommended that measurement of PN-IgE levels be repeated on a yearly or 2-year basis to monitor for tolerance.

In the Fleischer and colleagues' tree nut study, only patients with TN-IgE levels of $\leq$ 10 kU/L were challenged. Fifty-eight percent of patients with TN-IgE levels of $\leq$ 5 kU/L, 63% with TN-IgE levels of $\leq$ 2 kU/L, and 75% with undetectable TN-IgE levels passed challenges [17]. Positive skin tests can persist in patients who have achieved tolerance, and thus can be difficult to interpret. Skolnick and colleagues reported in their study that skin tests were performed in 23 of 48 patients who passed the

challenge and in 21 of 37 patients who failed. Skin tests were positive in 15 of 23 (63%) patients who passed the challenge, and in 19 of 21 (90%) who failed the challenge [18]. It is thus important to consider both the PN-IgE and the SPT together before concluding that an OFC is appropriate. For example, if in a 7-year-old child the peanut SPT produces a weal diameter of 5×5 mm, but the PN-IgE has trended down over several years and is ≤ 0.35 kU/L, then an OFC would more likely be performed if both parameters were considered together rather than just considering the skin test alone.

In summary, it is recommended that physicians always err on the side of caution and only challenge those who have the smallest signal by SPT and IgE, taking into consideration the age of the child as well. All challenges should occur in an appropriate setting and according to practice guidelines [43, 44].

Maintaining resolution (tolerance)

There is evidence that people who have outgrown peanut allergy may be at the risk of resensitization. In 2002, Busse and colleagues reported the cases of three children, all of whom were previously peanut-allergic but developed tolerance to peanut as demonstrated by passing an OFC. However, within approximately a year of the challenge, they all developed adverse reactions to peanut. It was speculated by the authors that their resensitization was due to infrequent ingestion of peanut [45]. Further to this, Fleischer et al. [46] carried out a study to determine the rate of peanut allergy recurrence, identify risk factors for recurrent peanut allergy, and develop specific recommendations for the treatment of patients with resolved peanut allergy. After evaluation with questionnaires, SPTs, and PN-IgE levels, children underwent DBPCFC if appropriate. Three of 15 patients who consumed peanut infrequently or in limited amounts had recurrences compared with no recurrences in the 23 patients who ate peanut frequently ($P = 0.025$). The recurrence rate was 7.9% (95% CI, 1.7–21.4%) [46]. These data suggest that the resolution of peanut allergy is not permanent, and that the immune system needs ongoing exposure to maintain tolerance.

This phenomenon has not been described after naturally developing tolerance to milk or tree nuts, but there is a case report of a recurrence of egg allergy after natural desensitization [47]. Early studies into the induction of tolerance to egg and cow's milk through OIT concur that ongoing exposure is necessary to prevent the re-emergence of adverse reactions. Rolinck-Werninghaus and colleagues described three patients who achieved temporary tolerance to cow's milk or egg, respectively, through OIT, as determined by OFCs. OIT was then held for 2 months, and the patients were put on a strict diet. Further to this, they were re-challenged and reacted. Once back on OIT again, they re-acquired tolerance as confirmed by OFCs [48].

This apparent necessity for ongoing exposure appears to conflict with the development of tolerance in allergic patients, which occurs while they are still strictly avoiding the food allergen. This apparent conflict is borne out of our limited understanding of how tolerance to allergens evolves. Boyle and colleagues reported that ongoing exposure to peanut is not adequate to avoid the re-emergence of intolerance. They report the case of a 3-year-old girl who reportedly passed a peanut OFC and then ingested peanut daily for 23 days, at which time she developed generalized urticaria [49]. Her original challenge, however, was only to 1.2 g of peanut protein, which is less than the commonly recommended top dose of peanut given in an OFC to determine tolerance to peanut, as well as below the cumulative dose of peanut given in such an OFC. Thus, it is likely that her peanut allergy had never truly completely resolved.

Ongoing OIT studies will hopefully give us a clearer understanding of tolerance and how to best maintain it. Currently, we recommend that patients and parents be counselled regarding the risk of recurrent peanut allergy and the potential value of regular peanut ingestion, emphasizing that there is no study to date indicating exactly how often and how much peanut a patient needs to consume to maintain tolerance. We recommend that, after passing an OFC to peanut, patients ingest peanut in some concentrated form, i.e. peanut butter or peanut-containing candy, at least weekly. This advice is based on the evidence that those who ate peanut frequently (at least once a month) or regularly (once a week) were less likely to develop re-emergence of peanut allergy [21]. This advice is also consistent with the recommendations in subsequent publications [50, 51]. Furthermore, an OFC to peanut may not be recommended in the first place to confirm a patient's tolerance, given this risk of a possible allergic reaction in the future, if it is the doctor's impression, upon discussion with a patient and their family, that the patient is unlikely to eat significant quantities of peanut on a regular basis if the patient passes the OFC. In light of the apparent risk of recurrence and in line with previous publications, Fleischer et al. [46] also recommended that patients continue to carry a self-injectable epinephrine until they have demonstrated persistent tolerance for 1–2 years.

Patients may also develop allergies to tree nuts over time. Clark and Ewan [14] found that as age increased, greater proportions of children were multi-sensitized (positive SPT), with 19% at 2 years and 86% at 5–14 years, and multi-allergic (based on clinical reaction) with 2% at 2 years and 47% at 14 years. Burks et al. [52] also recently performed a retrospective chart review of 201 patients with peanut allergy and concluded that at the time of peanut allergy diagnosis, almost one-third of patients

were sensitized to one or more tree nuts and became sensitized to an increasing number of tree nuts over with advancing age.

Induction of tolerance

The concept of actively altering the natural history of food allergy by inducing tolerance to specific food allergens has recently gained momentum. Although subcutaneous immunotherapy is the mainstay of inducing tolerance to aeroallergen sensitivity, it has not been a viable option in the treatment of foods allergy because injections of peanut extract resulted in repeated systemic reactions [53]. Currently, both OIT and sublingual-immunotherapy (SLIT)-induced tolerance are being studied closely with potentially promising results. Both methods involve the administration of serially increasing doses of antigen under close supervision in medical facilities. Factors that have been shown in murine models to affect oral tolerance induction include the size of dose (high- and low-dose tolerance), the form of the allergen ingested, age, and genetics of the host [28]. To date, most published data are on achieving tolerance to milk and egg [38–40, 54, 55]. In all groups, study numbers have been small. There are concerns that immunotherapy may merely cause only desensitization (raising the threshold of food needed to cause an allergic reaction), but not induce full tolerance.

Data from tolerance induction therapy to treat tree nut allergy are limited at this time. Enrique and colleagues performed SLIT in 23 patients with hazelnut allergy; 11 received active hazelnut SLIT (one withdrew consent on the first day of treatment), and 11 placebo SLIT. After 3 months of maintenance SLIT, both groups underwent a DBPCFC to hazelnut. Fifty percent of patients who underwent active treatment reached the highest dose of hazelnut (20 g), but only 9% did so in the placebo group [56]. Unfortunately, in each arm of the study, only five of the subjects truly had food-induced, IgE-mediated symptoms due to hazelnut allergy, including urticaria, angioedema, or anaphylaxis, while the remaining six patients in each group only had pollen food allergy syndrome-induced symptoms due to birch pollen cross-reactivity with hazelnut. Of the five patients in the active treatment group who all had a history of anaphylaxis, only three responded to treatment, and only two of the three reached the maximum 20 g during the DBPCFC.

Studies on inducing tolerance to peanut are becoming available only now. Clark and colleagues have recently described four children with peanut allergy who underwent OIT. Peanut flour was administered in daily doses, increasing in 2 weekly dose increments from 5 to 800 mg. In post-treatment OFCs, each child tolerated at least 10 peanuts (>2 g) [57]. Currently, maintenance therapy is continuing. Jones and colleagues describe 29 children with peanut allergy treated by an OIT protocol that had three phases: initial day escalation, build-up, and maintenance. After being on maintenance dosing at home for a median of 4.7 months (range, 4–22 months), they underwent food challenge. Twenty-seven of 29 (93%) reached the total peanut dose of 3.9 g [37]. It is not known whether these patients will achieve long-term tolerance to peanut. Other studies with both OIT and SLIT are ongoing (Consortium of Food Allergy Research, https://web.emmes.com/study/cofar/).

OIT must be regarded as an investigational procedure at this time, with significant risk of adverse reactions. Hoffman and colleagues reviewed the safety of a peanut OIT protocol and showed that the time of greatest risk was during the initial escalation day. Ninety-three percent of the 28 patients experienced symptoms, with 71% requiring treatment. In contrast, the risk of symptoms during the build-up phase was 46%, with only 3.5% during the home dosing phase [58]. However, certain 'augmentation factors', including concurrent illness, inadequately controlled asthma, physical exertion, menses, and timing of food ingestion, have been shown to induce intolerance to doses tolerated previously [59]. Clearly, OIT is not yet applicable for adaptation into the clinic setting due to the risk of adverse symptoms, especially during initial escalation.

Conclusions

It is now established that peanut and tree nut allergies have the potential to resolve in approximately 20% and 10% of cases, respectively. Thus, OFCs should be considered in patients whose SPT and PN-IgE or TN-IgE levels indicate that adverse reaction is less likely. A clear-cut confirmation of tolerance by OFCs allows patients and their families to safely lift both the dietary and associated social restrictions that peanut and tree nut allergies impose. Recurrence of allergy to peanut is rare and may be due to irregular exposure to it after resolution; recurrent tree nut allergy to our knowledge has not been reported. Manipulation of the immune system to achieve tolerance in allergic individuals is a new, exciting direction that will in turn further enlighten us to the underlying mechanisms behind natural evolving tolerance.

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