Rostrum

Managing Nut Allergy: A Remaining Clinical Challenge

Philippe A. Eigenmann, MD[a], Gideon Lack, FRCPCH[b], Angel Mazon, MD[c], Antonio Nieto, MD[c], Diab Haddad, MRCPH[d], Helen A. Brough, FRCPCH[b], and Jean-Christoph Caubet, MD[a]   *Geneva, Switzerland; London and Chertsey, United Kingdom; and Valencia, Spain*

Peanut and tree nut allergies have become a public health problem over the last 2 decades. The diagnostic procedure relies on a suggestive history, as well as on evidence of sensitization (skin prick testing and/or specific IgE blood testing), followed in selected cases by a food challenge. Standard IgE tests may be positive to more than 1 nut, due to cross-reactivity (allergens common to several nuts) or cosensitivity (frequently associated positive test results without cross-reactivity). Thus, many patients with a peanut or a tree nut allergy avoid all nuts, relying on positive test results without clinical evidence of reactivity. In addition, coexisting pollen sensitivity may add to diagnostic uncertainty due to potential cross-reactivity between pollens and nuts. In this article, we discuss challenges in diagnosis and clinical management of peanut and tree nut allergy related to cross-reactivity and cosensitization, as well as the avoidance of nuts tested positive to reduce the risk of reactions by cross-contamination. Studies to provide more accurate characterization of genuine clinically relevant cross-reactivity or cosensitivity to multiple nuts are needed.   © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:296-300)

[a]Pediatric Allergy Unit, University Hospitals of Geneva and University of Geneva, Geneva, Switzerland

[b]King's College London, Medical Research Council and Asthma UK Centre in Allergic Mechanisms of Asthma, Division of Asthma, Allergy and Lung Biology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

[c]Children's Hospital La Fe, Pediatric Pulmonology and Allergy Unit, Instituto de Investigacion La Fe, Valencia, Spain

[d]St Peter's Hospital, Chertsey, United Kingdom

In the first half of the 20th century, milk, cereal grains, and hen's egg were reported as the most common food allergens.[1] Reactions to nuts were then mostly anecdotal, such as in the report from 1931 by Vaughan in which peanut allergy is reported as a cross-reacting legume eliciting urticaria in a young female patient.[2] Systemic allergic reactions to tree nuts (commonly included in the tree nut family are almond, Brazil nut, cashew nut, hazelnut, walnut, pecan, pistachio, and macadamia nut) but also mostly to peanut have been increasingly reported only in the last quarter of the 20th century, leading to the concept of the "peanut allergy epidemic."[3-5]

To a large part, peanut and tree nut allergy has gained public attention due to the severity of the reactions. These foods have been identified as the main culprits of fatal or near-fatal reactions in 2 successive reports published in the United States in the late 1980s and early 1990s.[6,7] Strikingly, most of these children had a reaction to more than 1 nut. This led to the general recommendation in peanut- or tree nut—allergic patients to avoid all types of nuts, often regardless of positive or negative test results. In addition, preventive avoidance of nuts never eaten was advised although clear scientific evidence was lacking.[8] Overall, safety has been advocated also to avoid reactions by cross-contaminating nuts. These recommendations have largely contributed to the number of children avoiding all nuts in the community. Evidence is lacking as to whether extended or targeted avoidance influences the quality of life of these patients or their risk of future reactions.

> *Abbreviations used*
> *BAT- basophil activation test*
> *OFC- oral food challenge*

In this rostrum, we discuss peanut and tree nut allergy, and identify knowledge gaps to be addressed in future research for improvement of diagnosis and management of nut-allergic patients.

PEANUT AND TREE NUT ALLERGIES ARE COMMON, BUT UNEVENLY GEOGRAPHICALLY DISTRIBUTED

The prevalence of food allergy largely varies between studies but can be estimated to affect up to 10% of the population.[9] Epidemiological data commonly show that peanut allergy is affecting up to 3% of the population, with the highest numbers found mostly in the United Kingdom, Australia, and North America. A North American random telephone survey conducted by Sicherer et al[5] reported among 188 households the most common nut allergies to be as follows: peanuts (53%), walnut (22%), cashew (16%), pecan (26%), almond (25%), pistachio and Brazil nut (10%), hazelnut and macadamia nut (9%), and pine nut (6%). Overall, the estimated prevalence of peanut and/or tree nut allergies was 1.4%.[5] In a Canadian random telephone survey, the estimated prevalence was similar, with 1.4% for tree nut allergy and 0.93% for peanut allergy.[10] In the United Kingdom, a birth cohort study from the Isle of Wight estimated the prevalence of peanut allergy at 1.3%.[3] In an Australian population-based study with challenge proven allergy, Osborne et al[11] found peanut sensitization in 8.9% and sesame in 2.5% of 12-month-old infants, and peanut and sesame allergy in 3.0% and 0.8%, respectively. Peanut was also clearly identified as the second most common food eliciting allergy (in 24%) after egg (in 25%) in South African children with atopic dermatitis.[12]

Large efforts to define the food allergy epidemiology in Europe have been recently undertaken by the EuroPrevall research consortium with cross-sectional population-based studies in children and adolescents, as well as in adults. First analysis showed that hazelnut was overall the most common sensitizing nut in the adult EuroPrevall cohort at 9.3% (lowest, Iceland 1.3%; highest, Switzerland 17.8%), followed by walnut at 3.0% (lowest, Iceland 0.1%; highest, Spain 7.7%) and peanut at 2.7% (lowest, Iceland 0.5%; highest, Spain 7.2%).[13] Although for many years peanut allergy was found mostly in North America, the United Kingdom, and Australia, EuroPrevall data have shown that peanut has now also become a prevalent cause of food sensitization in many European countries. A recent meta analysis showed that in Continental Europe, the most prevalent tree nut allergy was hazelnut, with large geographical variations (depending on the studies between 17% and 100% of all tree nut allergies).[14] Unlike Continental Europe, walnut and cashew allergies are most common in North America, whereas Brazil nut and walnut allergies are among the most frequent nut allergies in the United Kingdom.[15,16]

However, in most studies, the estimates of the prevalence of peanut and tree nut allergies have been based on sensitization, and/or a convincing history, and rarely on a standardized food challenge, explaining the large heterogeneity of epidemiological data.

We have seen that peanut allergy is unevenly distributed, and one of the possible explanations for the low prevalence of peanut allergy in some countries such as Israel may be early introduction of peanuts into the infants' diet.[17] Nevertheless, other regions of the world such as Siberia also have low rates of peanut and nut allergy (<1%), albeit in the absence of early peanut introduction.[18] These observations suggest that the timing of introduction of a food is important, but it is only one factor among many influencing the development of food allergy.

POSITIVE TEST RESULTS TO NUTS MAY NOT BE CLINICALLY RELEVANT

Thirty-five percent of patients allergic to peanuts or tree nuts may present with multiple nut allergy as suggested in 1998 by Sicherer et al.[19] This questionnaire survey followed by examination and serologic testing of the patients showed that 92% had positive specific IgE test results and 37% had a reaction to more than 1 nut. Similar numbers were seen in a case-control study from the United Kingdom, in which one-third of the patients had experienced allergy to more than 1 nut. Most common allergies were to peanut, followed by Brazil nut, almond, and hazelnut.[20] Clark and Ewan[21] also showed that the number of nuts a child ate increased with age (23% eating more than 1 nut at 2 years, 73% by 10 years), and they postulated that this was leading to higher rates of multisensitization (19% at 2 years, 86% at 5-14 years) and multiallergy (2% at 2 years to 47% at 14 years).[21] In a retrospective study by Brough et al,[22] more than half of children previously tested for nut allergy were found to develop new nut sensitization over a 2- to 4-year follow-up and more than one-third developed a new nut allergy.

Allergy to certain well-defined combinations of nuts may be due to the presence of similar or closely related epitopes. Such closely related epitopes are more common in phylogenetically closely related nuts. This has been observed for pistachio and cashew nuts (extensive cross-reactivity between rPis v 3 and rAna o 1)[23] and for pecan and walnuts (between rCar i 4 and rJug r 4).[24] Nuts sharing proteins from similar families, for example, storage proteins such as vicillins, are also highly cross-reactive.[25]

The cross-reactivity due to shared storage protein family such as the vicillins may explain why nonrelated nuts such as tree nuts and peanuts can serologically and clinically cross-react. This raises the question whether nut-allergic patients are at risk of allergic reactions to seeds such as sesame, or even to pine nuts, because these may contain storage proteins similar to those of nuts. A survey among members of the UK anaphylaxis campaign asked about coexisting allergy to sesame and peanut. Eighty-four percent of the responders reported sesame seed allergy as well as tree nut and/or peanut allergy.[26]

In most cases, standard diagnostic workup does not allow differentiation between clinical cross-reactivity and coallergy, versus serological cross-reactivity and cosensitization in a given patient (Figure 1).

POLLEN SENSITIVITY IS A COMMON CAUSE OF CROSS-REACTIVITY IN NUT ALLERGY

Patients allergic to birch pollen show a high rate of cross-reactivity mostly to hazelnuts, but also to various other nuts.[27] These patients suffer from oral allergy syndrome, characterized by symptoms predominantly localized in the oropharynx. Ability to distinguish between patients with oral allergy syndrome and
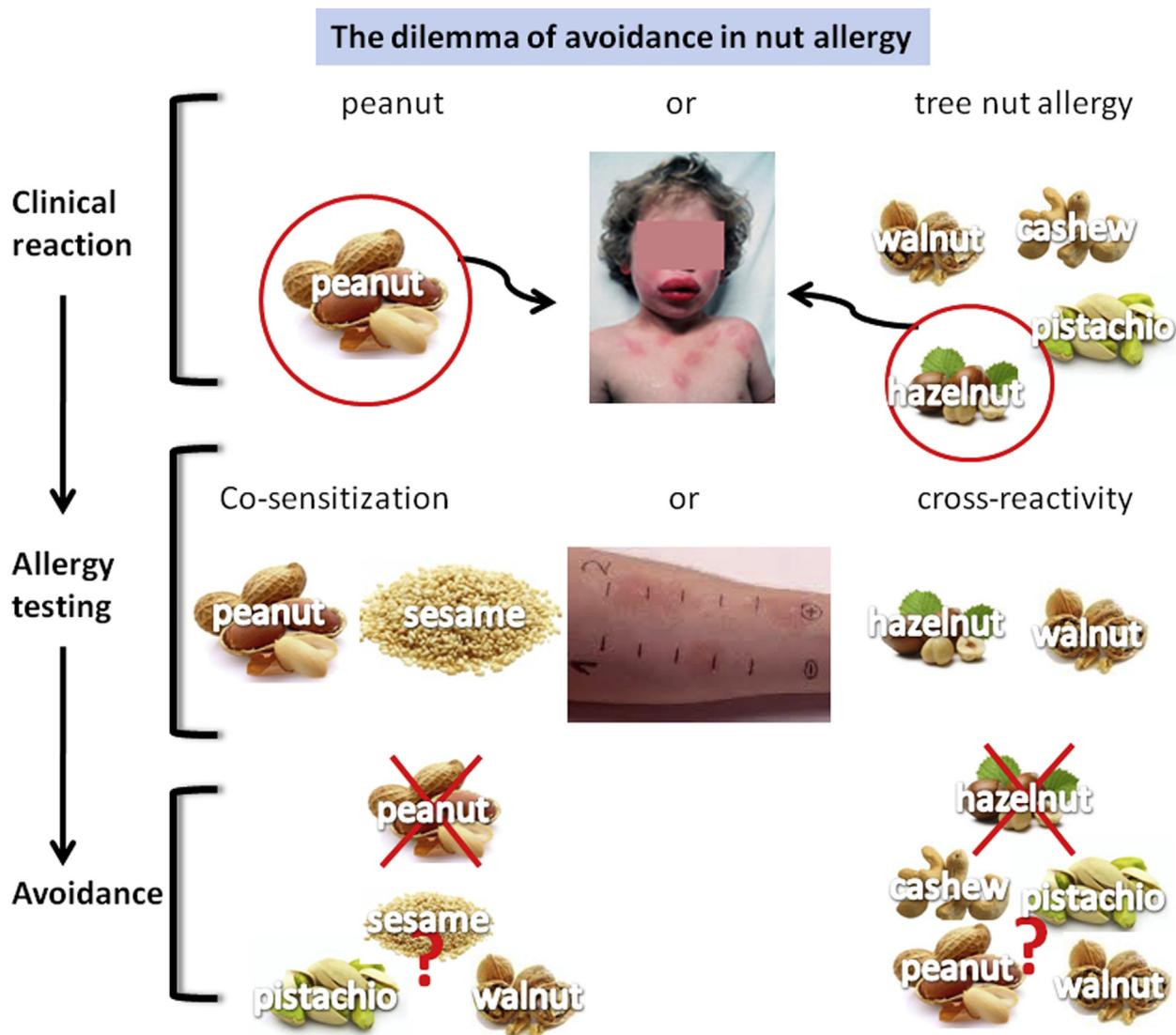
FIGURE 1. Dilemma in the management of peanut and tree nut allergies.

those with immediate-type reactions potentially leading to anaphylaxis is of prime clinical importance. In the absence of clear clinical information, for example, in young children with positive test results to hazelnut and primarily avoiding the food, interpreting positive serologic test results can be a major challenge. In addition to hazelnut, other tree nuts and peanut may display serological as well as clinical cross-reactivity with pollens.[28] Better tools for assessment of test results in relation to clinical reactivity are needed. Small series have attempted to investigate specific cross-reactivities such as pine nuts with pine pollen proteins,[29] or pine nuts with *Artemisia vulgaris* (mugwort).[30] A detailed characterization of cross-reacting allergens is however not available.

IN VITRO TESTING MAY CONTRIBUTE TO DEFINE CLINICALLY NONRELEVANT CROSS-REACTIVITY

Skin testing has in general a good negative predictive value, which may vary with the food tested.[31] However, interpretation

of a positive skin test result is largely hampered by the semi-quantitative interpretation of the wheal size.[32] IgE testing with recombinant allergen extracts has in the last decade provided some progress for the diagnosis of nut allergy although component allergens are not available for all protein families in all nuts. In this regard, several studies have clearly established that in patients with positive Ara h 2 IgE test results (a major peanut allergen), the diagnosis of peanut allergy is highly likely.[33,34] De Knop et al[35] have shown that in children and adults sensitized to birch and without symptoms to hazelnut or in whom symptoms were limited to oral allergy syndrome, IgE tests were positive only to the pollen protein-like profilin (PR-10) cross-reactive Cor a 1 allergens and not to Cor a 8 (lipid transfer protein) or Cor a 9 (seed storage protein).[35] Similar results showing the importance of Cor a 8 in systemic reactions in children have been reported by others even in a non-Mediterranean birch-endemic area.[36] In addition to Cor a 9, Cor a 14 is highly indicative of a systemic allergic reaction to hazelnut.[37,38] Meanwhile, IgE testing with major tree nut

TABLE I. Current options in the management of nut allergy

Options	Pro	Con
Avoid index nut	No other safe option	
Avoid all nuts, including clinically tolerated nuts	• Decreases the risk of accidental reactions due to cross-contamination • Easier avoidance of all nuts than specific ones	• Extensive dietary restriction possibly decreasing the quality of life • Possibly increased risk of becoming allergic to nuts previously tolerated
Continue eating nuts previously tolerated, and introduce nuts likely to be tolerated after OFC	• Tailored avoidance diet may increase quality of life • Possibly decreases the risk of also becoming allergic to these nuts	• Increases the risk of accidental reactions due to cross-contamination, or confusion in identifying nuts • Possibly increases the risk of becoming allergic to these nuts

allergens such as Jug r 1 for walnut, or Ana o 3 for cashew nuts, has improved the diagnosis to these nuts,[39,40] but currently little is known with regard to the value of recombinant IgE testing for the clinical relevance of cross-reactivity.

The basophil activation test (BAT) is another promising diagnostic tool in nut allergy, although not yet largely available to the clinical setting. The test is characterized by an activation of effector cells with serum IgE, and adds a functional dimension to allergy testing that is not present in serum IgE measurement. The value of the BAT in the diagnosis of peanut allergy was demonstrated in a study by Santos et al,[41] with the BAT providing additional information when quantitative serum IgE measurement to Ara h 2 was not able to accurately distinguish between peanut sensitization and allergy. In a 2-steps approach, with initial IgE testing followed by BAT in equivocal cases, the BAT decreased significantly the number of food challenges required for diagnosis by 97%.

In summary, currently available diagnostic tests for peanut and tree nut allergy can only partially identify clinically relevant cross-reactivity. Oral food challenges (OFCs) remain the best procedure to define nut allergy in patients with positive test results.

AVOIDANCE OR CONSUMPTION OF NUTS TESTED POSITIVE BUT CLINICALLY TOLERATED

It is yet unknown whether the consumption of a nut to which IgE testing is positive but is clinically tolerated may provoke allergy to the nut or even to a potentially cross-reacting nut. Alternatively, the opposite may be true, that eating the nut may prevent allergy and even potentially confer a cross-tolerance induction effect for another nut that the child is already allergic to. These questions are related to secondary prevention and therapeutic options, which need to be balanced with the risk of introducing nuts to which the individual has tested positive. In most cases, introduction of these nuts will need careful clinical evaluation with medically supervised food challenges, adding a significant constraint to the diagnostic procedure. Similarly, in patients with a nut allergy, it is not known whether eating a nut with a negative test will influence allergy (Table I).

In a context of mostly primary prevention, the Learning Early About Peanut Allergy (LEAP) study demonstrated that in infants at a high risk of developing peanut allergy (with a subgroup of children already sensitized), early high-dose peanut consumption reduced the risk of peanut allergy at age 5 years by 81%.[42] Participant adherence to the high-dose peanut consumption was remarkably good for the length of the trial (92% of adherence up to the age of 5 years). The risk of subsequent allergic reactions to peanuts in patients initially diagnosed with peanut allergy who passed a follow-up OFC and who subsequently did not regularly incorporate peanut into the diet has been reported previously.[43,44] This observation raised the question about the risk in children eating peanut for prevention of allergy to develop allergy when stopping eating the food. The follow-up of the LEAP patients for 1 year after the end of the trial without consuming peanuts has shown that there was no increased risk of developing allergy.[45] This suggests that sustained tolerance can be achieved by a prolonged regular consumption of an allergenic food despite a high risk of developing allergy. Introduction of nuts in toddlers as discussed above obviously implies avoiding whole nuts due to possible choking, and giving the nut as a bread spread or in baked goods.

MANAGING NUT ALLERGY AND ADDRESSING THE KNOWLEDGE GAPS

Patients and their families should have the choice of an extensive avoidance diet of all nuts including those to which clinical reactivity may be questioned (the safe option), or a targeted avoidance diet to the nuts the patient has been clearly defined to be allergic to (giving the possibility to eat clinically tolerated nuts). Nevertheless, the current diagnostic procedure for assessment of clinical reactivity (skin and/or IgE testing often followed by OFCs) can be tedious.

The clinical relevance of serological cross-reactivity between the various nuts, as well as between nuts and other foods (eg, peanut and sesame seed in cosensitization) needs to be better defined. Studies would be needed in which patients presenting with a nut allergy would need to be systematically fully tested to nuts and seeds other than the index nut. The sample size would need to be large enough to have sufficient numbers of patients with index nut allergies representing the various nuts to sort out combinations of cross-reactivities or cosensitizations. The diagnostic panel of the studies would also have to include various diagnostic tests to provide a reliable read-out for a biomarker that could accurately predict the likelihood of allergy versus sensitization to substitute time-consuming OFCs. Nevertheless, OFCs will remain the criterion standard for food allergy diagnosis.

Additional knowledge taking into consideration the pollen environment and common dietary exposure to specific nuts is also needed because this is known to strongly influence the pattern of nut allergy. Thus, it would be valuable to have similarly designed studies in various geographical areas or one study in several study sites.

Finally, it remains to be established whether consumption of tolerated nuts in the presence of positive IgE test results is safe

with regard to the development of new nut allergies. Is avoidance more constraining than consumption of tolerated nuts? It is not established whether selective avoidance increases the quality of life, or only leads to an increased risk of accidental exposure by cross-contamination to the nut to which the child has a known allergy. Selective avoidance may also increase the risk of accidental exposure due to possible confusions in identifying the various tree nuts.

Ultimately, patients should receive clear guidance for the daily management of their nut allergy. Current options that should be discussed with the patients and their families are either a targeted avoidance of nuts clearly identified for eliciting allergic reactions, or a general avoidance of all nuts. The discussion will have to include evaluation of potential risks and benefits of each option. Future research will have to better define the cross-reactivity or cosensitization between the various nuts, and the accuracy of IgE testing.

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