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BSACI guideline for the diagnosis and management of peanut and tree nut allergy

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Clinical & Experimental Allergy

Summary

Peanut nut and tree nut allergy are characterised by IgE mediated reactions to nut proteins. Nut allergy is a global disease. Limited epidemiological data suggest varying prevalence in different geographical areas. Primary nut allergy affects over 2% of children and 0.5% of adults in the UK. Infants with severe eczema and/or egg allergy have a higher risk of peanut allergy. Primary nut allergy presents most commonly in the first five years of life, often after the first known ingestion with typical rapid onset IgE-mediated symptoms. The clinical diagnosis of primary nut allergy can be made by the combination of a typical clinical presentation and evidence of nut specifc IgE shown by a positive skin prick test (SPT) or specific IgE (sIgE) test. Pollen food syndrome is a distinct disorder, usually mild, with oral/pharyngeal symptoms, in the context of hay fever or pollen sensitisation, which can be triggered by nuts. It can usually be distinguish clinically from primary nut allergy. The magnitude of a SPT or sIgE relates to the probability of clinical allergy, but does not relate to clinical severity. SPT of ≥ 8 mm or sIgE ≥ 15 KU/L to peanut is highly predictive of clinical allergy. Cut off values are not available for tree nuts. Test results must be interpreted in the context of the clinical history. Diagnostic food challenges are usually not necessary but may be used to confirm or refute a conflicting history and test result. As nut allergy is likely to be a long-lived disease, nut avoidance advice is the cornerstone of management. Patients should be provided with a comprehensive management plan including avoidance advice, patient specific emergency medication and an emergency treatment plan and training in administration of emergency medication. Regular re-training is required.

Keywords adrenaline, aetiology, almond, anaphylaxis, Brazil, cashew, diagnosis, epicutaneous immunotherapy, epinephrine, food, hazelnut, macadamia, macadamia food allergy, management, oral, oral allergy syndrome, peanut, pecan, pecan, pistachio, pollen food syndrome, sublingual, tree nut, walnut

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Introduction

Nut allergy is common and affects approximately 2% of children and 0.5% of adults in the UK. Resolution of peanut allergy is sometimes seen in young children. Clinical experience suggests that peanut allergy in teenagers and adults and tree nut allergy rarely resolve. The quality of life of the affected patients and their families is decreased because of the need for constant vigilance over food choices and the perceived likelihood of anaphylaxis, alongside the dietary and social restrictions that accompany food allergy [1, 2]. Current best management is directed at educating patients, families and caregivers on food allergen avoidance and how to treat food allergy emergencies [3].

Throughout this document, the term 'nut allergy' refers to both peanut and tree nut allergy, unless otherwise specified.

Evidence for the recommendations was collected by electronic literature searches of MEDLINE and EMBASE

using above keywords. Searches were conducted from 2011 to 2014. Additional references were hand-searched and provided by committee members, experts and reviewers from 2014 to 2017. Where evidence was lacking, a consensus was reached amongst experts on the committee. BSACI members, Allergy UK and Anaphylaxis Campaign were consulted, and all suggestions were carefully considered by the Standards of Care Committee. The guideline writing processes used by SOCC have been accredited by the National Institute for Health and Care Excellence (NICE) and are embodied in a manual, available on the BSACI website.

Executive summary

- Peanut and tree nut allergies are characterised by IgE-mediated reactions to nut proteins.
- Primary nut allergy affects 2% of children (B) and 0.5% of adults (C) in the UK.
- Infants with severe eczema and/or egg allergy have a higher risk of developing peanut allergy. (A)
- Primary nut allergy presents most commonly in the first five years of life, often after the first known ingestion, with typical rapid-onset IgE-mediated symptoms. (C)
- The clinical diagnosis of primary nut allergy can be made by the combination of a typical clinical presentation and evidence of nut-specific IgE shown by positive skin prick tests (SPTs) or specific IgE (sIgE) test. (B)
- Pollen food syndrome is a distinct disorder, usually mild, with oral/pharyngeal symptoms, in the context of hayfever or pollen sensitisation, which can be triggered by nuts. It can usually be distinguished clinically from primary nut allergy.
- The magnitude of a SPT or sIgE result relates to the probability of clinical allergy but not to clinical severity. (B)
- SPT of ≥ 8 mm or sIgE ≥ 15 KU/L to peanut is highly predictive of clinical allergy. Cut-off values are not available for tree nuts. Test results should be interpreted in the context of the clinical history. (A)
- Diagnostic food challenges are usually not necessary but may be used to confirm or refute the diagnosis when history and test results are conflicting. (D)
- Nut allergy is likely to be a long-lived disease nut avoidance advice is the cornerstone of management. (B)
- Patients should be provided with a comprehensive management plan including avoidance advice, patient-specific emergency medication and an emergency treatment plan, and training in administration of emergency medication. Regular retraining is required. (B)
- As part of the comprehensive management plans for children, all staff within the school and early years setting require appropriate training in managing an allergic reaction. (D)
- Nut allergy can lead to significant psychological burden as well as social and dietary restrictions that may affect quality of life. (C)
- Peanut oral immunotherapy can induce desensitization in peanut-allergic children. (A)

Definition

Nut allergy is characterised by a type I IgE-mediated reaction induced by nut proteins. There are two types of IgE-mediated nut allergy: primary nut allergy and pollen food syndrome (often referred to as oral allergy syndrome) associated with nuts (see Box 1).

Non-IgE-mediated immunological reactions to nuts will not be discussed in this guideline [4, 5].

Box 1. Phenotypes

> Primary nut allergy: is characterized by systemic and often severe reactions to nuts in patients with specific IgE against the major storage proteins e.g. Ara h2 for peanut.
> Pollen food syndrome (PFS), also known as oral allergy syndrome is characterized by seasonal allergic rhinitis and a history of reactions to fresh fruit, vegetables or nuts. Symptoms are typically mild and isolated to the oropharynx. Anaphylaxis can occur but is uncommon. Serum specific IgE is directed against heat-labile proteins (PR-10 homologues) homologous to those in pollen.

Background and epidemiology

Peanut and tree nut allergy were uncommon until the early 1990s following which there was a substantial rise in prevalence [6–10]. In the UK, peanut allergy affects between 0.5% and 2.5% of children [6, 9, 11, 12]. Although these variations could be ascribed to differences in populations examined, study design, age of children and time periods assessed (Table 1). There is evidence of increasing prevalence of peanut allergy in UK children. A meta-analysis of European studies showed peanut allergy prevalence varied from 0.5% to 2.5%, depending on the diagnostic criteria used [13]. In Australia, 3% of unselected 12-month-old infants had challenge-proven PA [14].

In adults in the UK, the self-reported prevalence of peanut allergy was 0.53% for 15- to 44-year-olds and 0.3% > 45-year-old. Studies outside the UK suggest a peanut allergy prevalence from 0.4% to 0.7%, although there are significant variations in diagnostic criteria [20]. As peanut allergy has affected 1–2% of children for over a decade, the prevalence in young adults is likely to exceed 1%.

Table 1. Prevalence of peanut and tree nut allergy based on UK studies

Author & publication year	Methodology	Diagnosis of nut allergy	Age	Prevalence, %
Peanut				
Perkin et al. (2016) [15]	Exclusively breastfed infants randomized at < 3/12 living in UK were enrolled from 2009 to 2012	Positive OFC or positive history and SPT ≥ 5 mm	3 years	2.5
Tariq et al. (1996); Venter et al. (2010) [6, 8]	Three Isle of Wight birth cohorts followed up	Positive OFC/DBPCFC or history of adverse reaction and evidence of sensitization		
	Cohort A: 1989		4 years	0.5
	Cohort B:1994–1996		4 years	1.4
	Cohort C:2001–2002		3 years	1.2
Venter et al. (2015) [16]	Isle of Wight birth cohort born 2001–2002 at 10 years	Positive OFC or history of adverse reaction and evidence of sensitization	10 years	1.5
Pereira et al. (2005) [9]	Isle of Wight birth cohort born 1987–1998 and 1991–1992 assessed 2002 to 2003	Positive OFC, physician diagnosis or positive history and sensitization	11 years 15 years	1 0.8
Hourihane et al. (2007) [11]	Assessed 1072 mother-child pairs from Southampton & Manchester	Positive DBPCFC or clinical reaction within last year and positive peanut SPT/IgE	4–5 years	1.8
Du et al. (2008) [12]	5171 Jewish children assessed by questionnaire in Greater London	Validated Food Allergy Questionnaire (FAQ)	4–18 years	1.85
Nicolaou et al. (2010) [5, 17]	The Manchester Asthma and Allergy Study birth cohort	Positive OFC or convincing clinical reaction and peanut sIgE ≥ 15 KU/L and/or SPT ≥ 8 mm	8 years	1.74
Emmett et al. (1999) [18]	16 420 British adults were interviewed	Self-reported peanut allergy followed by more in depth interview	15–44 years > 45 years	0.53 0.3
Tree nuts				
Tariq et al. (1996) [8]	Assessed children born on the Isle of Wight 1989–1990	History and positive SPT	4 years	0.2
Pereira et al. (2005) [9]	The FAIR study from IOW 1987–1998 and 1991–1992 assessed 2002 to 2003	Positive OFC, physician diagnosis or positive history and sensitization	11 years 15 years	1.2 2.2
Venter et al. (2008) [19]	The FAIR study from the IOW 2001–2002	Positive OFC or positive history and sensitization	3 years	0.7

OFC, Oral Food Challenge.

The prevalence of allergy to at least one tree nut in UK children is based on data from the Isle of Wight. The prevalence reported has varied from 0.2% to 2.2% (see Table 1). Individual tree nut allergy prevalence varies from 0.12% for walnut to 0.48% for Brazil nut [21]. The population prevalence of tree nut allergy was estimated by telephone survey in the United States at 0.2%, 0.5% and 1.1% in 1997, 2002 and 2008, respectively [22]. In adults, primary tree nut allergy ranged from 0% to 0.7%, whereas an estimated prevalence of pollen food syndrome (PFS) to hazelnut has been reported as high as 4.6% in an unselected population [20, 23, 24].

A systematic review and meta-analysis of fatal food anaphylaxis estimated an incidence of fatal peanut anaphylaxis was 0.73–4.25 per million person years [25]. Over a 20-year period from 1992 to 2012, there were 69 fatalities attributed to peanut and tree nuts in the UK [26].

Risk factors for development of nut allergy

Most children with primary nut allergy present with a clinical reaction on first known ingestion of nuts [27, 28]. This contrasts with PFS, where patients have often previously consumed the nut without symptoms prior to developing their PFS symptoms.

Eczema is a significant risk factor for primary nut allergy. Peanut allergy may develop through transcutaneous sensitization in children with an impaired skin barrier function such as eczema (dual-allergen hypothesis) [29]. Filaggrin (FLG) plays a role in skin barrier

formation and eczema. FLG mutation carriers are at increased risk of peanut allergy [30, 31]. Early-life environmental peanut exposure is associated with an increased risk of peanut sensitization and allergy in children who carry an FLG mutation [32]. In addition, use of eczema creams containing peanut oil is an independent risk factor for the development of peanut allergy [33]. High levels of household peanut consumption by family members in the households of infants with eczema are also a risk factor presumably due to skin exposure [34]. Recent data demonstrate with increasingly severe eczema, and earlier onset of eczema, the risk of peanut sensitization increases as well as the risk of peanut allergy [35–38]. Lastly egg allergy is a significant risk factor for peanut allergy [36].

Risk factors for the development of tree nut allergy have not been as extensively investigated as for peanut allergy. However, it is clear that peanut allergy and tree nut allergy often coexist [39, 40] and data suggest one specific tree nut allergy commonly coexists with another tree nut allergy.

Risk factors for severe reactions

A previous severe reaction in a patient is a risk factor for future severe reactions [41–43]. Most patients with mild reactions do not go on to have severe reactions. Severity appears to relate to the amount of nut ingested [44]. Hospital-based challenges are not helpful in predicting severity of accidental reactions [45–47].

Allergy testing (skin prick test, or serum-specific IgE) does not predict clinical severity, although if a patient is found to be sensitized only to PR-10 homologues and has a clinical history of oral allergy symptoms from a significant nut exposure (for instance hazelnut or peanut), the risk of a future severe reaction is low (as this would suggest a diagnosis of PFS) (see Diagnosis section). The basophil activation test has been shown in research studies to predict severity and threshold reactivity in peanut-allergic children [48].

A clinical history of asthma in food allergy increases the risk of a severe allergic reaction, [49, 50] and a recent UK study demonstrated that 78% of those with fatal anaphylaxis to food had asthma. Increased severity of asthma can increase the risk of anaphylaxis [51], and the risk of fatal food anaphylaxis is higher in patients with asthma [25, 26, 52].

The majority of severe non-fatal and fatal accidental reactions occur in teenagers and young adults [53, 54]. Several factors are thought to be involved. These include risk-taking behaviour such as failure to avoid trigger(s), failure to carry an adrenaline autoinjector (AAI) and use of alcohol [55].

Diagnosis

History/clinical presentation

The clinical history is the cornerstone of a diagnosis of nut allergy (Box 1). A detailed allergy history should be taken before testing is considered [56]. A history of nut allergy reactions is often typical; patients usually suspect the diagnosis following an allergic reaction. A convincing history of an immediate reaction to peanuts on two separate occasions has an 80% probability for predicting primary nut allergy [57]. A clinical history alone, however, is insufficient to make a diagnosis of nut allergy.

Nut allergy presents with rapid onset of IgE-mediated symptoms, within minutes of ingestion. The nature of the symptoms is often related to the site and amount of exposure, with ingestion of large quantities generally being responsible for more severe reactions. It is rare for a severe reaction to occur following only cutaneous exposure [58]. Following ingestion, immediate local mucosal symptoms of oral itching and swelling of the lips are common.

Young children may not be able to describe this experience and will often spit the food out and become distressed. Alternatively, the nut protein may be masked within the food carrier, and it may not cause any upper GI tract symptoms [59]. If sufficient allergen has been ingested, then after a short period of time, other organ systems may become involved. Peanut allergen is absorbed rapidly across the oral mucosal, or more gradually through the gut causing colicky central abdominal pain, which is often accompanied by profuse vomiting. Generalized urticaria and angioedema commonly occur, often accompanied by rhinoconjunctivitis. Symptoms of a more severe reaction include a sensation of throat tightening, wheezing and breathlessness. Collapse due to hypotension is a rare presentation and is usually due to hypoxia secondary to respiratory failure. Nut allergy is the commonest cause of anaphylactic death in adolescents and young adults [26]. Young children may not be able to describe the symptoms of upper airway narrowing, but suggestive features are a change in the pitch of their voice, hoarseness or a loss of the voice, stridor, excessive drooling of saliva and breathlessness. Symptoms usually resolve quickly with treatment, and it is unusual therefore to still have symptoms the following day.

Tree nuts such as brazil and cashew nut cause symptoms of airway narrowing more often that peanut, and cashew nut in particular has been associated with more severe reactions and more frequent use of adrenaline injections to treat reactions [60]. The allergic reactions to nuts may be more severe in adults than children [61].

Primary nut allergy and PFS can usually be differentiated by clinical history; however, they can coexist (see Box 1). Care should be taken not to misinterpret primary nut allergy causing only oral symptoms as PFS.

Allergy tests

Before considering any allergy test, it is necessary to consider the clinical context (history) to determine the pre-test probability of nut allergy (see Figs 1 and 2). Positive specific IgE (sIgE) or SPTs by itself (a state of sensitisation) do not make a diagnosis [36, 62]. A suggested approach to diagnosis of peanut and tree nut allergy is illustrated in Figs 1 and 2.

Skin prick test. SPTs are performed with standardized nut extracts and in some cases supported by prick-to-prick testing with individual nuts. A recent typical clinical history of peanut or tree nut allergy with SPT weal size of at least 3 mm is sufficient to make a clinical diagnosis of allergy (see Figs 1 and 2). However, using a SPT $\geq$ 3 mm cut-off alone for peanut in a paediatric population without the appropriate clinical context has a poor predictive value and should not be used [63, 64].

However, a cut-off with a SPT diameter < 3 mm performs well for excluding allergy. The exception is in the context of a typical clinical history of nut allergy with a SPT < 3 mm, where further investigations will usually be required (Figs 1 and 2).

SPT weal diameter cut-off values for diagnosis of peanut allergy have been proposed. Larger SPT weals have been proposed to improve SPT performance. Table 2 shows the sensitivity, specificity, LRs and positive predictive values (PPV) for peanut SPT values. A SPT $\geq$ 8 mm has a low sensitivity and high specificity and in the majority of studies provides a PPV >95% (Table 2) [63, 65].

There are fewer studies assessing the diagnostic values of SPT weal size in tree nut allergy. In one study, a

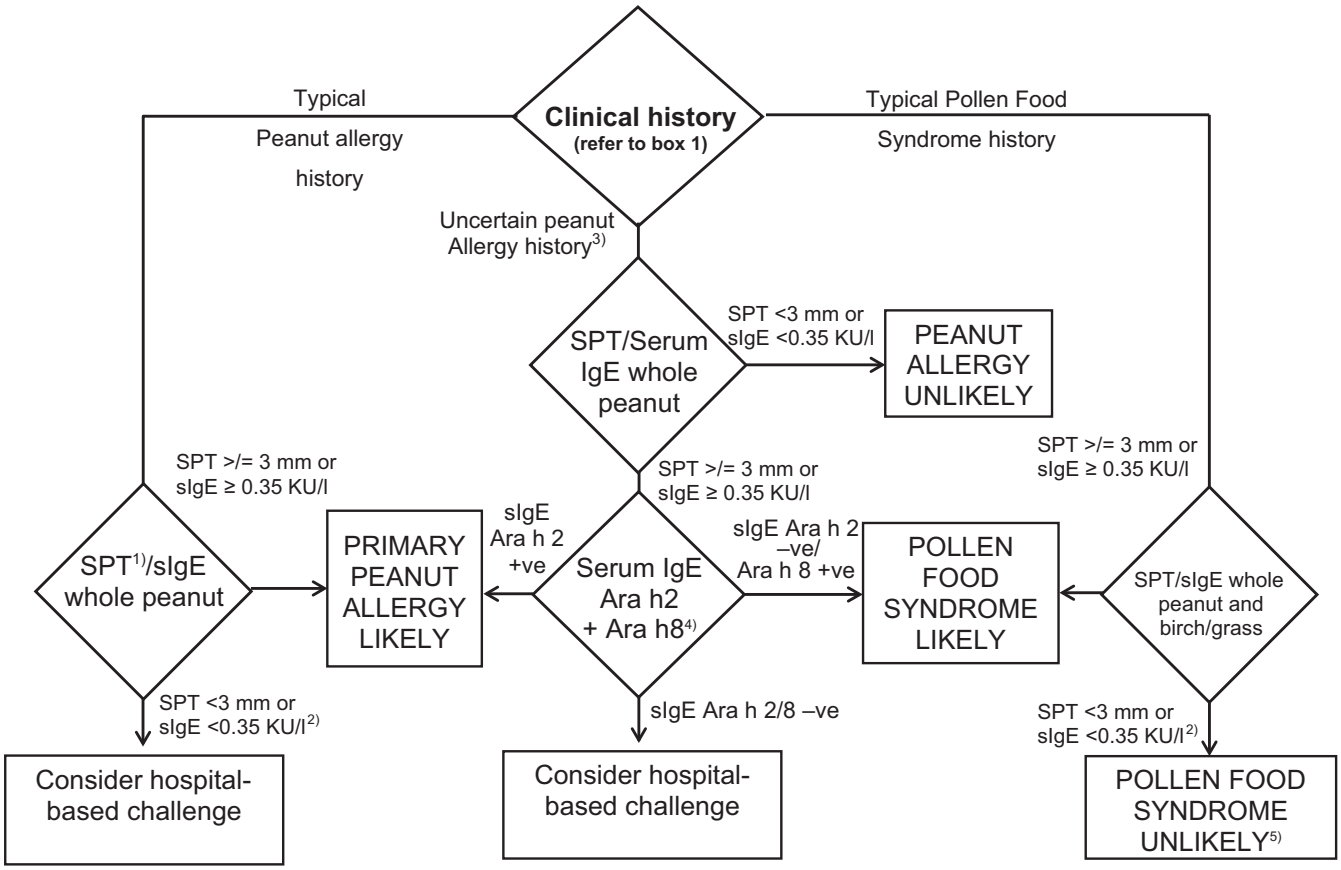

Fig. 1. Suggested algorithm for the diagnosis of peanut allergy. [1)]In infants and young children with a typical history, a SPT weal of 2 mm may indicate clinical allergy; [2)]Either sIgE or SPT should be negative on two occasions or both sIgE and SPT negative; [3)]This may include mild or OAS/FPS symptoms; [4)]sIgE components do appear to be more sensitive and specific than peanut sIgE. Data in children suggest that sIgE components are no better than SPT. Consider performing Ara h 1, 3 & 9 as it is possible for one of Ara h 1, 3 or 9 to be positive as well as Ara h 8 positive and Ara h2 negative. This indicates an increased likelihood of primary peanut allergy; [5)]Consider food challenge

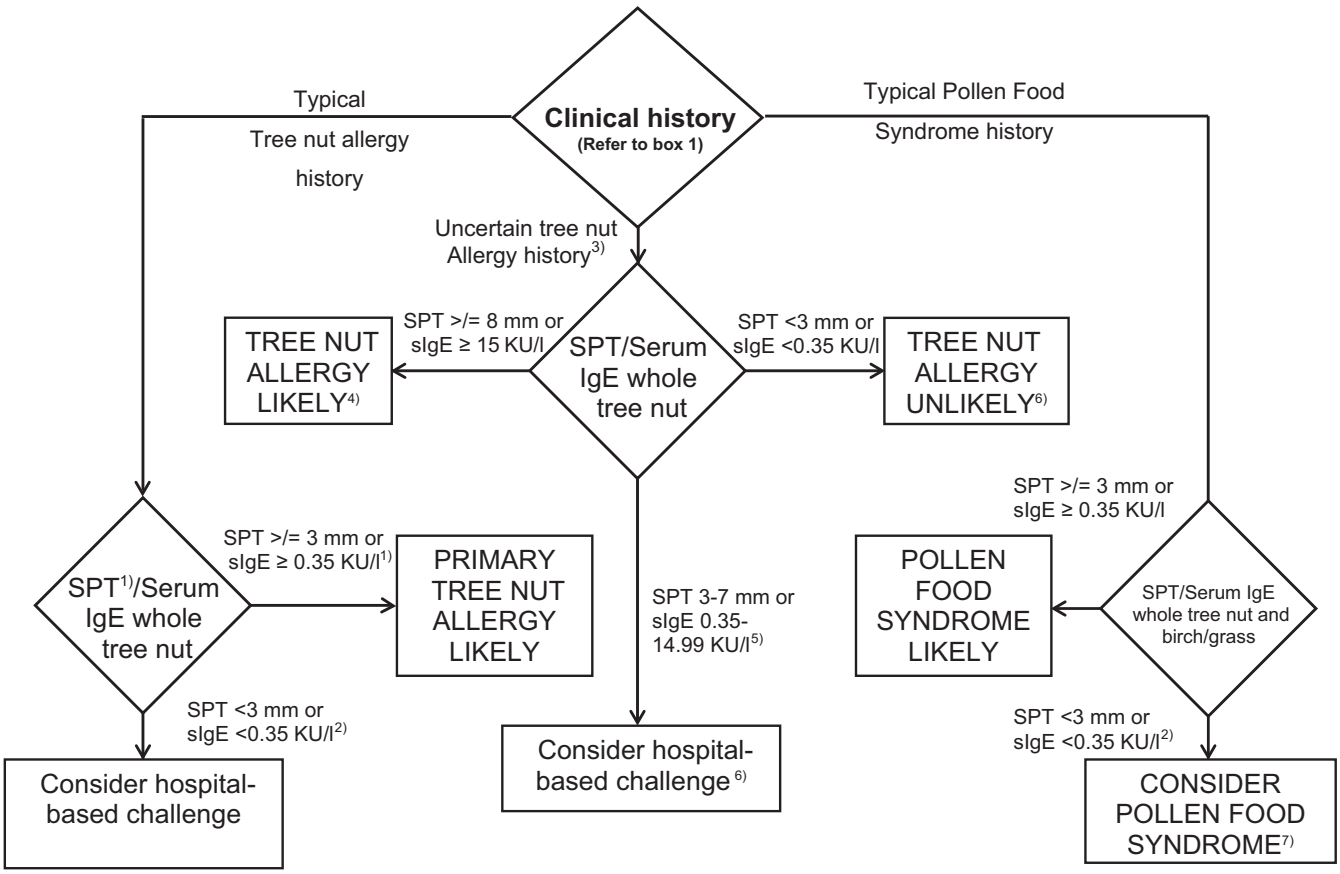

Fig. 2. Suggested algorithm for the diagnosis of tree nut allergy. [1)]In infants and young children with a typical history, a SPT weal of 2 mm may indicate clinical allergy; [2)]Either sIgE or SPT should be negative on two occasions or both sIgE and SPT negative; [3)]This may include mild/OAS symptoms or poor recall; [4)]It may not be possible to differentiate between pollen food syndrome (PFS) and primary tree nut allergy based on SPT/sIgE. sIgE components and food challenges may be able to differentiate between the two better; [5)]sIgE components for hazelnut should be considered. Evidence for other tree nuts is lacking; [6)]A decision to perform a challenge will depend on the clinical context; [7)] Consider component testing for hazelnut and consider food challenge

SPT ≥ 8 mm for cashew, hazelnut and walnut had a PPV >95% [70]. In contrast, a further study with hazelnut showed a SPT ≥ 8 mm and ≥ 17 mm with a PPV of 74% and 100%, respectively [75]. However, it is generally accepted that a cut-off SPT ≥ 8 mm for a specific tree nut is highly suggestive of clinical allergy [76]. Skin testing is safe, and systemic reactions are extremely rare. The skin prick test weal size does not correlate with clinical severity.

Serum-specific total nut IgE. Nut serum sIgE testing is more widely available than SPTs in primary and secondary care. A sIgE ≥ 0.35kU/l is usually considered to represent a positive result, although this cut-off is arbitrary. Using peanut sIgE as an example, a sIgE ≥ 0.35 KU/L has a high sensitivity and low specificity and PPV (see Table 3) and is therefore not a reliable test to diagnose allergy in isolation.

However, a peanut sIgE ≥ 15 KU/L is highly specific with a PPV in excess of 90% and thus on its own without a history of tolerating peanut would be highly suggestive of peanut allergy. This cut-off has a low sensitivity and therefore lower sIgE values must be interpreted with the clinical history to make a correct diagnosis. For all nuts, one study comparing specific IgE with history found 40% of positive tests were misleading (patients were tolerant) and 22% of negative tests were falsely reassuring.

In children, hazelnut sIgE ≥ 15 KU/L has a PPV of 57% and therefore if interpreted in isolation without the clinical history is not a good diagnostic test, but a sIgE < 0.35 KU/L has a NPV of 95% and therefore can effectively exclude hazelnut allergy [75]. A hazelnut sIgE ≥ 0.7 KU/L provides a PPV of 92%, but a poor sensitivity and specificity [86]. The data on hazelnut-specific IgE reflect variations in populations studied but also variations amongst different age groups studied and it is difficult to use specific cut-offs to diagnose hazelnut allergy.

Walnut sIgE ≥ 18.5 KU/l has a PPV of 99%, and a specificity 98% suggesting that values above this

Table 2. Diagnostic value of SPT to peanut

Author	Patient group	Age	Methods	SPT cut-off	Sensitivity	Specificity	Positive predictive values (PPV)	Likelihood ratios (LR)
Sampson and Albergo (1984) [66]	Children with atopic dermatitis	1.5–19 years (median 8.5 years)	33 challenges to PN (Overall 238 food challenges; 155 DBPCFC)	≥ 3 mm	100%	58%	44%	2.38
				≥ 3 mm + sIgE ≥ 0.35 KU/l	100%	76%	57%	4.17
Eigenmann et al. (1998) [64]	Children with AD suspected as having IgE-mediated FA	Children (ages not available)	35 DBPCFC to PN (Overall 250 DBPCFC)	≥ 3 mm	80%	47%	61%	1.51
Rance et al. (2002) [63]	Children referred to allergy clinic	Median 4 (0.1–15.9 years)	DBPCFC (363 DBPCFC)	≥ 16 mm	14.7%	100	100%	∞
				≥ 3 mm	100%	66.1%		2.95
Sporik et al. (2000) [67]	Patients referred to tertiary allergy clinic	Median age 57.8 months (range 1.5–168)	95 open OFC to PN (overall 555 OFC in 467 children)	≥ 8 mm	55%	100	100%	∞
Kagan et al. (2003) [68]	Atopic children with 42/47 with another FA	47 children	47 children undergo open OFC	≥ 6 mm	95.7 (95.7–99.9)	37.5 (18.8–59.4)	59.5%	
				≥ 10 mm	52.2%	87.5%	80	4.2
Roberts and Lack (2005) [69]	Children referred to tertiary allergy clinic or from large cross-sectional birth cohort (ALSPAC)	Mean age 7rs (1–16.4 years)	161 open OFCs	≥ 8 mm	25.4%	98.5%	94.4%	16.9
Ho et al. (2006) [70]	Tertiary paediatric allergy clinic	4 months–19 years	680 open OFC	> 2 years				
				≥ 3 mm	95%	51%	64%	1.93
				≥ 6 mm	69%	91%	87%	7.25
				≥ 8 mm	30%	99%	96%	28.4
				< 2 years				
				≥ 3 mm	82%	79%	67%	3.88
				≥ 4 mm	74%	100%	100%	∞
Nolan et al. (2007) [71]	Paediatric allergy clinics in Western Australia	Median 6.3 years (age 3.7–14.8 years)	51 open OFC	≥ 6 mm	89%	93%	89%	LR 12.71
				≥ 7 mm	83%	97%	93%	27.67
Wainstein et al. (2007) [72]	Tertiary allergy clinic	Mean age 4.5 years (11 months–17 years)	81 open OFC (a further four children included with history of reaction within 3 months and sensitization)	≥ 8 mm	75%	66.7%	78%	2.25
				≥ 15 mm	5.8% (95% CI 1–16)	Spec 100% (95% CI 89–100)	100%	LR = ∞
Nicolaou et al. (2010) [5, 17]	A population-based birth cohort study	All 8 years of age	79 open OFC	≥ 8 mm	31.6%	99.9%	85.7%	277
Johannsen et al. (2011) [73]	Paediatric allergy clinics and research database	Median age 40 months (range: 10–59 months)	49 PN OFC	≥ 7 mm	83%	84%	83%	5.19

(continued)

Table 2 (continued)

Author	Patient group	Age	Methods	SPT cut-off	Sensitivity	Specificity	Positive predictive values (PPV)	Likelihood ratios (LR)
Peters et al. (2013) [74]	Population-based, study with recruitment from immunization clinic	Mean age 12 months	438 OFC offered to all children with peanut SPT ≥ 2 mm	≥ 8 mm	54% (95% CI 46–62),	98% (95% CI 95–99)	95% PPV SPT ≥ 8 mm (95% CI 7.2–9.3)	22.2

Many studies have suggested specific cut-offs demonstrating the 95% positive predictive value (95% PPV) and 95% negative predictive values (95% NPV) of SPT or sIgE tests. However, these figures are population dependent and not transferrable to other populations seen routinely in one's individual clinic. However, these figures are often quoted in the literature and utilized. Likelihood ratios (LR) on the other hand are not meant to be population dependent, so LRs are transferrable to most populations. Utilizing LRs suggest that a LR ≥ 10 is strongly suggestive of nut allergy, and a LR ≤ 0.1 is strongly suggestive of no allergy. As a general rule, the higher the SPT or sIgE, the more likely it is to be allergy. However, even with the above information these test results cannot be taken in isolation of the clinical context.

cut-off are likely to represent walnut allergy. Unfortunately, the sensitivity is low (17%). Diagnosing walnut allergy based on sIgE alone is unreliable [40]. Data on other tree nuts' sIgE cut-offs are limited although it has been suggested that a cut-off ≥ 15 KU/L for individual tree nuts is likely to represent clinical allergy [76]. Measurements of serum IgE reactivity against individual recombinant or native protein components can be made, which represent the major allergenic proteins of each nut (see Table 4).

Component specific IgE testing. Most data on sIgE components relates to ImmunoCAP, although the various methods used are not comparable. Ara h 2 is the major peanut allergen, and sIgE directed against this shows better discrimination than total peanut IgE [62, 83, 88]. Several studies have established cut-off values for the peanut component Ara h 2 (see Table 5). The reported predictive value of Ara h 2 varies amongst different populations. Measurement of Ara h 1, 3 and 6 appears less useful [84, 89–93]. However, if peanut sIgE is positive and sIgE Ara h 2 is negative, then other peanut components can be useful in combination with the clinical context.

There are few data comparing performance of peanut SPT to sIgE peanut components. One study demonstrated that the performance of both sIgE Ara h 2 and SPT was similar in correctly identifying young children with peanut allergy and peanut sensitization [83].

Similarly, sensitization to the hazelnut component Cor a 9 and Cor a 14 are more specific for primary hazelnut allergy compared to hazelnut sIgE [88, 96–99] as with Ara h 2, there is variation amongst different populations in the predictive values of a specific IgE level.

An isolated sIgE to PR-10 Bet v 1 (birch pollen) suggests the possibility of PFS rather than primary nut allergy. Isolated sIgE to Cor a 1 or Ara h 8 is often associated with clinical tolerance or mild, subjective oral symptoms [96, 100]. Sensitization to PR-10 nut components in addition to seed storage components (e.g. Ara h 1,2,3 & 6 or Cor a 9 & 14) requires further evaluation of the history as this suggests the a diagnosis of primary nut allergy.

Less commonly in the UK, clinical reactions to nuts may reflect sensitization to non-specific lipid transfer proteins (nsLTP, e.g. Ara h 9, Cor a 8) [101]. This pattern of sensitization has been associated with both mild and severe systemic reactions. Serum sIgE to cashew components in children performs better than cashew-specific IgE or SPT [93] and Ana o 3 appears the best predictor of cashew nut allergy [102, 103].

Jug r 1 is a clinically important major walnut component associated with systemic allergic reactions to walnut [104]. The roles of sIgE to walnut and Brazil nut components are not yet established [98, 105, 106].

Table 3. Diagnostic value of sIgE peanut

Author	Patient group	Age	Methods	sIgE cut-off	Sensitivity	Specificity	Positive predictive values (PPV)	Likelihood ratios (LR)
Sampson and Albergo (1984) [66]	Children from clinic with atopic dermatitis	1.5–19 years (median 8.5 years)	238 challenges of which 155 DBPCFC. (33 PN challenges)	≥ 0.35 KU/L	100%	58%	44%	2.38
Sampson and Ho (1997) [77]	Children with AD from tertiary allergy clinic	0.6–17.9 years (mean 2 years)	494 DBPCFC in 196 children (41 PN DBPCFC)	15 KU/L	73%	92%	> 95%	9.1
Rance et al. (2002) [63]	Children referred to allergy clinic	0.1–15.9 years. (Median 4 years)	363 PN DBPCFC	≥ 0.35 KU/L	96.6 (92.7–99%)	62.4 (55.0–69.3)	71%	2.54
				≥ 14 KU/L	44%	95.2%	Not available	9.17
				≥ 57 KU/L	15.3%	100%	100 (87.2–100)	∞
Bernard et al. (2003) [78]	Patients seen in allergy clinic with suspected peanut allergy	Median 4.5 years (range 1.5–16 years)	96 open OFC	0.35 KU/L	93%	40%	85%	1.55
				1 KU/L	87%	45%	88%	1.58
				5 KU/L	63%	90%	96%	6.3
				15 KU/L	52%	100%	100%	∞
Perry et al. (2004) [79]	Patients referred to tertiary allergy clinic	0.9–43 years (median 4.8 years)	169 open OFCs	≥ 0.35 KU/L	84.5%	44.9%	52.6%	1.53
Roberts and Lack (2005) [69]	Children referred to tertiary allergy clinic or from large cross-sectional birth cohort (ALSPAC)	Mean age 7rs (1–16.4 years)	161 open OFCs.	≥ 15 KU/L	28.4%	96.8%	91.3 (72–99%)	8.87
Wainstein et al. (2007) [72]	Tertiary allergy clinic	11 months–17 years (Mean age 4.5 years)	51 had a +ve open OFC or recent reaction within 3 months and +ve sIgE and 33 negative open OFC	≥ 0.37 KU/L	98.1% (95% CI 90–100)	33.3% (95% CI 18–52)	70%	1.47
				≥ 10 KU/L	54% (95% CI 39–67)	100%(95% CI 89–100)	100%	∞
van Nieuwaal et al. (2010) [80]	Children referred with suspected peanut allergy to a tertiary allergy clinic	5–10.3 years (median age was 6.7 years)	103 children had a sIgE performed within 6 months of a DBPCFC to peanut	> 10.4 KU/L	66%	92%	90%	8.25
				> 24.1 KU/L	48%	98%	95%	24
				> 26.5 KU/L	48%	100%	100%	∞
Nicolaou et al. (2010) [17]	A population-based birth cohort study	All 8 years of age	79 open OFC	15 KU/L	57.9 (36.3–76.9)	99.8 (99.0–100.0)	91.7 (64.6–98.5)	325
DunnGalvin et al. (2011) [5, 81]	Pos history or pos SIgE without previous ingestion	Mean age 7 years	124 open OFC	≥ 0.35 KU/L	75%	46%	Not available	1.37
Johannsen et al. (2011) [5, 73]	Paediatric allergy clinics and research database	Median age 40 months (range: 10–59 months)	49 PN OFC	≥ 0.35 KU/L	95.8%	25%	56%	1.28
				≥ 2 KU/L	79%	83%	82%	4.75
Ebisawa et al. (2012) [82]	Children referred with primary care diagnosis	Median age 6 years (range 2–13 years old)	57 PN OFC	≥ 0.35 KU/L	100%	23%	52%	1.29

(continued)

Table 3 (continued)

Author	Patient group	Age	Methods	sIgE cut-off	Sensitivity	Specificity	Positive predictive values (PPV)	Likelihood ratios (LR)
	of peanut allergy to allergy clinic							
Dang et al. (2012) [83]	Unselected population from immunization sessions in Australia (Healthnuts-5276 children)	Age 11–15 months old	200 randomly selected (100 with PA based on open OFC and 100 peanut tolerant based on open OFC)	> 0.35 KU/L	91 (95% CI 83–96)	68 (95% CI 58–77)		2.8
				> 14.9 KU/L	26 (95% CI 18–36)	98 (95% CI 93–100)		13
Lieberman et al. (2013b) [84]	Children referred with suspected peanut allergy (Sweden and United States)	Median age 11.7 years	167 OFC	> 0.35 KU/L	93%	17%	63%	1.12
Peters et al. (2013) [74]	Unselected population from immunization sessions in Australia (Healthnuts-5276 children)	Mean age 12 months	370 open OFC	≥ 34 KU/L	14% (95% CI 8–21)	99% (95% CI 96–100)		14
Eller and Bindslev-Jensen (2013) [85]	Patients investigated for peanut allergy in a tertiary allergy centre	Mean 5.6 years (range 1–26 years)	205 peanut food challenges (165 OFC, 40 DBPCFC)	≥ 2.6 KU/L	76%	80%		3.8
				> 16.7 KU/L	43%	100%		∞

Many studies has suggested specific cut-offs demonstrating the 95% positive predictive value (95% PPV) and 95% negative predictive values (95% NPV) of SPT or sIgE tests. However, these figures are population dependent and not transferrable to other populations seen routinely in one's individual clinic. However, these figures are often quoted in the literature and utilized. Likelihood ratios (LR) on the other hand are not meant to be population dependent, so LRs are transferrable to most populations. Utilizing LRs suggest that a LR ≥ 10 is strongly suggestive of nut allergy, and a LR ≤ 0.1 is strongly suggestive of no allergy. As a general rule, the higher the SPT or sIgE, the more likely it is to be allergy. However, even with the above information these test results cannot be taken in isolation of the clinical context.

Table 4. Allergen components for individual nuts [87]

	Storage proteins			Pathogenesis-related proteins				
	11s Albumin	7s globulin	2s Albumin	PR-10 Bet v 1 homologues	PR-14 nsLTP	Oleosin	Profilin	Defensin
Peanut	**Ara h 3**	**Ara h 1**	**Ara h 2**	**Ara h 8**	**Ara h 9**	Ara h 10	Ara h 5	Ara h 12
			Ara h 6		Ara h 16	Ara h 11		Ara h 13
			Ara h 7		Ara h 17	Ara h 14		
						Ara h 15		
Almond	Pru du 6				Pru du 3		Pru d 4	
Brazil nut	Ber e 2		**Ber e 1**					
Cashew	**Ano o 2**	Ano o 1	**Ano o 3**					
Hazelnut	**Cor a 9**	Cor a 11	**Cor a 14**	**Cor a 1**	**Cor a 8**	Cor a 12	**Cor a 2**	
						Cor a 13		
Pecan	Car 1 2		**Car I 1**					
Pistachio	Pis v 2	Pis v 3	**Pis v 1**					
Walnut	Jug r 4	**Jug r 2**	**Jug r 1**		**Jug r 3**			

Bold denotes whether it is commercially available.

Specific IgE or SPT to non-index nuts. Children with one nut allergy have a significantly increased risk of allergy to other nuts and often do not have any history of ingestion or have not consumed the nut for a considerable length of time. Performing SPT or sIgE to the other nuts in this situation may be helpful. If the weal diameter is large (equal to and >8 mm) or sIgE is high, then allergy is likely. Similarly if the SPT is negative or sIgE < 0.35 KU/L, then clinical allergy to those nuts is unlikely [107, 108]. Skin prick test weals 3–7 mm are indeterminant as patients could be tolerant or allergic [109]. A food challenge may be required to make a definitive diagnosis depending on the management plan agreed between the clinician and patient. Testing for IgE to nuts which are tolerated in the diet should be avoided.

Diagnostic peanut/tree nut challenge. Oral food challenges to nuts may be required occasionally in clinical practice to make a definitive diagnosis (see Figs 1 and 2). Challenges need to be performed in an appropriate setting with access to resuscitation equipment [110]. Such challenges should be performed by competent and trained staff with experience in food allergy and the skills to manage acute allergic reactions (including anaphylaxis). There also needs to be appropriate governance for food challenges such as clear guidelines on whom to challenge and protocols in place for undertaking challenge tests. An example of a challenge protocols for peanut is found in Appendix 1.

Quality of life/burden

There is evidence that food allergy is associated with increased stress and anxiety in children and an impaired quality of life (QoL), even compared to other chronic conditions such as diabetes [1, 112, 113]. This is related to constant fear of a severe/fatal allergic reaction when eating, the burden of constant vigilance when making food choices and the resulting social restrictions.

The impact of peanut allergy is not exclusive to the child but also impacts on other members of the family [112, 114]. Therefore, psychological impact and QoL of children with nut allergy should be considered.

Management

A comprehensive management plan is essential and should include advice on avoidance of nuts, individual nut recognition, treatment of allergic reactions and provision of, and training in the use of emergency medications including adrenaline self-injectors. Detection and management of allergic comorbidities, particularly active management of asthma, are especially important, because of the association between poor asthma control and severe allergic reactions.

Additionally, in nut-allergic children the management plan needs to be delivered to the wider family (e.g. grandparents if appropriate, nursery, preschool and school). It is also essential to include and establish links with healthcare professionals who provide education of staff in schools and early years settings. Reactions to accidental exposures are frequent, but with good management, further reactions can be reduced in both frequency and severity.

Dietary management

All patients and their families/carers require clear information on nut avoidance. Dietitians can play a key role in educating patients and families on how to avoid nuts and

Table 5. Diagnostic value of sIgE to Peanut Component Ara h 2

Author	Patient group	Ages	Methods	Ara h 2 IgE Cut-off (KU/L)	Sensitivity	Specificity	Positive predictive values (PPV)	LR
Bernard et al. (2003) [78]	Patients seen in allergy clinic with suspected peanut allergy	Median 4.5 years (range 1.5–16 years)	96 open OFC	≥ 0.35	71%	85%	94%	4.7
				≥ 1	64%	95%	98%	12.8
				≥ 5 (Enzyme Allergosorbent test)	50%	100%	100%	∞
Ebisawa et al. 2012) [82]	Children with suspected peanut allergy referred to an allergy clinic	Median age 6 years (range 2–13 years)	57 open OFC	≥ 0.35	88%	84%	82%	5.5
				≥ 0.66 (ImmunoCAP)	88%	90%		8.8
Klemans et al. (2013) [94]	Children with suspected peanut allergy visiting an allergy clinic	Median 6 years (interquartile range 4–8 years)	100 children had OFC (100 randomly selected from 200 children)	≥ 0.2	94%	66%	71%	2.76
				≥ 0.35	91%	72%	74%	3.25
				≥ 2	70	91%	87%	7.78
				≥ 10 (ImmunoCAP)	43	100%	100%	∞
Dang et al. (2012) [83]	Unselected population from immunization sessions in Australia (Healthnuts-5276 children)	Age 11–15 months old	200 randomly selected (100 with PA based on open OFC and 100 peanut tolerant based on open OFC)	≥ 0.35	81% (95% CI 72–88)	93% (95% CI 86–97)		11.6
				≥ 1.19 (ImmunoCAP)	60% (95% CI 50–70).	98% (95% CI 93–100)		30
Nicolaou et al. (2010) [17]	Population-based cohort and 12 further patients with peanut allergy from clinic	7–14 years old	OFC in 69 patients. 12 patients with diagnosis based on convincing Hx and PN SPT ≥ 8 mm or pN sIgE ≥ 15 KU/l were also included	≥ 0.35	100	96		25
				≥ 0.87 (ImmunoCAP)	90	100		∞
Eller and Bindslev-Jensen (2013) [85]	Patients who were routinely investigated for peanut allergy in a tertiary allergy centre	Mean 5.6 years (range 1–26 years)	205 peanut OFC (165 open OFC, 40 DBPCFC)	≥ 0.35	89	60		2.2
				≥ 1.28	76	97		25.3
				> 1.63 (ImmunoCAP)	43	100	100	∞
Lieberman et al. (2013) [84]	Children referred with suspected peanut allergy (Sweden and United States)	Median age 11.7 years	167 OFC	≥ 0.35 (ImmunoCAP)	80	92	94	10
Keet et al. (2013) [95]	Subjects with suspected peanut allergy	Mean age 7 years (range 3–19 years)	60 OFC	≥ 0.23	92.3% (74.9–99.1)	60% (42.1–76.1)	63.2 (46–78.2)	2.3
				≥ 0.35	88.5% (69/8–97.6)	71.4% (53.7–85.4)	69.7 (51.3–84.4)	3.1
				≥ 2 (ImmunoCAP)	23.1 (9–43.6)	94.3 (80.8–99.3)	75 (34.9–96.8)	4.1

Many studies have suggested specific cut-offs demonstrating the 95% positive predictive value (95% PPV) and 95% negative predictive values (95% NPV) of SPT or sIgE tests. However, these figures are population dependent and not transferrable to other populations seen routinely in one's individual clinic. However, these figures are often quoted in the literature and utilized. Likelihood ratios (LR) on the other hand are not meant to be population dependent, so LRs are transferrable to most populations. Utilizing LRs suggest that a LR ≥ 10 is strongly suggestive of nut allergy, and a LR ≤ 0.1 is strongly suggestive of no allergy. As a general rule, the higher the SPT or sIgE, the more likely it is to be allergy. However, even with the above information these test results cannot be taken in isolation of the clinical context.

how to give advice on an individual basis. This should also be supported by the relevant written information.

Food labelling

Two main types of labelling exist on pre-packed food: the first is the ingredients list. Legislation (Consumers Regulation (EU) No. 1169/2011) requires the following specific nut terms to be highlighted in the ingredients list: peanuts, almond, hazelnut, walnut, cashew nut, pistachio nut, Brazil nut, pecan nut, macadamia nut or Queensland nut [115]; the second is the 'may contain' or 'not suitable for' statements referred to as precautionary allergen labelling (PAL). This type of caution is voluntary and may or may not refer to a specific nut type [116] and is not required to be highlighted.

Patients should be advised to read both the ingredients list and the PAL on any food product they intend to consume even if it has been consumed before as recipes can change. Patients should be made aware that foods imported from outside the EU may lack allergy labelling.

Precautionary allergen labelling

Food manufacturers should make a thorough risk assessment, adhere to good manufacturing practice and provide information about the risk of nut contamination; but this often results in the use of PALs. No consistent terminology for PAL exists, and patients often find them difficult to interpret. Foods with and without PAL both carry a low risk of nut contamination. However, some foods with PAL such as snack foods are likely to pose a higher risk. Advice should be individualized; those with a history of very severe past reactions, uncontrolled asthma or a very low threshold for reactivity may benefit from more strict avoidance of PAL food. Patients with clinically diagnosed PFS do not need to avoid foods with PAL.

Eating out

Legislation requires restaurants, and cafes to provide clear information about nuts in non-packaged foods. When eating out and food is prepared by a third party, it is important to consider potential risks. In restaurants, patients should liaise directly with staff to ensure they can provide a nut-free meal. In the United States and the UK, allergic reactions to nuts have occurred with food bought from Asian restaurants, ice cream shops and bakeries [117]. The UK Food Standards Agency provides resources for food businesses including technical guidance, online training tools and materials for businesses and consumers [118].

Single vs. all nut exclusion

Many healthcare providers advise patients with peanut allergy to also avoid tree nuts [3, 119, 120].

This recommendation aims to simplify the message and improve avoidance while eating in schools and restaurants. It also addresses the issues of cross-contamination, substitution and misidentification of nuts. There is an increased incidence of tree nut allergy in patients with peanut allergy. A comprehensive management plan, including advice to avoid all nuts, reduces the annual risk of an accidental reaction after exposure to peanut to 3% [3]. Other studies have shown an annual prevalence of accidental reaction to be 14–45% although these studies have not explicitly reported on the dietary advice provided [50, 121, 122]. Similarly in patients with tree nut allergy, it is recommended that they avoid other tree nuts and peanuts, unless they are known to be tolerant or have negative tests.

Clearly, complete nut avoidance including avoiding all pre-packed and non-packed snack foods as well as products with PAL is the safest approach and, if followed, results in very few accidental reactions. However, in practice this is difficult to achieve and can result in a significant restriction of certain food products. There are also nutritional, cultural and immunological arguments for allowing consumption of other nuts [123]. If a patient is already consuming a nut they are not allergic to, it would appear reasonable to continue consuming it on a regular basis, but to be aware of the risks of cross-contamination and PAL. Safe nuts should still be avoided within a restaurant environment, due to the risk of misidentification of nuts or inadvertent substitution of other nut types.

Whichever dietary approach is undertaken, it is essential to have an individualized plan for each patient and the family provided with sufficient information to enable them to be fully informed so that they can manage their nut allergy as effectively as possible. It also needs to be recognized that increased resources may be required to deliver individualized management plans. Management plans should be reviewed regularly as family circumstances change, for example transition from secondary school to higher education/employment.

Nut-specific advice

Peanut allergy often coexists with tree nut allergy (see section on risk factors for development on nut allergy) and therefore this will need to be considered in the management plan employed. Peanut-allergic individuals may be sensitized to legumes (soya, pea and chickpea); however, the rate of allergy is low in the UK and USA. In addition a specific tree nut allergy can coexist with another tree nut allergy. Allergy to cashew nut is

commonly associated with co-sensitization and allergy to pistachio [124–126]. Cashew nut is often present in pre-packaged pesto sauce.

There is evidence for similar co-sensitization between walnuts and pecan nuts [127]. Medicines containing peanut oil are unlikely to cause an allergic reaction. Arachis oil BP is made from refined peanut oil, containing clinically insignificant quantities of peanut protein.

Medical management

Provision of emergency medication

Oral antihistamines. All patients should be supplied with oral antihistamines. Long-acting antihistamines with rapid onset of action, e.g. cetirizine are preferred. These should be used at the onset of any mild/moderate reaction, not requiring adrenaline.

AAI provision and training. The decision to provide an AAI should follow a risk assessment. The allergist should lead on advice and should consider and discuss views of the family/patient. Clear indications to provide injectable adrenaline include any previous episodes of anaphylaxis to a nut. Published BSACI guidelines advise on the provision of AAI [128]. Patients with PFS normally do not require an AAI, unless there have been severe reactions or another indication for an AAI is present. UK data suggest that children who are not at risk are being prescribed AAI [129]. All at-risk patients will require adrenaline to treat an episode of anaphylaxis. However, most patients will only need one injection of adrenaline [128, 130]. The decision to recommend one or more AAIs must be individualized with each patient and also requires a thorough risk assessment [128]. The provision of AAI training does significantly improve the ability to use an AAI effectively but over time, this ability diminishes [131–133]. In addition, specific training is required prior to switching between brands of any AAI device [134]. Even though AAI provision has greatly increased over recent years [129], patients often do not carry prescribed AAIs with them, when outside the home environment [5, 50, 135]; encouraging patients to carry AAI at all times is an essential part of training. The provision of written emergency action plans is essential [130, 136–138].

Patient follow-up. The role of follow-up for primary nut allergy is the provision of ongoing education on preventing and managing future reactions (see Box 2). Allergy tests can be repeated periodically depending on resources and patient's symptoms. Follow-up in a patient with PFS is often not required unless there has been a severe reaction.

Box 2. Management at follow up appointments

1 Take history of reactions to inadvertent exposure to nut and identification of new allergies
2 Ongoing education on nut avoidance measures
3 Resolution of nut allergy- Periodic measurement of nut SPT +/- nut sIgE. Resolution may have occurred if there has been no reaction following accidental ingestion or there has been a significant reduction in SPT/sIgE (see figure 1 and 2). Testing can also be used to determine tolerance or allergy to other nut
4 Training for emergency treatment of accidental reactions, including reviewing written emergency action plans and AAI retraining. Emphasis on carrying AAI on person at all times
5 Management of co-morbidities, especially asthma (including asthma management plan), rhinitis and eczema

Schools

Section 100 of the Children and Families Act 2014 [139] places a duty on governing bodies of maintained schools, proprietors of academies and management committees of pupil referral units (PRUs) to make arrangements for supporting pupils at their school with medical conditions. In the case of food allergy, specific recommendations have been provided by an EAACI/GA2LEN task force (Box 3) [140].

Box 3. Recommendations for schools adapted from Ref. [140]

1 Ensure there is a system to identify food-allergic children to staff, especially catering or new/temporary staff
2 Clear allergen labeling should be available for any food provided by the school. Menus could be made available to the family in advance with ingredients clearly stated
3 Staff should be made aware of how to handle potential food allergens safely, including effective cleaning of surfaces and utensils
4 Schools should consider the impact of provision of foods containing nuts on nut allergic children
5 Discourage trading or sharing food, and sharing utensils or containers.
6 Ensure lessons avoid the use of provoking food allergens (e.g. using peanuts during science or art lessons)
7 Educate staff and pupils regarding allergen avoidance and recognition of food allergy reactions
8 Separating children from their peers during mealtimes is unnecessary, provided the other measures described are instituted

Natural history

There are no data on resolution and long-term outcome of patients with PFS with respect to nuts. Therefore, this section specifically focuses on primary nut allergy. There are few data on the natural history

of both peanut allergy and tree nut allergy to determine whether patients become tolerant. In children under 2 years of age diagnosed with peanut allergy, 21% outgrew their allergy [111, 141, 142]. The weakness of all these studies is that the initial PA diagnosis was not based on strict criteria such as a positive OFC. One more recent study confirmed PA at 1 year of age by OFC and by 4 years of age, 22% had resolved PA [143]. A decreasing SPT weal size predicted tolerance, whereas an increase weal size predicted persistence. Looking more longitudinally, spontaneous resolution of peanut allergy predominantly occurred by 6 years of age and occurs at a much lower frequency after 10 years of age [144]. One study on tree nut allergy examined the natural history of tree nut allergy in children and approximately 9% of children outgrew their tree nut allergy [145]. This must be interpreted with caution as many had a diagnosis based on sensitization only and patients were carefully selected to determine resolution.

Prevention of nut allergy

Early introduction of peanuts into the weaning diets of atopic infants at high risk of peanut allergy can prevent the development of peanut allergy. A single UK study suggests infants with egg allergy or severe eczema and a negative peanut oral challenge benefit from consuming peanut products regularly (at least 2 g of peanut protein 3 times a week) to prevent the development of peanut allergy [36]. There was a 70–86% risk reduction of developing peanut allergy and it was greatest in the SPT-negative group (SPT = 0 mm). No conclusion can be made for children with SPT > 4 mm as they avoided peanut. Similarly, it is not known if prevention of PA would result if smaller quantities of peanut were consumed on a weekly basis. There is no evidence to support the delayed introduction of peanut into the infant's diet. In exclusively breastfed infants from the general population who were randomly assigned to the early introduction of six allergenic foods including peanut from 3 months, or to the current practice recommended in the UK of exclusive breastfeeding to approximately 6 months of age [15], there was no significant difference in peanut allergy in the early-introduction group. In those that achieved the required peanut ingestion, the prevalence of peanut allergy was however significantly lower.

Health economic benefits and public health methods of administering these approaches have not been established. For infants who do not have eczema, asthma or other food allergies, it is reasonable for them to have peanut butter cautiously introduced into their diet at home. There are no data on prevention of tree nut allergy.

Testing siblings of nut-allergic children

The prevalence of peanut allergy in siblings of children with peanut allergy is 5–9%, [11, 146–148]. In siblings of children with peanut allergy who would like to introduce peanuts into their diet and do not have eczema, asthma or other food allergies, it is reasonable for them to cautiously introduce peanut into their diet at home. In higher risk siblings or high level of parental anxiety, a negative SPT or sIgE will exclude allergy [148].

Positive tests may require oral challenge which is time- and resource consuming. Each case needs to be assessed on its merits after a careful assessment by a clinician. There are no data available about tree nut allergy.

Immunotherapy

Clinical trials of peanut oral immunotherapy (OIT) have shown promising results [149–152]. Various routes of allergen administration are being explored, including the oral (OIT), sublingual (SLIT) and epicutaneous (EPIT) route. Although SLIT and EPIT appear to have a favourable safety profile, SLIT appears ineffective, and the effect of desensitization with EPIT is unknown [153]. Further evaluation of the use of immune modulators (anti-IgE and probiotics) in peanut OIT is required [150, 154].

The acquisition of long-term tolerance (where participants are able to consume peanut *ad lib*, without any need for ongoing therapy) vs. sustained unresponsiveness (ability to tolerate substantial gaps in nut ingestion) vs. transient desensitization (an increase of the threshold of reactivity to peanut, which requires regular consumption in order to be maintained), following the administration of peanut immunotherapy, is under investigation [155].

Future work and research

- The role of sIgE components in tree nut allergy
- The role of basophil activation test in clinical practice for diagnosis of nut allergy and determining severity and thresholds of reactions.
- Long-term outcome of patients undertaking complete nut avoidance compared to single nut avoidance
- Provision of improved information for consumers on the risk of potential nut contamination in pre-packed foods
- Prevention of peanut and tree nut allergy in clinical practice
- Description of long-term outcomes from peanut immunotherapy
- Development of standardized immunotherapy products that are well tolerated and effective

- Tree nut immunotherapy
- Cost-effectiveness of approaches to exclusion/diagnosis of nut allergy in siblings of nut-allergic patients
- Working with industry, manufacturers, restaurants to promote a safe environment to eat for patients with nut allergy

This *guideline* informs the management of peanut and tree nut allergy. Adherence to this guideline does not constitute an automatic defence for negligence and conversely non-adherence is not indicative of negligence. It is anticipated that this guideline will be reviewed 5 yearly.

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Appendix 1 Examples of peanut challenge protocols

A peanut challenge protocol is provided as an example of current clinical practice. It is not intended to be proscriptive and may be adjusted according to local practice and experience. The challenge doses should be adjusted according to the clinical history. The lower doses may be adjusted, so that a lower dose than 1/16th is used as the first ingested dose. The total dose should equate to a portion considered appropriate for the patient. This would equate to approximately 15–20 peanuts in older children and adults, so an extended challenge may be required. Whole nuts should not be used in challenges in children under 3 years due to the risk of choking. An alternative amount of smooth peanut butter may be used. An interval of 15 min between initial doses is usually sufficient. It should also be emphasized that continued regular ingestion should be recommended following a negative challenge [111].

Dose	Description	Time	Reaction (Y/N)
1	Cut peanut to touch lower oral mucosa 15-m observation	:	
2	1/16th of a peanut half, eaten 15-m observation	:	
3	1/8th of a peanut half, eaten 15-m observation	:	
4	1/4 of a peanut half, eaten 15-m observation	:	
5	1/2 of a peanut half, eaten 30-m observation	:	
6	1 entire peanut half, eaten 30-m observation	:	
7	1 whole peanut (2 halves) eaten 30-m observation	:	
8	2 whole peanuts, eaten 30- to 60 m observation	:	
9	5 whole peanuts, eaten Minimum 60 m observation	:	

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article: