

Challenge-confirmed peanut allergy in older patients: Performance of skin tests, specific immunoglobulin E, and ara h 2



Peanut allergy is a major public health issue and dramatically impacts on quality of life of those affected.^{1,2} Diagnosis of peanut allergy involves history, skin prick testing (SPT), specific immunoglobulin E (sIgE) to whole peanut, component-resolved diagnostics, and oral food challenges (OFCs). sIgE to the storage protein Ara h 2 (dominant allergen) provides improved diagnostic accuracy compared with whole peanut sIgE.³ Nevertheless, OFC remains the “gold standard” to either confirm or exclude allergy. To avoid OFC, various SPTs and sIgE cut-offs have been described.^{4–7} Based almost exclusively on studies in infants or children, they have been widely extrapolated into clinical use for adult patients without validation. The predictive value of the SPT and sIgE in older patients remains uncertain, especially in the absence of a convincing history or when there is low pretest probability. In this retrospective study, we reviewed the usefulness of clinical parameters, SPTs, sIgE to whole peanut, and Ara h 2 in predicting the OFC outcome to determine optimal cut-offs for adolescent and adult patients.

We reviewed the clinical data and investigation results of patients referred for suspected peanut allergy who underwent OFC at Guy's and St Thomas' Hospital (London, UK) and Cambridge University Hospital (Cambridge, United Kingdom) NHS Foundation Trusts between 2007 and 2016. Patients with a clinical history suggestive of oral allergy syndrome (OAS) were clinically excluded.⁷ All patients underwent SPT with either commercially available solution (Allergopharma, Germany, or ALK, Denmark) or prick-to-prick testing with roasted peanuts. All staff performing SPTs were fully trained in standardized technique according to standard operating procedures established by the British Society for Allergy & Clinical Immunology.^{8,9} Whole peanut, Ara h 2, and Ara h 8 sIgEs were measured (ImmunoCAP, Phadia, Sweden). Patients with diagnostic uncertainty (inconsistent history and/or investigation results) were selected for graded OFC after evaluation by an allergist. These patients had a low-to-medium pretest probability and there were no absolute SPT or sIgE cut-offs. OFCs were considered positive if objective signs suggestive of an IgE-mediated response developed (eg, acute rash/urticaria, angioedema, and wheeze, or significant drop in peak flow rate, oxygen saturation, or blood pressure). The top cumulative OFC dose was 31.5 g of peanut. OFCs causing only oral pruritus, suggestive of OAS, were not considered positive.

Association analysis was performed with the χ^2 test, independent samples *t* test, and binary logistic regression. SPSS Statistics version 20 (IBM SPSS, Armonk, New York) was used to calculate the receiver-operating characteristic (ROC) curves for SPT and sIgE to whole peanut and Ara h 2.

Records were available for 64 patients (median, 20 [range, 12 to 82] years of age; male:female ratio, 1:1.8). In this cohort, 16 of 64 (25%) patients had a positive OFC: of which 11 of 16 (69%) had mucocutaneous (urticaria, angioedema, flushing, rash), 7 of 16 (44%) gastrointestinal (nausea, vomiting, abdominal pain), 7 of 16 (44%) respiratory (rhinitis, dyspnea, wheeze, stridor), and 2 of 16 (13%) cardiovascular (dizziness, syncope, hypotension) symptoms. Emergency treatment with antihistamines, corticosteroids, bronchodilators, and intramuscular adrenaline was administered in 15 (94%), 12 (75%), 3 (19%), and 2 (13%) patients, respectively.

Association analysis between patients with positive vs negative OFC showed that the positive OFC group had significantly larger mean SPT wheal diameter (7.9 [SEM, 0.8] vs 2.6 [SEM, 0.5] mm,

$P < .01$). Although the positive OFC group mean age was also younger (18.8 [SEM, 1.0] vs 27.5 [SEM, 2.1] years, $P < .01$), the difference in SPT remained significant after adjustment using multivariate logistic regression ($P = .004$).

In contrast, there was no difference in whole peanut (6.8 [SEM, 4.1] vs 4.3 [SEM, 1.3] kUA/L, $P = .45$) and Ara h 2 (3.4 [SEM, 2.5] vs 0.1 [SEM, 0.1] kUA/L, $P = .21$) sIgE values. Ara h 8 results were available for 47 patients and there was no significant difference in Ara h 8 values between the groups (4.06 [SEM, 2.16] vs 8.84 [SEM, 3.08] kUA/L, $P = .30$).

There were also no differences in other variables between patients with positive and negative OFCs, including gender (male, 75% vs 50%, $P = .21$), atopic dermatitis (56% vs 38%, $P = .25$), allergic rhinitis (69% vs 56%, $P = .38$), asthma (63% vs 48%, $P = 0.31$), tree (63% vs 54%, $P = .77$), and grass pollen (75% vs 63%, $P = .36$) sensitization, or manifestations during index reactions (mucocutaneous: 63% vs 38%, $P = .08$; respiratory: 31% vs 25%, $P = .62$; gastrointestinal: 19% vs 13%, $P = .53$; cardiovascular: 0% vs 4%, $P = .41$).

Similarly, ROC curve analysis for SPT demonstrated excellent performance with area the under curve (AUC) = 0.945 ($P < .01$). In contrast, the AUCs for whole peanut and Ara h 2 sIgEs were only 0.489 ($P = .26$) and 0.779 ($P < .01$), respectively (Fig 1). Based on the ROC curve, the optimal cut-off, maximizing both sensitivity and specificity, for SPT was ≥ 5 mm. All patients with a positive OFC had SPT ≥ 5 mm (sensitivity = 100%), and 37 of 44 patients with a negative OFC had SPT < 5 mm (specificity = 84%).

In this selected cohort of predominantly younger adults, SPTs were superior in predicting allergy than sIgEs to whole peanut or Ara h 2. Peanut allergic patients had significantly larger SPTs. The optimal cut-off was ≥ 5 mm with 100% sensitivity and 84% specificity.

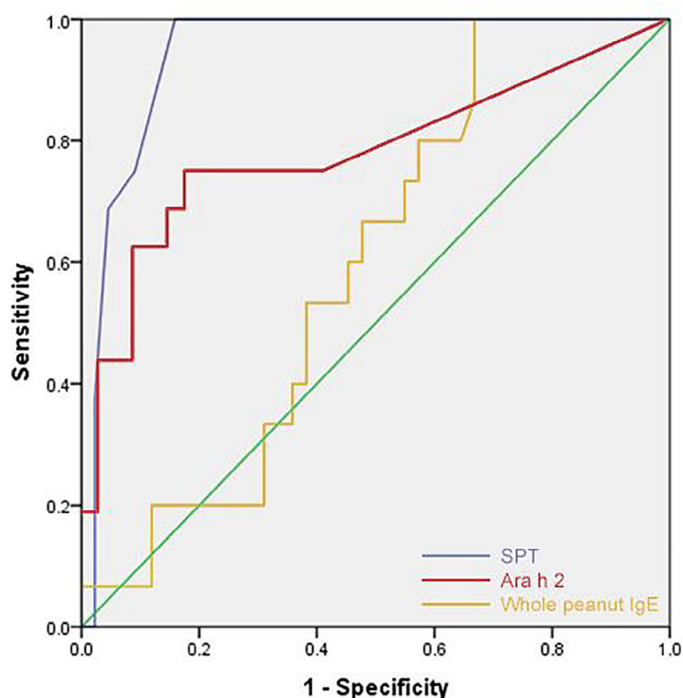


Figure 1. Receiver-operating characteristic curves for skin prick test, Ara h 2, and whole peanut specific immunoglobulin E, and performance of various skin prick test cut-offs.

In contrast, a ≥ 7 -mm cut-off yielded a greater specificity of 95%, but lower sensitivity of 69%.

There is no universal definition of “optimal” cut-offs. The 95% and 50% positive predictive values are commonly quoted, but these are influenced by disease prevalence and they are specific to their respective study cohorts. This may also partly explain why our findings contrast with those based primarily on pediatric studies.^{4–7} In our study, we objectively derived our optimal cut-off from the ROC curve that maximized both sensitivity and specificity. We also excluded patients with history or OFC outcomes suggestive of OAS, which can be a potential confounder. However, because our cohort was selected for suspected peanut allergy (ie, higher pretest probability), it is likely our “optimal” cut-off may not be applicable to unselected individuals.

Further larger, population-based studies are required to determine more generalizable age-specific diagnostic SPT and sIgE cut-offs for patients with suspected peanut allergy. There was a wide variation in sIgEs to whole peanut and Ara h 2, making them less useful in predicting true peanut allergy. More importantly, it is crucial to individualize risk-benefit assessment prior to OFC. We would caution against overgeneralization of specific cut-offs and recommend considering age-appropriate thresholds such as SPT ≥ 5 mm in this selected cohort during investigation of peanut allergy in adolescent and adults.

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Cross-reaction of recombinant termite (*Coptotermes formosanus*) tropomyosin with IgE from cockroach and shrimp allergic individuals



The incidence of allergic diseases appears to be increasing and poses substantial health, psychological, and economic burdens.^{1,2} In the United States, asthma affects approximately 40 million individuals, and 15 million people have food allergies. Cockroaches are considered a major class of airborne allergens that contribute to allergic disease in urban areas worldwide.³ Tropomyosin is a major allergen in cockroaches, house dust mites, and shellfish and is considered a panallergen.⁴ Cockroach tropomyosin is a 31-kDa protein with multiple IgE-binding sites that cross-react with IgE from shrimp allergic patients.

Cockroaches and termites are closely related evolutionarily within the order Blattodea, and they have some behavioral similarities.⁵ Although the German cockroach *Blattella germanica* resides in the Blaberoidea superfamily, the American cockroach *Periplaneta americana* and the Formosan subterranean termite *Coptotermes*

formosanus reside in the Blattoidea superfamily albeit within different families. Termites are a significant pest and typically live within and around urban centers, especially in the Southern United States. Termite colonies can be made up of millions of insects, which can lead to the accumulation of a high concentration of potential allergens. Humans may come into contact with termite allergens when a home is actively infested with termites that defecate potentially allergenic frass (termite droppings) or create mud tubes for travel and during termite mating season when they are attracted to light sources and swarm in populated areas.

Recently, whole body extracts from the Formosan subterranean termite *Coptotermes formosanus* have been demonstrated to cross-react with cockroach-specific antibodies and to compete for IgE binding in serum from cockroach allergic individuals.⁶ Tropomyosin contained within whole body extracts of *C formosanus* was implicated as one of the cross-reacting proteins. *C formosanus* tropomyosin (accession No. AGM32377.1) is predicted to be a 256-amino acid protein (29,354 Da) and is a member of the eukaryotic tropomyosin 1 superfamily. *C formosanus* tropomyosin is nearly identical to tropomyosin from American (99% identity to Per a 7) and German (98% identity to Bla g 7) cockroaches. It also has significant percentage identity to tropomyosins from human body lice (Ped h 7, 93% identity), house dust mite (Der f 10, 81% identity), and multiple crustacean tropomyosins, including tiger shrimp (Pen m 1, 83% identity), with which it shares sequence similarities to several mapped shrimp tropomyosin IgE epitopes.⁷

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