Recent advances in the management of nut allergy

Elise Midun[a]*, Suzana Radulovic[b], Helen Brough[b] and Jean-Christoph Caubet[c]

ABSTRACT

Peanut/tree nut allergy is common and has been associated with particularly severe reactions. Epidemiological data have shown that the prevalence ranges between 0.05% and 4.9% for tree nut and between 0.5% and 3% for peanut. These large variations can be explained by differences in the age of included patients and the geographical region. In addition, the food consumption modality (ie, raw versus roasted) plays a major role, as heat treatment has the capacity to modify the allergenicity of nuts and legumes. Nut allergies tend to persist into adulthood and consequently have a high impact on quality of life.

Recently, it has been demonstrated that a significant proportion of nut allergic patients are able to tolerate other nuts. As opposed to the avoidance of all nuts, this approach is currently proposed in several tertiary allergy centers. However, diagnosis of nut allergy is particularly difficult due to co-sensitization leading to high rate of false positive skin prick tests and/or specific IgE to whole allergen extracts. The use of component resolved diagnosis leads to major improvement of diagnosis, particularly to distinguish between primary and secondary nut allergies. The basophil activation test has been suggested to be useful but is still used mainly as a research tool. Thus, diagnosis remains mainly based on the oral food challenge, which is considered as the gold standard.

Regarding treatment, avoidance remains the cornerstone of management of nut allergy. Oral immunotherapy is increasingly proposed as an alternative management strategy.

Keywords: Food allergy, Tree nut, Peanut, Cross reactivity, Oral immunotherapy

INTRODUCTION

Peanut and Tree nut (TN) allergies are one of the most common food allergies worldwide and constitute a major public health problem. The estimated prevalence of peanut/tree nut allergies is approximatively 2%.[1-4] There is a large variation in prevalence reported in different countries, ie, from 0.05% to 4.9% for tree nut and between 0.5% and 3% for peanut.[1,3,5–7] Peanut allergy is the most common nut allergy. The allergy prevalence for each tree nut seems to vary in different parts of the world.[1,7–10] Indeed, hazelnut allergy is the most frequent tree nut allergy in continental Europe; Brazil nut, walnut and almond are most commonly reported in the United Kingdom;[1,11] and walnut and cashew nut allergy are the most common tree nut allergies in the United States.[1,12] These differences are

[a]Pediatric Allergy Unit, University Hospitals of Geneva and University of Geneva, Rue Willy Donzé 6, 1205 Geneva, Switzerland, University Lyon 1 Claude Bernard, 43 Boulevard Du 11-Novembre-1918, 69100, Villeurbanne, France
*Corresponding author: elisemidun@live.fr
Full list of author information is available at the end of the article

	Proportion of co-sensitization	Proportion of self-reported co-allergy	Proportion of co-allergy confirmed by OFC
Sicherer et al.[21]		34%	
Maloney et al.[24]	86%	34%	
Anagnostou et al.[25]	80%		
Cousin et al.[26]	87,1%		43,2%
Ball et al.[27]	23,4% of peanut-allergic patients are sensitized to nuts. 25,4% of patients allergic to nuts are sensitized to peanuts or other nuts.		32% of peanut-allergic patients are sensitized to nuts. 38% patients allergic to nuts are allergic to peanuts or other nuts.
Yang et al.[28]	51% of patients allergic to nuts are sensitized to peanut 73% of patients allergic to peanut are sensitized to nuts		
Clark et al.[29]	At 2 yr of age: 19% of children were multi-sensitized At 5-14 yr: 86% were multi sensitized	2% of children were multi allergic At 14yr: 47% of children were multi-allergic	
Elizur et al.[30]	60,6 %to 96,7%		<30%
Couch et al.[31]			12%
Brough et al.[11]			60,7%

Table 1. *OFC: oral food challenge, yr: year.*

mainly due to the variation of nuts consumed in different countries. However, prevalence variations have also been reported within the same country, highlighting the possible influence of environmental factors such as pollen exposure.[1,4]

An important aspect of nut allergy is the risk of potentially life-threatening allergic reactions. Indeed, nut allergies have been associated with severe allergic reactions more commonly than the majority of other foods. Recent studies reported that peanut/TN allergies account for 70-90% of fatalities from food-induced anaphylaxis, with TN alone accounting for 18–40%.[13] Peanut and TN allergies also tend to persist, and the acquisition of natural tolerance to peanut/TN occurs in only 9%–20% of peanut/TN allergic patients.[4] Despite years of research and clinical efforts, strict

avoidance of the incriminated nut (peanut/TN) remains the cornerstone of management. Thus, quality of life (QoL) is reduced with increasing stress and anxiety due to the need for constant vigilance.[14,15]

Although other treatment options, such as oral immunotherapy, have been largely investigated for peanut and TN allergic patients, their use currently remains limited.[16]

Management of patients with peanut/TN allergy is often quite complex. The distinction between cross-sensitization and clinically relevant cross-reactivity between TN and also peanut can be difficult and often requires multiple investigations and oral food challenges (OFC). While avoidance of all nuts has been the rule for a long time in patients allergic to one nut, the possible

introduction of other nuts has recently been investigated in several studies.[17-20]

For the purpose of this review, we will discuss these different aspects constituting advances in the management of nut allergies.

Proportion of patients reacting to multiple nuts

Prevalence of co-sensitization and co-allergy

Co-existent allergy peanut and TN have been described for many years. Initially, in the 90s, Sicherer et al reported that 34% of patients allergic to peanut or 1 TN may present with multiple nut allergy.[21] However, further studies reported a large variation in the proportion of patients reacting to multiple nuts, ranging from 12% to 96.7%.[4,15,21-28] These data have been summarized in Table 1.

The influence of pollen allergy, the population studied as well as its ethnicity are all confounding factors that might influence the results. In addition, these differences can be explained by differences in the methodology of the studies.

Thus, studies that reported on specific IgE found that the co-sensitization rate among TN and peanut ranged between 60.6% and 96.7%.[24-26,28-30]

When a positive clinical history is required to diagnose nut allergy, but without a confirmatory OFC, the proportion of patients with multiple nut allergy is lower than expected, ranging between 23% and 68%[4,21-25] (Table 1).

Studies including OFCs to prove co-existent peanut/TN allergy, considered as the gold standard, report a rate co-existent allergy of 12%–38.8% and confirmed initial data by Sicherer[4,15,26,27] (Table 1). However, a recent prospective multicenter study in Europe (Pronuts study) based on 122 patients that underwent sequential OFC to determine allergy versus tolerance, showed a higher rate of co-existent peanut/TN or sesame seed allergy at 60.7%.[11] These results could be explained by the fact that the Pronuts study was prospective as opposed to retrospective in the previous studies,[27,31] assessed all 9 TNs (compared to other studies testing less TNs),[27,30] and included sesame seed which belongs to the Pedaliaceae (seeds) family.

The NutCracker study which was also a prospective study including OFCs, reported a lower prevalence of multiple nut allergy below 30%,[30] however, this study (based on a cohort of 83 children with TN allergy in Israel) included only OFCs to a subset of TN (walnut, pecan, cashew, pistachio, hazelnut, and almond), which could potentially underestimate the rate of co-existent allergy.[30] Couch et al in a recent retrospective study, found similar results; 67 patients with a history of TN allergy underwent an OFC to another TN to which they were sensitized, but not exposed to before. Interestingly, only 14% of the included patients had a positive OFC to another TN. However, this study was retrospective and patients in this study had relatively low levels of specific IgE (90% of these patients had a sIgE <2 kU/L and at least half had a level <0.35 kU/L); thus, these patients were probably selected for OFC based on lower IgE tests to confirm non-allergy by OFC and this would have contributed to an underestimation of co-existent peanut/TN allergy.[31]

Development of peanut/TN allergy

The age of participants may also play a role in the rate of co-existent peanut/TN allergy. Indeed, although most TN allergies become apparent when a patient is young, many studies have shown that the rate of co-existent allergy between peanut and TN increases with age. The HealthNuts study showed that children who had peanut allergy at 1 year old had a 27% chance of having an OFC-confirmed TN allergy at 6 years of age.[15] Brough et al in a retrospective study reported similar results.[32] This increase can be explained particularly by the fact that nuts are introduced later than other foods. Indeed, Clark and Ewan showed that the number of nut consumption increased with age (23% eating more than one nut at 2 years, versus 73% by 10 years); they postulated that this could lead 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).[29] Conversely, Elizur et al proposed the opposite hypothesis, that elimination of TN in multiple-food-allergic patients could promote the development of sensitization and allergy to TN years later.[33] Peanut/TN co-sensitizations are

	Component	Protein Family	Co Sensitization/Cross Reactivity
Tree nut			
Hazelnut[18,36]	Cor a 1	PR-10	
	Cor a 2	Profilin	
	Cor a 8	LTP	Ara h 9, Jug r 3
	Cor a 9	legumin	
	Cor a 11	Vicilin	
	Cor a 12	Oleosin	
	Cor a 13	Oleosin	
	Cor a 14	2S albumin	
Cashew[18,36]	Ana o 1	Vicilin	Pis v 5
	Ana o 2	Legumin	Pis v 2
	Ana o 3	2S albumin	Pis v 1
Pistachio[18,36,158]	Pis v 1	2S albumin	Ana o 3
	Pis v 2	Legumin	Ana o 2
	Pis v 3	Vicilin	
	Pis v 4		
	Pis v 5	Legumin	Ana o 1
Walnut[36,110]	Jug r 1	2S albumin	Car i 1
	Jug r 2	Vicilin	
	Jug r 3	LTP	Cor a 8, Arah 9
	Jug r 4	Legumin	Car i 4
	Jug r 5	PR-10	
	Jug r 6	Vicilin	
	Jug r 7	Profilin	
Pecan[18,36]	Car i 1	2S albumin	Jug r 1
	Car i 2	Vicilin	
	Car i 4	Legumin	Jug r 4
Almond[125]	Pru du 1	PR-10	
	Pru du 2	PR-5	
	Pru du 3	LTP	
	Pru du 4	Profilin	Ara h 9, Cor a 8, Jug r 3
	Pru du 5		
	Pru du 6	Legumin	

	Component	Protein Family	Co Sensitization/Cross Reactivity
Brazil nut[18,36]	Ber e 1	2S albumin	
	Ber e 2	Legumin	
Legumes			
Peanut[40,159,160]	Ara h 1	Vicilin	Gly m 5
	Ara h 2	2S albumin	Gly m 8
	Ara h 3	Legumin	Gly m 6
	Ara h 4	Legumin	Gly m 6
	Ara h 5	Profilin	Gly m 3, lup a 5
	Ara h 6	2S albumin	
	Ara h 7	2S albumin	
	Ara h 8	PR-10	Gly m 4
	Ara h 9	LTP	Glym 1, Cor a 8, Jug r 3
	Ara h 10	Oleosin	
	Ara h 11	Oleosin	
	Ara h 12	Defensin	Gly m 2
	Ara h 13	Defensin	Gly m 2
	Ara h 14	Oleosin	
	Ara h 15	Oleosin	
	Ara h 16	LTP	
	Ara h 17	LTP	
	Gly m 1	LTP	Ara h 9
	Gly m 2	Defensin	Arah 12, 13
	Gly m 3	Profilin	Ara h 5, Lup a 5
	Gly m 4	PR-10	Ara h 8
	Gly m 5	Vicilin	Ara h1
	Gly m 6	Legumin	A ra h 3-4
	Gly m 7		
	Gly m 8	2S albumin	Ara h 2
Lupin[40,159,160]	Lup a 1	Vicilin	
	Lup a vicilin	Vicilin	
	Lup a 5	Profilin	
	Lup an 11S	Vicilin	

	Component	Protein Family	Co Sensitization/Cross Reactivity
Seed			
Sesame seed[161]	Ses i 1	2 S albumin	No available data
	Ses i 2	2 S albumin	No available data
	Ses i 3	Vicilin	No available data
	Ses i 4	Oleosin	No available data
	Ses i 5	Oleosin	No available data
	Ses i 6	Legumin	No available data
	Ses i 7	Legumin	No available data

Table 2. (Continued) *PR-10: pathogenesis related protein type 10, LTP: lipid transfer protein.*

common and distinguishing asymptomatic sensitization from clinical food allergy is currently based on OFCs, whicht may lead to life-threatening reactions. The clinical relevance of serological cross-reactivity between peanut/TN therefore needs to be better defined.

Peanut/TN allergy has 2 main dimensions. One is the cross-reactivity for the components, and another is severity. Recent advances in the field of component resolved diagnostics (CRD) provides the clinician with more information as to whether the patient has secondary nut allergy due to pollen food syndrome (also known as oral allergy syndrome) or primary nut allergy, more likely to lead to systemic symptoms.

Co-allergy and co-sensitization

Indeed, there are different sensitization profiles in peanut/TN allergy. Patients can be, therefore, sensitized to different families of proteins within the nut. The physico-chemical properties of the proteins to which peanut/TN allergic patients may be sensitized are responsible for allergic reactions of varying severity. The most well-known protein family is the seed storage protein family (eg, Ara h 2, Cor a 9, Cor a 14) responsible for severe anaphylactic reactions, explained in part by their thermostability and digestive resistance. Other families of proteins that are also responsible for severe reactions are the oleosins, defensin and LTP family.

Other sensitization patterns can lead to less severe symptoms in the majority of cases, such as the reprensented sensitization to PR-10 and profilins family. This is due to the fact that these protein families are degraded by heat and digestion.[34]

Components, protein families and cross-reactivity between components are referenced in Table 2.

Structural homology

Allergies 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 such as cashew and pistachio, walnut and pecan,[13,24,35,36] peanut and soybean.[34,37-40]

Thus, the Pronuts and NutCracker studies found that 97%–100% of pistachio and pecan allergic children were allergic to cashew nut and walnut, respectively.[11,30] Moreover, 64.2%–83.3% of patient allergic to cashew or walnut were respectively co-allergic to pistachio and pecan.[11,30] In a retrospective study, Andorf and al reported similar results.[35] Pistachio and cashew nuts belong to the same Anarcadiaceae family (homology 79% between rPis v 3 and rAna o 1, and homology 66% between Pis v 1 and r Ana o 3).[13,41] High homology between pecan and walnut protein sequences, which belong to the same botanical family (the Juglandaceae family), have also been described. Indeed, 2S albumin allergens in walnut (Jug r 1) and pecan (Car i 1) have 88% sequence identity and legumin allergens in walnut (Jug r 4) and pecan (Car i 4) have 95% sequence identity.[13]

Other studies have reported lower prevalence of co-allergy between cashew nut and pistachio. Indeed, Van der Valk et al and the HealthNut studies found that only 31%–36% of the cashew-allergic patients reacted to pistachio.[15,42] There is an uni-directionality of the co-existent allergies, as a lower proportion of patients allergic to walnut and cashew are allergic to pecan and pistachio, respectively. This suggests that some allergenic proteins are shared while others are unique to cashew and walnut and therefore result in mono-allergy.[30]

For peanut and soybean, studies have demonstrated similarities between both legumes allergens, such as Ara h 1, Ara h 3, and Ara h 8 with Gly m 5, Gly m 6, and Gly m 4, respectively, between 38,4%–70%[34,37–40] (Table 2). Despite this homology, studies show a low rate of cross sensitization and cross reaction. Indeed, in a study from several years ago, 31% of peanut-allergic children had cosensitization with soy, and only 3% had clinical reactivity to soy.[43] In other studies, the cross-reactivity rate has been estimated to be between 6.5% and 15%.[44,45] Another study by Savage et al reported that 98% of patients with a soy allergy also had a peanut allergy.[46] As with nut allergies, these data suggest that some proteins are common to peanut and soybean and some are specific to soybean and peanut.

Protein families

Different families of proteins such as the seed storage protein families (vicillins, 2 S albumins and legumes), the family of lipid transfer proteins (LTP) family, and pathogenesis-related protein type 10 (PR-10) family also help explain the cross-reactivity among peanuts and other legumes (eg, peanut-lupine). In addition, they also help explain, in part, why unrelated nuts such as TN and peanuts may exhibit serological and clinical cross-reactivity.[3,26,27]

Seed storage protein family

Peanut and lupine have a high degree of cross-reactivity; therefore, risk associated with cross reaction is also high as compared to other legumes. Studies show that 14.5%–89% of peanut allergic patients were sensitized to lupine however this cross sensitivity is clinically significant in only 4%–35% of cases.[50-55] (Table 2). Cross-reactivity has

been reported to be mediated by Lup a 1 (vicilin-like protein)[40,51] (Table 2). In 2017, the lupine profilin Lup a 5 was registered, which is highly cross-reactive to other profilins (eg, Ara h 5) and which is recognized by the sera of both lupine and peanut-allergic patients (www.allergome.org).

Lipid Transfer Protein family

Due to structural homology, lipd transfer proteins (LTPs) from different allergen sources are generally IgE cross-reactive; however, sensitization profiles are extremely heterogeneous, and individual cross-reactivity patterns may range from a single LTP to many different LTPs (from food or pollens).[56,57]

Some studies report a significant number of peanut/TN allergies associated with LTP sensitization, which may be responsible for severe systemic reaction.[58,59] The peach LTP Pru p 3 has been shown to be the primary sensitizing allergen for cross-reactivity with other LTP, including peanut (Ara h 9), hazelnut (Cor a 8), walnut (Jug r 3), and almond (Pru du 3)[60] (Table 2). It has been shown that sensitization to LTP leads to a large variety of clinical manifestations; although oral allergy syndrome (OAS) is probably the most frequent clinical expression, LTPs can be also responsible for severe systemic reactions.[57,58] Thus, it is the most frequent cause of primary food allergy in the Mediterranean area.[61,62]

LTP sensitization can occur via the gastrointestinal tract, but the predominant presence of the LTP syndrome only in the Mediterranean region suggests that environmental factors play a major role. Indeed, Vereda et al showed that in peanut allergic patients, LTP sensitization rate varied by country: in Spain, 60% of patients are sensitized to peanut LTP (Ara h 9) while these proportions were 7.7% and 14.3% in the United States and in Sweden, respectively.[59] The reasons for these geographical distributions are still poorly defined. Studies hypothesize that these distributions are in part due to variations in environmental homologous pollen allergens exposures in LTP-endemic areas such as Art v 3 from mugwort, or Pla a 3 from plane tree.[56,58] In agreement with Pastorello,[63] Scala et al reported that, in LTP allergic patients, co-sensitization with PR-10 proteins, is associated with milder symptoms.. In addition, the higher the levels of

birch pollen in a certain area, the lower the prevalence of LTP hypersensitivity.[64]

PR-10 family

TN and peanut allergy may display serological as well as clinical cross-reactivity with pollens.[65] The majority of these patients suffer from OAS. Patients initially allergic to birch pollens through sensitization to a PR-10 protein, may develop a secondary allergy (pollen-food syndrome) to peanuts or TN (OAS);[65,66] they develop mainly mild symptoms limited to the oropharynx, with pruritus, tingling, erythema, and mild edema of the mouth upon ingestion of peanut or TNs(67). Pollen food syndrome (PFS) is triggered by a cross-reaction between allergens in pollen and allergens in peanuts/TN.[65,66] Homologous proteins have been identified between hazelnut, walnut, peanut, and soybean and have been shown to cross-react with Bet v 1.[68-70]

The prevalence of PFS ranges from 4.7% to greater than 20% in children sensitized to pollens.[66,67] The PR-10 family also plays a significant role in PFS. Bet v 1 from birch pollen is well known of these proteins[67] and is one of the major pan-allergens in PFS.[66] Uotila et al in a retrospective study found that among subjects with birch sensitization, 84% were cosensitized to hazelnut, 71% to almond, and 60% to peanut; amongst these nut-sensitized patients, 40% of patients sensitized to hazelnut, 34% of those sensitized to almond, and 36% of those sensitized to peanut reported typical symptoms of PFS.[65] A retrospective review from Northern France, where there is a high level of birch pollen exposure, reported a 43.2% co-existent TN allergy rate amongst patients with peanut allergy (43,2%), with hazelnut being the most common TN allergy observed.[26]

Symptoms associated with PR-10 sensitivity are mainly mild.[69,71-73] However, the thermostability of the proteins in this family are variable. Heat processing such as roasting significantly reduces the rosacea fruit protein allergenicity in patients with birch-pollen allergy, but some sensitized individuals can still experience positive reactivity toward roasted peanut, soy, and TNs.[72]

Diagnostics for peanut and tree nut allergy

Peanut and TN allergy is typically diagnosed based on a combination of a convincing history of a IgE mediated allergic reaction, SPT, serum-specific IgE and, if necessary, an OFC.[74-77] For example, peanut allergy is diagnosed based on the clinical history of reaction, the presence of risk factors (severe atopic dermatitis) and if needed additional tests such as SPT, sIgE, and component resolved diagnosis (CRD). Although the cut-off points for determining allergy vary in different regions/clinical settings, these tests have led to a major improvement of the diagnosis of peanut allergy. If history and allergy tests are discordant, the gold standard for diagnosis of food allergies is the double-blind, placebo-controlled, food challenge (DBPCFC).[34]

One of the major issues in clinical practice is the difficulty in distinguishing asymptomatic sensitization (false positives) from primary allergy and from secondary allergy (PFS); this is particularly complex for nut allergies due to the high prevalence of pollen co-sensitization.[18]

Double-blind, placebo-controlled, food challenge

Although the DBPCFC is the gold standard for diagnosis of food allergies, this is costly, resource and time-consuming, and carries the risk of potentially life-threatening reactions. Some patients or their parents refuse to perform an OFC due to the fear of triggering a severe reaction. In the Pronuts study, Brough et al reported that 8.2% of children did not perform an OFC due to fear of reaction or history of previous severe reaction on exposure to the incriminated nut.[11] In this clinical setting, not performing an OFC can potentially lead to unnecessary and prolonged peanut/TN avoidance, which may have the unintended risk of increasing peanut/TN allergy risk.[78] However, it is necessary to find new, less invasive diagnostic tools for the diagnosis of peanuts/TN allergies. Studies have shown that combination of SPT, sIgE, and basophil activation test (BAT) improved the ability to identify allergic and tolerant patients. In the case of peanut allergic patients, this approach could potentially lead to a reduction of OFC of 76.6%–97%.[30,79]

SPT and specific IgE to whole extract allergen

As for other allergies, it is of major importance to interpret peanut/TN SPT and sIgE in the context of the clinical history. The diagnostic value of SPT and specific IgE to whole allergen extracts has been found to vary significantly among studies. Indeed, those different results might be explained by differences in the population studied, prevalence of pollen allergy, and the methodology used in the study.[30,65,80,81] These data have been summarized in Table 3. As an example, while a SPT <3 mm has a good negative predictive value;[82-85] SPT<3 mm still requires further investigations in the context of a convincing clinical history of nut allergy. In contrast, a SPT ≥3 mm to a specific nut, without an appropriate clinical context has a poor predictive value and is associated with high rate of false positives.[83,86,87] Clark et al showed that amongst patients with a history of reaction to peanut or TN, a SPT ≥8 mm had a predicted clinical reactivity greater than 95% accuracy.[88] Ho et al confirmed this threshold value for cashew, hazelnut, and walnut.[89]

Specific IgE to whole allergen extracts of peanut/TN are more widely available than SPTs and improve the management of patients with a suspicion of nut allergy. However, similarly to SPT, there is a large variation regarding the reported diagnostic values of sIgE.[24,30,90-92] Data are summarized in Table 3. As an example, Sampson et al showed in the 1990s that a peanut sIgE ≥15kU/L could predict clinical reactivity with greater than 95% certainty.[93] Clark et al confirmed and extended this result to TN allergy.[88,94] Fleisher et al reported that only 63% of patients with a history of clinical TN allergy and TN sIgE levels <2 kU/L passed their OFC.[4] In a retrospective study, Couch et al reported a higher proportion of patients with a negative OFC (89%) with similar levels of sIgE (<2kU/L).[31]

Specific IgE and SPT are routinely performed as a first-line procedure to support the diagnosis of allergy; however, false negatives can occur. These false negatives can be explained in part by the fact that commercial extracts (SPT and sIgE) do not contain extracts of oleosins (lipid-bound allergens) that are responsible for some allergic reactions. Modified skin prick testing (using the actual nut or

nut butter), or the use of CRD to measure oleosins (e.g Ara h 10 and 11 for peanut) or in the basophilic activation test would therefore be valuable diagnostic tools, but these data need to be confirmed by further studies.[95]

Component resolved diagnosis

During the last decade, the introduction of CRD has led to a major improvement in the diagnosis of nut allergies.[18,78,96]

It is now possible to identify patients who have developed sIgE against seed storage proteins that are associated with a high risk of systemic reactions. The most well-known example is sIgE to Ara h 2, which is a peanut seed storage protein. It has been shown that 80%–100% of patients with primary peanut allergy are sensitized to Ara h 2.[62,97-100] Cut-off decision points for Ara h 2 sIgE have been determined in multiple studies, but there is a large variation of the reported values (Table 3). Hazelnut also contains seed storage proteins, ie, Cor a 9 and Cor a 14, and sIgE to these proteins have also been associated with systemic reactions.[101,102] These tests have been found to be highly specific and more sensitive than sIgE and SPT to whole allergen extract to diagnose a primary hazelnut allergy.[101] However, there is again a large variation of reported diagnostic values, particularly for sIgE to Cor a 14.[98,101-106] In addition, some studies have highlighted specific factors affecting the variation of the diagnostic values of sIgE to Cor a 9 and Cor a 14. Particularly, the age of the child may affect the diagnostic value of these tests. Thus, it has been found that Cor a 9-sIgE specificity decreases with age, while Cor a 14-sIgE specificity increases with age.[102,107,108] Specific IgE to seed storage proteins found in other TNs (ie, Jug r 1, Jug r 4 in walnut or Ana o 3 in cashew nut) have also been found to improve diagnostic accuracy of allergy to these nuts.[109-112] Regarding walnut, sIgE to Jug r 1 and Jug r 4, were reported to provide the best distinction between walnut allergy and sensitization.[113,114] Indeed, sIgE to Jug r 1 and Jug r 4 have been found to be positive in 75% and in 56.7-66% of walnut allergic patients, respectively.[115,116] The NutCracker study found that IgE levels ≥0.35kU/L to Jug r 1 and Jug r 4 provided the best diagnosis method for identifying walnut allergic

Food	Cutoffs for sIgE to extract allergen	Cutoffs for specific IgE to main components	Cutoffs for specific skin prick test
Peanut	≥15 kU/L, 95% PPV[162-164]		≥4 mm–15mm, 95%–100% PPV[83]
		Ara h 2 sIgE: 0.35–42.2 kU/L had 90%–95% PPV[79,98,99,165-168]	
		Arah 8 : 0.6 kU/L to 100 kU/L[69]	
		Arah 9: no available values	
Hazelnut	≥0,7kU/L- 15 kU/L or greater 57%-92%PPV[92,102]		≥8 mm–17mm or greater, 74%-100% PPV[89,169]
	≤0,35kU/l, 95%NVP[102]		
		Cor a 9 sIgE: 1 kU/L had 83% accuracy[102]	
		Cor a 14 sIgE: 0.72-47.8 kU/L had 87%–90% accuracy[98,103]	
		Cor a 1: no available values	
		Cor a 8: no available values	
Walnut	≥5.07 kU/L −18,5kU/L or greater, 95%–99% PPV[24,81]		≥8 mm, 95%PPV[30,89]
		Jug r 1 sIgE: 0.1 kU/L had 91% PPV(113), ≥0,35kU/l, accuracy 0,93(81)	
		Jugr 4 ≥ 0,35kU/L, accuracy 0,93(81)	
		Jug r 3: no available values	
Pecan			≥7 mm, 75% PPV[89]
Cashew	≥8 kU/l – 149.5kU/L or greater: 95%PPV[89,170]		≥8 mm, 95%PPV[89] ≥10–12 mm, 95% PPV[30,171]
		Ana o 3 sIgE: 0.16 kU/L had 97.1% accuracy for cashew and/or pistachio nut allergy[109]	
Pistachio	≥88 kU/l, 90% accuracy[24]		
Almond			
		Pru du 1 (PR-10)	
Brazil nut	≥3,5kU/l 100% PPV[91]		≥6 mm, PPV 100%[91] ≥9 mm, accuracy ≥95%[88]
		Ber e 1 sIgE: 0.25 kU/L had 94% PPV[172]	

Table 3. *PPV: positive predictive value, NPV: negative predictive value, PR-10: Pathogenesis related protein type 10.*

patients (accuracy 0,93) (Table 3). In addition, the NutCracker study reported that patients with walnut and pecan dual allergy were more frequently sensitized to Jug r 4 compared to patients with isolated walnut allergy.[81] Regarding cashew nut, 2 European studies have shown that up to 93% of children with cashew allergy are sensitized to Ana o 3.[109,117] Ana o 3 sIgE level ≥0.16kU/L had 97.1% accuracy for cashew and/or pistachio nut allergy.[109,117,118] (Table 3). Specific IgE to Ana o 3 have been reported as a highly accurate diagnosis marker also for pistachio allergy.[36,109]

Peanut/TN allergies may be the expression of a sensitization to LTP family (eg, Arah 9, Cor a 8, Jug r 3). Hazelnut has received the most extensive evaluation. Studies reported that sensitization to a hazelnut LTP (eg, Cor a 8) is a risk factor for objective symptoms in children from a Mediterranean region.[119-121] Hansen et al, in a multicenter study performed in Switzerland, Spain, and Denmark, reported that amongst patients with hazelnut allergy, 28% had positive sIgE to rCor a 8. The highest rate of sensitization to the LTP rCor a 8 was reported in Spain (71%), followed by Switzerland (15%), then Denmark (5%). LTP sensitization was present in 5 out of 7 patients (71%) with severe symptoms to hazelnut and in 11 out of 52 patients (21%) with milder reactions.[122] Diagnostic values of sIgE vary significantly between studies and cut-offs have not been clearly established. There are many confounding factors such as pollen influences, patterns of sensitization (food or pollen) and geographic distribution.

Distinction between primary and secondary allergy is a challenge and use of CRD can help differentiate phenotypes of peanut/TN allergy and co-sensitization. Uotila et al found that in a birch pollen endemic region, patients with peanut sensitization without associated symptoms and peanut allergic patients were equally sensitized to PR-10 proteins (Bet v 1 90%). In this cohort, over 90% avoided TNs but only 6%–44% presented with specific sensitizations to seed storage protein to TNs.[123] Hence, an accurate diagnosis based on CRD might have helped to decrease the rate of unnecessary avoidance. Proteins of the PR-10 family have been identified for walnut (Jug r 5),[110] hazelnut (Cor a 1),[124] almond (Pru du 1),[125]

and peanut (Ara h 8).[69] As with primary allergies, the clinical expression of sensitization to PR-10 might be dependant on the specific IgE levels.[126]

Basophil activation test

The BAT is another promising diagnostic tool for nut allergy.[20,64] This test is not yet largely available in the clinical setting, because it requires appropriate equipment and trained personnel. Thus, Santos et al proposed to restrict the use of BAT to selected cases, for which the results of routinely used tests do not allow a precise diagnosis.[79] Several studies reported that in the diagnosis of peanut/TN allergies, BAT had a sensitivity ranging between 81.3% and 98%, and a specificity ranging between 77 and 100%.[30,107,127] However, cut-offs determined for the BAT can vary according to the population studied, the design of the study, and the methodology adopted for the BAT procedure and data analyses.[79]

Regarding peanut allergy, Santos et al and Ocmant et al determined optimal cut-off points for CD63 at 4.78% and 9.1%, respectively.[79,128] Basophil reactivity in peanut-allergic subjects was found to be associated with the severity of allergic reaction, and it has also been shown that BATs may be useful in monitoring patients undergoing OIT.[128-130] However, studies are still needed to confirm these results.

Studies evaluating the diagnostic value of the BAT for TN allergy are limited. Regarding hazelnut allergy, it has been found that the BAT has a sensitivity ranging between 85% and 100% and specificity ranging between 80% and 97%.[127,131-133] Recently, it was suggested that the use of the BAT in combination with SPT was useful for the diagnosis of TN allergies. Preliminary results report that the combination of BAT with SPT and clinical co-existent allergy knowledge enable the differentiation of co-allergenicity patterns in patients sensitized to walnut, pecan, cashew and pistachio.[30] However, these data should be examined in a prospective study with a larger patient population. In addition, BAT has been also shown to be potentially useful in identifying the culprit allergen in cases of PFS.[131,134-136]

MANAGEMENT

The basic approach to peanut/TN allergy management does not defer from current management approaches to other food allergies. It includes short-term, immediate treatment of symptoms after the exposure and long-term strategies assuring strict avoidance of culprit nut and minimising risk of any future reactions.[16]

The management of mild reactions has been based on the same therapies for many years, namely non-sedating antihistamines.[137] Epinephrine is the cornerstone and first-line treatment for anaphylaxis.[138] Early recognition of signs of anaphylaxis and prompt administration of epinephrine are absolutely key, and patients with potential anaphylaxis to peanut/TN should have easy access to epinephrine autoinjectors in the community.

Improved understanding of the pathophysiological mechanisms involved in allergic reactions may give rise to additional useful treatments. Vadas et al reported on the role of PAF and the activity of PAF acethylhydrolase in anaphylactic reactions.[139] Arias et al, in an experimental study in peanut-sensitized mice, reported that PAF antagonists significantly decrease the duration and severity of the anaphylactic reaction compared to other therapeutics (histamine receptor antagonist, 5 lipooxygenase inhibitor). Indeed 83% of PAF-treated versus 43% of untreated mice reached recovery within 120 min after peanut challenge. In addition, they also report that the combination of PAF receptor antagonists and histamine receptor antagonists allows for better management and an even more significant reduction in the severity and duration of the reaction.[140]

Long-term strategies assuring avoidance of index nut are quite complex and require a multidisciplinary approach, involving good education of patients and their families. This education involves teaching parents and their children to read food labels and recognise their allergen appropriately. Identifying and clearly listing the most common food allergens has become a legal requirement in many countries, but practices differ throughout the world. Many food companies also choose to add Precautionary Allergen Labels (PAL), such as "may contain", but it is not always clear what these labels mean, and consumers often do not fully understand this.[6]

Historically, the main management approach to nut allergy was strict, blanket avoidance of all nuts in all peanut and TN allergic patients. Although avoiding all nuts simplifies the management and may decrease the risk of reactions secondary to cross-contact or misidentification, it has many pitfalls. As peanut/TN are long-term allergies, patients must avoid all nuts (ie,. peanuts and TN) even if they might be clinically tolerant to selective nuts, which puts an additional and unnecessary restriction on patients' diet and social activities, which in turn reduces quality of life[141] and increases anxiety levels.[14] Strict avoidance of all nuts may lead to development of new allergies, as well as nutritional consequences, and influence growth, particularly in children with other food allergies.[33,142-144]

On the other hand, introducing selective nuts in the diet of patients allergic to some types of nuts can be complicated, requires multiple investigations, and often multiple in-hospital OFCs, which are limited not only by the available resources and time, but also carry risk, as reactions occurring during these OFCs can be severe.[11] Another important safety aspect of selective nut consumption is patients' and their families' ability to correctly recognise and distinguish the correct nuts themselves. A study involving 1105 participants conducted by Hostetler et al investigated the ability of children and adults to appropriately identify peanut/TNs. Participants were shown 19 different pictures of peanuts and TNs, and the mean number of correct responses was only 8.4. There was a significant difference between children and adults, but parents with nut allergic children did not perform any better than parents of children without a known nut allergy.[145]

Healthcare professionals' approach to the matter of nut avoidance in peanut/TN allergies management has changed; patient populations and their preferences have also changed. Patients and their families prefer having more freedom in making choices and tend to get more involved in their management decisions and wish dietary restriction to have less repercussions on their daily life. Management of their peanut/TN allergies

should be tailored to each patient, taking into consideration many aspects in addition to test results, such as age, history of previous reactions, concomitant conditions, patients' and families' understanding of their allergies, tendency towards risk taking, anxiety level, quality of life, and ultimately, what our patients and their families want as part of shared decision making.[146]

Building up immune tolerance in mainly peanut but also TN allergies has been a major focus of food allergy research over the past decade. The number of double-blind placebo controlled trials (with several trials including large numbers of participants) investigating oral, sublingual, and epicutaneous routes have showed this treatment approach to be efficacious in desensitizing the individual (increasing their threshold dose of reactivity), with quite a good safety profile.[147-149] However, the question of safety of different routes of peanut/TN immunotherapy and the benefit/risk ratio of this type of treatment remains a concern. A systematic review and meta-analysis published by Chu. et al showed that patients undergoing peanut oral immunotherapy (OIT) had a significant increase in anaphylaxis risk and frequency.[150] Authors concluded that peanut OIT achieved a modest degree of desensitization but caused more allergic and anaphylactic reactions in participants receiving treatment with peanut (albeit mostly during the updosing phase in hospital), when compared with the placebo group. On the other hand, as much as other routes such as epicutaneous or sublingual might have a better safety profile, they might not be as effective as the oral route.[151] This question will not be answered accurately unless large double-blind multiple arm studies comparing different routes of peanut/TN immunotherapy are performed.

Another approach to TN OIT would be using nut clusters such as cashew/pistachio,[11,19] walnut/pecan,[11,19] and pecan/walnut/hazelnut/macadamia nuts[11] as a treatment approach. Indeed, Elizur et al showed in their open label study investigating efficacy of walnut oral immunotherapy in 73 participants in which 55 participants received active treatment, all children with co-existing pecan allergy were also desensitised to pecan and 93% of children who were co-allergic to hazelnut were desensitised after their course of OIT with walnut.[19] Although these results

seem promising, there is a lack of substantial evidence, and this might be quite an interesting and large area for future research.

Lastly, the question of TN allergy prevention still remains open. There is quite substantial evidence for the early introduction of peanuts being protective against development of peanut allergy in high risk infants. The LEAP (Learning Early About Peanut Allergy)randomised controlled trial showed a relative reduction in school-aged peanut allergy prevalence of 86.1% in peanut skin prick test negative and 70% in skin prick positive infants who started eating peanuts by the age of 11 months, when compared with the group who avoided peanut.[152] This finding was sequentially supported by the results from the EAT (Enquiring about tolerance) study in the per protocol group and in children with positive sIgE >0.1kU/L.[153,154] In addition, as the follow up LEAP-On Study showed, this protective effect remained beyond time of intervention, and 1 year of peanut avoidance was not associated with an increase in peanut allergy.[155]

It is not known whether a similar approach to tree nut allergy prevention would be effective, but previous data looking into development of sensitization/allergies to TN suggested this is likely. Unfortunately, as the LEAP study has shown, early introduction of peanut seems to be allergen specific and early peanut introduction was not effective in prevention of TN allergies.[156] There might be a practical limitation to this approach. As the prevention strategy requires an early intervention, families might find it difficult to introduce the required amounts of multiple TNs into the child's daily diet, which could greatly influence the success of prevention strategy. Other areas targeting the skin for the prevention of food allergies may be an alternative approach.[157] This is certainly a very interesting field for future research.

CONCLUSION

The specific difficulty with peanuts and TN allergies is the presence of cross-reactivity between them, and with pollens, making diagnostic and therapeutic management complex. Many diagnostic tools such as SPT, sIgE, CRD, and BAT are available to help make an accurate diagnosis, but

the OFC remains at the present time the gold standard despite the drawbacks that this entails. Healthcare practitioners often propose the avoidance of the index nut or of all nuts, as decided with the parent and child where appropriate. Peanut specific immunotherapy has shown benefits for desensitization but not tolerance induction once the treatment is stopped;[126] however, it is not widely available clinically. Recently, studies have also shown a benefit of immunotherapy with hazelnuts.[127-129] Regarding the primary prevention of TN allergy, data are missing; however, given the clear evidence for prevention for peanut allergy through early peanut introduction, it seems legitimate to also research this area. Targeted research is still required to answer some controversies in peanut and TN allergy treatment and prevention.

Abbreviations
Tree nut: TN; Oral allergy syndrome: OAS; Component-resolved diagnostic: CRD; Skin prick test: SPT; Pathogenesis related protein type 10: PR-10; Lipid transfer protein: LTP; Oral food challenge: OFC; Double-blind, placebo-controlled, food challenge: DBPCFC; Oral induction tolerance: OIT; Platelet-activating factor: PAF; Pollen-food syndrome: PFS; Precautionary Allergen Labels: (PAL)

Author's contribution
Elise Midun wrote the chapters: introduction, Proportion of patients reacting to multiple nuts, Co-allergy and co-sensitization, Diagnostics for peanut and tree nut allergy, and Conclusion, Suzana Radulovic wrote the chapter: Management. Helen Brough read and corrected the review, Jean-Christoph Caubet read and corrected the review.

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Author details
[a]Pediatric Allergy Unit, University Hospitals of Geneva and University of Geneva, Rue Willy Donzé 6, 1205 Geneva, Switzerland, University Lyon 1 Claude Bernard, 43 Boulevard Du 11-Novembre-1918, 69100, Villeurbanne, France. [b]Paediatric Allergy Group, Department of Women and Children's Health, King's College London, London, United Kingdom, Paediatric Allergy Group, Peter Gorer Dept of Immunobiology, School of Immunology & Microbial Sciences, King's College London, Guys' Hospital, London, United Kingdom, Children's Allergy Service, Evelina Children's Hospital, Guy's and St. Thomas' Hospital NHS Foundation Trust, London, United Kingdom. [c]Pediatric Allergy Unit, University Hospitals of Geneva and University of Geneva, Rue Willy Donzé 6, 1205, Geneva, Switzerland.

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