
The predictive value of a positive prick skin test to peanut in atopic, peanut-naïve children

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Background: Although allergy testing before food ingestion is generally not recommended, many peanut-naïve children undergo prick skin tests (PSTs) to peanut because of atopy. Children with positive PSTs are generally advised to avoid peanuts either indefinitely or until a definitive diagnosis is made through challenge.

Objective: To describe peanut challenges in atopic, peanut-naïve children with PST to peanuts ≥ 3 mm and the PST properties in this population.

Methods: Between 1994 and 2001, 47 patients were identified who had a positive peanut PST, no previous peanut ingestion, and had undergone a peanut challenge.

Results: Forty-nine percent of the challenges were positive. The mean of the largest wheal diameter (95% confidence interval [CI]) of the PST in children having a negative and positive challenge was 6.3 mm (CI, 5.3 to 7.3) and 10.3 mm (CI, 8.9 to 11.8), respectively. At a PST cutoff of ≥ 5 mm, the sensitivity and negative predictive value (95% CI) was 100% (85.2 to 100) and 100% (29.2 to 100), whereas the specificity and positive predictive value (95% CI) was 12.5% (2.7 to 32.4) and 52.3% (36.7 to 67.5), respectively.

Conclusions: We show that 49% of atopic, peanut-naïve children sensitized to peanut developed allergic symptoms during oral provocation with peanut. Although the sensitivity of the PST at ≥ 5 mm for the detection of peanut allergy in this study was 100%, our small sample size limits the applicability of this value. Further investigation is needed to determine whether children with wheal diameters of 3 or 4 mm, perhaps coupled with low peanut-specific IgE, could undergo less resource-intensive, accelerated challenges.

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INTRODUCTION

With an estimated prevalence of approximately 1%,^{1–5} peanut allergy is one of the leading causes of food-related anaphylaxis in North America and Europe.⁶ In both North America and Europe, peanut allergy has become a serious public health concern, and there is a suggestion that the prevalence has increased over the past decade.⁵ Irrespective of the severity of the initial allergic reaction, subsequent reactions carry a lifelong risk of potential anaphylaxis.⁷ Therefore, it is not surprising that individuals with peanut allergy and the caregivers of children with peanut allergy have a heightened sense of anxiety regarding the risk of accidental peanut exposures and the severity of the allergic reaction that can occur.⁸

Despite the recent recognition that peanut allergy can resolve in a subset of patients, most peanut-allergic individuals retain the allergy indefinitely.^{7,9–11} Treatment is limited to exercising dietary vigilance to reduce the risk of accidental exposures and to the prompt recognition and treatment of allergic reactions with adrenaline. Accurate diagnosis of peanut allergy is necessary so that allergic patients can receive appropriate education about how to minimize the risks of an inadvertent exposure and appropriate instruction on self-administration of necessary medications.

The diagnosis of peanut allergy rests with the demonstration of either a positive prick skin test (PST) or specific IgE to peanut in the context of allergic symptoms following the isolated ingestion of peanut products. Prick skin testing to peanut generally has excellent sensitivity and negative predictive value if good quality extracts or crude peanuts are used, but the specificity and positive predictive value are very poor.^{12–14} Except in instances when isolated ingestion of peanut results in immediate allergic symptoms and the peanut PST is positive or when a history is not suggestive of immediate allergic symptoms and the PST is negative, the result of the PST to peanut has limited predictive value for true peanut allergy.^{12–15} The usefulness of performing a peanut PST in individuals who have never knowingly ingested peanut has not yet been established.

Some children undergo a PST with peanut despite never having eaten peanuts. Often, the tests were performed be-

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cause of parental anxiety resulting from peanut-allergic siblings or because of strong personal or family history of atopy or, in some instances, as part of a battery of allergy tests. Hourihane et al¹⁶ have demonstrated that the prevalence of peanut allergy in siblings of peanut-allergic children is 7%. In our center, children with strong personal or family history of atopy are advised to delay the introduction of peanuts until the age of 3 years; children without a strong history of atopy are not given specific instructions on age of introduction. Children who have not been exposed to peanuts and who have a negative PST to peanut are advised to gradually introduce peanuts at home at the parent's discretion. However, children with a positive PST, despite the absence of a history of peanut ingestion, are routinely offered peanut challenges. In some situations, particularly when the PST result was exceptionally large and the likelihood of true peanut allergy was consequently felt to be quite high, challenges may not have been offered by the treating physician, or the family may have declined the challenge. In these cases, the family was counseled on peanut avoidance measures and provided with auto-injectable epinephrine. Our study describes the results of challenges in atopic, peanut-naïve children with a PST result ≥ 3 mm to peanuts as well as the properties of the PST in this population.

SUBJECTS AND METHODS

Through a chart review of children offered peanut challenges at the Montreal Children's Hospital Allergy Clinic between 1994 and 2001, 47 patients were identified who had a positive PST to peanut and no antecedent history of peanut ingestion. Permission was obtained from the hospital's director of professional services to conduct the chart review. We have already published on challenges conducted on 16 of these patients.¹⁴

The PST was performed by specially trained pediatric allergy nurses. The PST was performed by standard technique, by placing a drop of commercial peanut extract on the volar aspect of the forearm and pricking through the drop. Glycerinated food extracts (1/10 Hollister-Stier, Toronto, Ontario, Canada) were pricked into the superficial layer of the skin with a smallpox scarification needle. Positive and negative controls were placed at least 2.5 cm apart. Histamine (1 mg/mL) was used as the positive control; saline was used as the negative control. Results were reported 12 to 15 minutes after the PST was placed. The result was reported as the greatest diameter of the wheal, recorded in millimeters. Positive tests were those where the greatest diameter of the wheal was at least 3 mm greater than the negative control.

In patients challenged in the latter years of the observation interval, peanut-specific IgE was measured with the CAP-system fluoroenzyme immunoassay (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). Briefly, the blood samples were procured, and the serum was separated and stored at -20°C until analysis. Results are reported in kilounits of peanut-specific antibody per liter (kU_A/L). The lower and upper assay limits were $0.35 \text{ kU}_A/\text{L}$ and $100 \text{ kU}_A/\text{L}$, respectively.

Peanut challenges were either performed openly or single-blinded. For open challenges, incremental amounts of peanut butter were administered every 15 to 30 minutes, with starting doses beginning typically with 0.1 mL of peanut butter. Blinded challenges were conducted with peanut flakes, according to previously published protocols.¹⁷⁻¹⁹ Blinding was achieved by disguising the taste and texture of peanut flakes in grape jelly or applesauce; however, the number of steps of each challenge was left to the discretion of the treating allergist. The patient and physician were blinded to the challenge, but the nurse administering the challenge was not. The placebo contained cracker crumbs to provide a similar texture. Patients were observed for 2 to 4 hours after completion of a negative challenge or up to 4 hours after treatment was administered for a positive challenge. In general, negative challenges concluded with the ingestion of a normal portion of either peanut butter or equivalent peanut containing foods (8 to 10 g of peanut); however, 5 of 24 children with negative challenges consumed a maximum of only 1,100 to 1,400 mg peanut. Challenges were considered positive if any of the following signs occurred: flushing, urticaria, facial swelling, abdominal pain and vomiting, or wheezing. Patients were instructed to avoid antihistamines for 96 hours and β -agonists for 12 hours before the challenge.

STATISTICAL ANALYSIS

Descriptive statistics, including means, medians, SDs, and ranges, were computed for continuous variables and percentages for dichotomous variables. Separate summaries are provided for those having negative and positive food challenges. Variables evaluated included age of children at the time of challenge, largest wheal diameter of the PST, peanut-specific IgE values, and proportion of children with other atopic conditions, such as asthma, atopic dermatitis, and other food allergies. The sensitivity, specificity, and predictive values and 95% confidence intervals (CIs) of alternative thresholds for wheal size, with respect to the outcome of the challenge, were then computed. Finally, the latter were plotted on a receiver operating characteristic curve, with sensitivity on the y-axis and $(1 - \text{specificity})$ on the x-axis. Each point thus represents a potential wheal diameter, which can be considered the cutoff value beyond which patients may be classified as truly peanut-allergic. The area under the receiver operating curve provides the probability that a randomly selected positive and a randomly selected negative subject will be correctly classified by the test. Therefore, it is an overall measure of the diagnostic ability of a continuous test.

RESULTS

Subjects were offered challenges as close to entry to primary school as was possible. Forty-seven patients with a positive PST to peanut and no previous history of having ingested peanuts were challenged to peanut. There were 24 negative and 23 positive challenges. Five of the 24 challenges considered negative did not complete the open challenge and consumed between 1,100 to 1,400 mg of peanut without adverse

Table 1. Demographic and Clinical Characteristics of Children Undergoing Challenges

	Negative challenges (N = 24)	Positive challenges (N = 23)
Age in years at time of PST, $\bar{x}$ (SD)	5.6 (2.6)	4.5 (1.7)
(95% CI)	(4.5 to 6.7)	(3.8 to 5.3)
Age in years at time of challenge, $\bar{x}$ (SD)	6.4 (2.7)	5.2 (1.6)
(95% CI)	(5.3 to 7.6)	(4.5 to 6.0)
Interval between PST and challenge, $\bar{x}$ (SD)	0.8 (0.7)	0.7 (0.5)
(95% CI)	(0.5 to 1.1)	(0.5 to 0.9)
PST in mm, $\bar{x}$ (SD)	6.3 (2.3)	10.3 (3.4)
(95% CI)	(5.3 to 7.3)	(8.9 to 11.8)
Peanut-specific IgE in kU _A /L median	0.63	13.1
(Range)	(0.34 to 15.2) (n = 9)	(2.28 to 98.6) (n = 5)
Patients with atopic features, n (%)		
Asthma	10 (41.7)	13 (56.5)
Atopic dermatitis	9 (37.5)	15 (65.2)
Rhinitis	8 (33.3)	7 (30.4)
Other food allergies	21 (87.5)	21 (91.3)
Egg allergy	10 (41.7)	14 (60.9)
Asthma and other food allergy	9 (37.5)	12 (52.2)

Abbreviations: CI, confidence interval; PST, prick skin test.

reaction. Two of these children currently eat precautionary-labeled foods, but do not consume peanuts; 1 child avoids peanuts because the sibling is peanut-allergic; and 2 children (challenges in 1995 and 1997) could not be reached for follow-up.

The mean ages (95% CI) of the children in the two groups were 6.4 years (5.3 to 7.6) in the negative challenge group and 5.2 years (4.5 to 6.0) in the positive challenge group. The 95% CI for mean ages as well as for collateral allergic features were too wide to draw any conclusions about between-group differences; however, there was a trend to increased atopic features in the positive challenge group (Table 1).

The mean of the largest wheal diameters (95% CI) of the PST in children having a negative and positive challenge were 6.3 mm (5.3 to 7.3) and 10.3 mm (8.9 to 11.8), respectively, indicating that, on average, those with a negative challenge had a lower PST wheal diameter. The median (range) peanut-specific IgE value of nine subjects in the

negative challenge group was 0.63 kU_A/L (0.34 to 15.2), compared with 13.1 kU_A/L (2.28 to 98.6) for the five subjects in the positive challenge group. Too few samples were available for comparison with the PST.

All subjects (n = 3) with a PST <5 mm had negative challenges. Thus, in this group of subjects, the sensitivity and negative predictive value (95% CI) for a PST ≥5 mm was 100% (85.2 to 100) and 100% (29.2 to 100), respectively (Table 2). However, the specificity and positive predictive value (95% CI) was only 12.5% (2.7 to 32.4) and 52.3% (36.7 to 67.5), respectively.

The performance of the PST at alternative thresholds for wheal size was computed based on the outcome of the food challenge. As the PST increased above 5 mm, sensitivity was lost, but specificity and positive predictive value were gained. At a PST value ≥10 mm, the positive predictive value (95% CI) was 80% (51.9 to 95.7) and at a PST value ≥12 mm, the positive predictive value (95% CI) was 90% (55.5 to 99.7).

Table 2. Properties of Prick Skin Tests at Varying Wheal Diameter Thresholds in Atopic, Peanut-Naïve Children with Prick Skin Tests ≥3 mm

Test cutoff (mm)	Number exceeding threshold	Number of positive challenges among those exceeding threshold	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Positive predictive value (%) (95% CI)	Negative predictive value (%) (95% CI)
≥ 3	47	23	100.0*	0.0*	48.9 (34.1 to 63.9)	
≥ 5	44	23	100.0 (85.2 to 100.0)	12.5 (2.7 to 32.4)	52.3 (36.7 to 67.5)	100.0 (29.2 to 100.0)
≥ 6	37	22	95.7 (95.7 to 99.9)	37.5 (18.8 to 59.4)	59.5 (42.1 to 75.2)	90.0 (55.5 to 99.7)
≥ 10	15	12	52.2 (30.6 to 73.2)	87.5 (67.6 to 97.3)	80.0 (51.9 to 95.7)	65.6 (46.8 to 81.4)
≥ 11	12	10	43.4 (23.2 to 65.5)	91.7 (73.0 to 99.0)	83.3 (51.6 to 97.9)	62.9 (44.9 to 78.5)
≥ 12	10	9	39.1 (19.7 to 61.5)	95.8 (78.9 to 99.0)	90.0 (55.5 to 99.7)	62.2 (44.8 to 77.5)
≥ 13	6	6	26.1 (10.2 to 48.4)	100.0 (85.8 to 100.0)	100.0 (54.1 to 100.0)	58.5 (42.1 to 73.7)

Abbreviation: CI, confidence interval.

* Sensitivity is fixed at 100% and specificity at 0% by the design of the study (see Discussion).

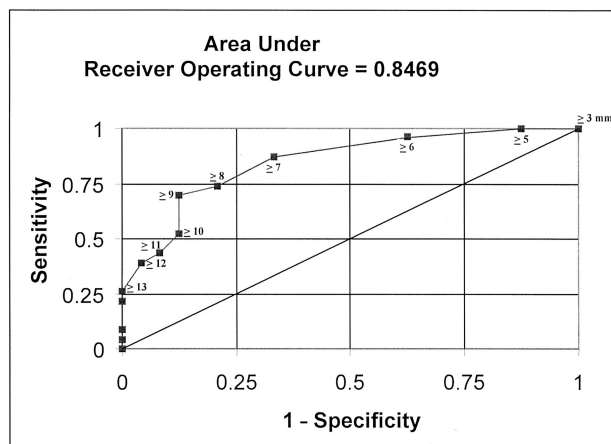


Figure 1. Receiver operating curve for peanut prick skin tests (PSTs) in atopic, peanut-naïve children with PSTs ≥ 3 mm.

A receiver operator curve was generated to determine how the PST wheal diameter could be used as a measure of the predictive power for peanut allergy (Table 3).

DISCUSSION

In this retrospective study, we have demonstrated that 49% of children sensitized to peanut without known antecedent exposure developed clinical allergic symptoms during oral provocation to peanut. Unlike most food allergies, where a clear history of sensitization is elicited before the development of an allergic reaction, up to 80% of children with peanut allergy develop allergic symptoms the first time that peanuts are introduced into their diet.²⁰ Skolnick and Spergel^{10,11} in their reports of peanut resolution have reported positive challenges in presumably peanut-naïve children with positive skin tests. Spergel et al¹¹ challenged 13 children with positive PST to peanut who had refused to eat peanut, and 38% of these children had a positive challenge. Recently, Grundy et al,⁵ in her study on peanut prevalence, reported that 8 of 24 peanut-naïve children with positive PST had positive challenges. Our study sought to specifically review children with no known antecedent peanut exposure and a positive peanut PST.

Because a PST is generally used to confirm suspected food allergy following symptoms consistent with an IgE-mediated allergic reaction, and because sensitization in the absence of clinical symptoms is not clinically relevant, performing a PST before known ingestion of a food is not generally recommended. However, peanut allergy appears to differ, as most allergic children react on their first known ingestion. Additionally, because peanut allergy has been associated with a significant risk of anaphylaxis, identifying the “at-risk” children would be useful before the first “field” reaction.^{6,7} Hence, we recommend peanut avoidance until age 3 years followed by PST to peanut for all children with a strong personal or family history of atopy. Those with a positive PST should undergo definitive diagnosis, which current^{21,22}

recommendations suggest should include peanut-specific IgE measurements followed by a peanut challenge in selected patients.

In our institution, challenges were offered if the largest diameter of the PST wheal was at least 3 mm more than the negative control and there was no history of previous peanut ingestion. The PST, at a cutoff of 3 mm, has excellent negative predictive value, exceeding 75%, making it a very good test at excluding the likelihood of peanut allergy.^{12–14} However, the positive predictive value, particularly in the absence of a suggestive history of IgE-mediated food allergy, is poor. Even when the history is moderately suggestive of an IgE-mediated reaction, the positive predictive value, at a cutoff of 3 mm, rarely exceeds 60%.^{12–15}

In this group of children who had never knowingly ingested peanut-containing foods before the oral challenge, the sensitivity and the negative predictive value (95% CI) at a cutoff value of 5 mm was 100% (85.2 to 100) and 100% (29.2 to 100), respectively. Thus, in our study sample and in our previous review of peanut challenges,¹⁴ if a PST value is considered positive only if ≥ 5 mm, all peanut-allergic children were identified. A larger PST wheal, however, is likely to be more predictive of true peanut allergy. Only 3 of the 17 subjects with a PST ≥ 10 mm had negative challenges; of these 3 subjects, peanut-specific IgE values were available for 2 of them. Both had values ≤ 1.51 kU_A/L. Thus, although a large PST does not preclude a negative challenge, it is much less likely. However, as the positive predictive value increases, sensitivity and the negative predictive value decrease, making it more likely that if we recommend a larger wheal diameter as the threshold, more truly peanut-allergic children will be incorrectly reassured that they are not peanut-allergic. In the setting of no history of previous ingestion, although it may eventually be demonstrated appropriate to accept a 5-mm wheal as a cutoff for a positive test, we and others⁹ cannot propose with certainty a mean PST wheal diameter that will ensure that no truly peanut-allergic children are misclassified, while minimizing the number of nonallergic children who are misidentified. Future studies may suggest that although children with a PST of 3 or 4 mm, perhaps coupled with low peanut-specific IgE values, still require physician-supervised challenges, it may be safe to conduct them in an accelerated, less resource-intensive manner.

The role of the peanut-specific IgE may prove to be of greater interest in the setting of small wheal diameters. Although the values in the negative group ranged from <0.35 to 15.2 kU_A/L, only one subject had a negative challenge at a peanut-specific IgE value above 2.0. Conversely, the median peanut-specific IgE value for positive challenges was 13.1 kU_A/L, and the lowest value was 2.28 kU_A/L. Because we had insufficient samples to compare the two groups, we cannot comment on the role that peanut-specific IgE has in this setting. It seems promising but requires further investigation in other populations and with larger sample sizes.^{10,21,23}

Possible explanations for occult sensitization in these children who have not knowingly ingested peanuts include maternal

ingestion of allergenic foods during pregnancy or while breast-feeding, unrecognized peanut proteins present in topical preparations for skin hydration, or through small amounts of peanut contamination in foods being introduced to the infant.^{24–26}

The limitations of this retrospective study restrict the extent to which our results can be applied to the general population. Although the majority of patients seen at the Montreal Children's Hospital who have a positive PST but no history of previous peanut exposure are offered peanut challenges, not all physicians in our group routinely offer challenges, particularly if the PST is sufficiently large; additionally, not all families agree to a challenge. It is probable that had all those peanut-naïve children with large positive peanut PSTs undergone a challenge, the percentage of positive challenges would exceed 50%. Furthermore, peanut-naïve children with a PST <3 mm are assumed to tolerate peanut and are not offered a challenge.

Our estimates of the sensitivity, specificity, and predictive value for the peanut PST apply to our population of atopic, peanut-naïve children with a PST wheal diameter ≥ 3 mm. It is likely that the properties would be different if those with a PST <3 mm were also included. Including only children with a PST ≥ 3 mm results in the estimation of specificities and negative predictive values that are lower and sensitivities that are higher than if all children were considered. As an illustrative example, we have calculated a specificity of 0% for the peanut PST at a threshold of 3 mm; this is because we are attempting to calculate the probability of having a negative PST or a PST <3 mm in those who are truly not peanut-allergic. However, given that we only include those with a PST ≥ 3 mm, it is impossible to have among this group of subjects a case with a PST <3 mm. We have calculated a sensitivity of 100% for the peanut PST at a threshold of 3 mm. This results because we are expressing the probability of having a positive PST or a PST ≥ 3 mm in those who are truly peanut-allergic (ie, those who have a truly positive PST and those who have a falsely negative PST <3 mm). Given that our sample includes only those with a PST ≥ 3 mm, it is impossible to have a case with a PST <3 mm. However, if our sample included those with a PST <3 mm, it would theoretically be possible (although unlikely) to have a false negative PST and hence a sensitivity <100%.

Furthermore, although the majority of children under the age of 5 years react to their first exposure to peanuts, some children may only develop peanut allergy upon subsequent exposure. It is possible, therefore, that sensitization occurred during the challenge, suggesting a negative challenge may not preclude peanut allergy with certainty. Incomplete data are available on the follow-up of these patients, and many families have chosen to introduce only precautionary-labeled peanut products, while continuing to avoid overtly peanut-containing foods. Additionally, in this series, 5 of 24 children challenged did not consume the usual maximum 8 to 10 g of peanuts and thus cannot unequivocally be reported as negative challenges. None of these patients had peanut-specific IgE measured. Thus, it is possible that they may have reacted

at higher doses and should have been included with the positive challenges. This, of course, would suggest that we have underestimated the positive predictive value of the PST in this population.

CONCLUSION

This study illustrates both the risk of peanut allergy in atopic peanut-naïve children, while demonstrating the limitations of the PST as a diagnostic tool. Consistent with previous reports, the positive predictive value of peanut allergy skin testing is relatively poor and thus it is likely that half of the children with a positive PST but without antecedent peanut exposure are not peanut-allergic. Assigning these children the diagnosis of peanut allergy would require their families to commit to strict peanut avoidance and to carry self-injectable adrenaline, thus creating important social and health implications that would not otherwise be necessary. Thus, establishing an accurate diagnosis is both relevant and imperative. However, 49% of the subjects developed allergic symptoms during the challenge, despite having had no previous peanut exposure. Given the significant association of peanut allergy with a lifelong risk of anaphylaxis and the significant risk of experiencing a life-threatening allergic reaction at the first known exposure, identifying these children before they develop allergic reactions at home, school, or other public places would be useful.^{7,20} Performed in a controlled environment, under the supervision of experienced medical staff, oral food challenges are safe and should be incorporated into the standard of care for these atopic children with a positive peanut PST and no previous peanut exposure. Identifying both children who are at risk for peanut allergy before they develop symptoms as well as those who have a positive PST but are not likely to be peanut-allergic are important priorities.

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