

Letter to the Editor

Diagnostic accuracy of skin prick testing in children with tree nut allergy

To the Editor:

We read with interest the article by Fleischer et al¹ on the natural history of tree nut allergy, which demonstrated how allergists could be guided in selecting the appropriate timing for tree nut challenges based on predictive decision points for tree nut-specific serum IgE. However, allergists in Australia,² Britain,³ and France,⁴ among others, often rely on skin prick testing (SPT) in the diagnosis of food allergy. We would therefore like to share our experience in defining cutoff values for SPT wheal diameters that predict positive challenge outcomes to tree nuts and sesame. We have also included previously published data for

peanut² because this allergy commonly occurs in children and adults with tree nut allergy.

We performed an analysis of the computerized records of all patients who underwent SPT and challenges to peanut, tree nuts, and/or sesame between 1995 and 2005 at a university-affiliated children's allergy center. SPTs to cashew, hazelnut, walnut, pecan, Brazil nut, and almond were performed using a single-lancet technique with commercial allergen extracts (Dome-Hollister-Stier, Spokane, Wash).⁵ Testing for pistachio nut and sesame seed (tahini) was performed by the prick-to-prick technique with fresh foods.⁵ Histamine (1 mg/mL) and a negative control solution were used for internal validation. SPTs were applied on the back of infants or the forearm of older children. The SPT wheal diameter (mm) to

TABLE I. Diagnostic accuracy of skin prick wheal diameter in children with tree nut allergy aged 4 mo to 19 y

Food item	Wheal diameter (mm)	Sensitivity	Specificity	PPV	NPV	LR ⁺
Tree nut type						
Cashew	0	—	—	—	0.89	0.00
N = 86	≥3	0.96	0.52	0.82	0.87	2.01
	≥6	0.68	0.96	0.98	0.57	17.1
	≥8	0.39	1.00	1.00	0.42	∞
Hazel	0	—	—	—	1.00	—
N = 58	≥3	1.00	0.36	0.31	1.00	1.56
	≥6	0.75	0.86	0.6	0.92	5.25
	≥8	0.08	1.00	1.00	0.79	∞
Walnut	0	—	—	—	0.95	0.00
N = 29	≥3	1.00	0.43	0.64	1.00	1.75
	≥6	0.50	0.79	0.7	0.61	2.33
	≥8	0.14	1.00	1.00	0.54	∞
Almond	0	—	—	—	0.89	—
N = 28	≥3	0.67	0.52	0.14	0.93	1.39
	≥6	0.33	0.84	0.20	0.91	2.08
	≥7	0.33	0.92	0.33	0.92	4.17
Pistachio	0	—	—	—	1.00	—
N = 22	≥3	0.91	0.60	0.71	0.86	2.27
	≥6	0.55	0.90	0.86	0.64	5.45
Pecan	0	—	—	—	1.00	—
N = 14	≥3	0.5	0.07	0.07	0.50	0.54
	≥7	0.5	0.96	0.75	0.90	12.5
Brazil nut	0	—	—	—	1.00	—
N = 10	≥3	0.75	0.25	0.17	0.83	1.00
	≥8	0.75	0.95	0.75	0.95	15
Sesame	0	—	—	—	0.50	—
N = 60	≥3	0.94	0.40	0.74	0.80	1.57
	≥6	0.50	0.85	0.86	0.49	3.33
	≥8	0.26	0.98	0.95	0.43	10.78
Peanut	0	—	—	—	0.90	—
Age > 2 y	≥3	0.95	0.51	0.64	0.92	1.93
N = 551	≥6	0.69	0.91	0.87	0.76	7.25
	≥8	0.3	0.99	0.96	0.63	28.4
Age ≤ 2 y	0	—	—	—	0.92	—
N = 48	≥3	0.82	0.79	0.67	0.90	3.88
	≥4	0.74	1	1	0.85	∞

N, Number of challenges.

histamine was measured at 10 minutes and to allergens at 15 minutes after application. Irregular shapes were recorded as the mean of 2 perpendicular diameters. The SPTs were analyzed against formal oral food challenges performed within 3 months of skin testing. The challenge procedure for tree nuts and sesame was adapted from our previously described method for peanut.² In brief, $\frac{1}{8}$ to $\frac{1}{4}$ teaspoon increments of finely ground unsalted nuts were administered at intervals of 20 to 30 minutes, as tolerated, until a total dose of 20 g was reached. Double-blind, placebo-controlled challenges were performed only if the open challenge was inconclusive. A negative challenge outcome was reviewed by telephone survey on day 7 and a clinical assessment on day 28. On day 7, a standard set of questions was asked to ensure the compliance with the challenge protocol and to verify any late symptoms. On day 28, patients were assessed as to whether true tolerance to the tree nut in question was achieved.

We studied 906 tree nut and peanut challenges in 680 consecutive children and teenagers, ages 4 months to 19 years, referred for assessment of suspected nut allergy. Based on our data, the traditional 3-mm wheal cutoff for a negative SPT was associated with a high rate of false-positive and false-negative results. The diagnostic accuracy of SPT increased when higher cutoff wheal diameters were used. We identified the SPT wheal diameters that predicted a positive food challenge with >95% accuracy (cashew, hazel nut, walnut, and sesame: ≥ 8 mm). We could not confidently determine the 95% positive predictive value (PPV) for almond, pistachio, pecan, and brazil nut. For pecan (≥ 7 mm) and brazil nut (≥ 8 mm), the PPV remained below 95%, despite a high specificity and high positive test likelihood ratio. This may be a result of a relatively small sample size for some of the tree nuts. These findings are summarized in Table I.

Using these predictive SPT decision points, the need for a formal oral food challenges to make a definitive diagnosis in our cohort was reduced by 33% (peanut), 56% (tree nuts), and 53% (sesame), respectively (data not shown). Monitoring for possible development of tolerance by repeated SPT may enable clinicians to assess resolution of tree nut allergy over years. SPT offers advantages in terms of cost and the turnover time of results. It is important to emphasize that the SPT wheal diameter correlates with the likelihood of a positive nut challenge but not with the clinical severity of adverse reactions.³ SPT should be interpreted in the context of specific techniques. The single-headed lancet, used in our study, reportedly has a lower intraoperator and interoperator variability than other methods, such as the bifurcated (as in the study by Fleischer et al¹) or multiheaded lancet systems.⁶ Skin reactivity is known to vary with age.⁷ This is reflected in separate cutoff values for SPT wheal diameters to peanut in children <2 years or older.² Similar age-specific cutoff values are not yet available for tree nuts or sesame. Commercial SPT extracts are often not standardized, and the concentration of major allergens, such as Cor a 8 (lipid transfer protein), may vary significantly between different manufacturers or even within batches of the same

product.⁸ Our findings may therefore be limited to extracts by Dome-Hollister-Stier and may not be transferable to extracts by other manufacturers. This highlights the need for standardization of the allergen content of diagnostic SPT extracts.

Positive and negative predictive values (NPVs), as presented in Table I, are a convenient way of expressing the probability, for instance, that according to a test cutoff value, the patient does or does not have a particular condition. One important limitation of PPV and NPV is that they vary according to the prevalence of the condition in the population. Likelihood ratios (LRs) may provide an alternative to predictive values, although the interpretation of LR is less intuitive. The LR expresses the likelihood of a positive test in a patient with nut allergy in relation to the likelihood of the same result occurring in a patient without allergy. Clinically useful tests generally have a LR of greater than 10.⁹ The advantage of this statistical model is that the LR is independent of the prevalence of the condition tested. It can therefore be used for patients in tertiary care as well as in the primary care setting.

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