

Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level

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Cutoffs (decision points) of the peanut skin prick test (SPT) and specific IgE level for predicting peanut allergy have been proposed. It is not known whether decision points indicating a significant risk of severe reactions on challenge differ from those indicating probable allergy. We aimed at determining the usefulness of allergy tests for predicting the risk of anaphylaxis on challenge following the ingestion of up to 12 g of peanut in peanut-sensitized children. Children attending the Allergy Clinic who had a positive peanut SPT and completed open-label in-hospital peanut challenges were included. The challenge protocol provided for challenges to be continued beyond initial mild reactions. Eighty-nine in-hospital peanut challenges were performed. Thirty-four were excluded as the challenge was not completed, leaving 55 for analysis. Children who completed the challenge and did not react ($n = 28$) or reacted without anaphylaxis ($n = 6$) represented the comparison group ($n = 34$). The study group comprised 21 children whose challenge resulted in anaphylaxis. The mean peanut SPT wheal size and specific IgE level were associated with the severity of reactions on challenge. Among the 21 children, who developed anaphylaxis, in only 3 cases was anaphylaxis the initial reaction. Unexpectedly, a history of anaphylaxis was not predictive of anaphylaxis on challenge. Anaphylaxis developed at cumulative doses of peanut ranging from 0.02 to 11.7 g. Provided that a fixed amount of peanut is ingested, available tests for peanut allergy may assist in predicting the risk of anaphylaxis during challenge in peanut-sensitized children.

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Sensitization to peanut ranges from around 3% in the general population (1) to 5% in atopic populations (2). The population prevalence of clinical peanut allergy is somewhat lower at around 1%, although there is evidence that it is rising (1). The risk of a severe reaction to peanut in a highly atopic population of Australian

children has been estimated to be around 0.25% and as low as 0.036% in the general childhood population (2). The risk of a severe reaction requiring treatment with adrenaline in children known to have clinical peanut allergy has been estimated to be approximately 10% (2). Accidental exposure to peanut despite avoidance is common (3–5). Therefore, patients sensitive to trace amounts of peanut (6–13) may also be at risk of anaphylaxis despite vigilant avoidance and would therefore require an adrenaline

Abbreviations: SPT, Skin prick test; ROC, Receiver operator curve; PPV, Positive predictive value; NPV, Negative predictive value; LR, Likelihood ratio.

autoinjector (e.g., EpiPen[®], Alphapharm Medical, Globe, NSW, Australia). On the other hand, peanut-sensitized patients with higher threshold levels for reactions may be at lower risk.

At present, the best predictors of the risk of future anaphylaxis following peanut exposure include a previous severe reaction (3, 4), older age (3), and significant comorbidities such as asthma (3–5). It has been suggested that sensitivity to multiple peanut allergens, or multiple epitopes, may correlate with the severity of reactions (14).

However, a number of pediatric patients presenting to allergists do not have significant clinical risk factors for anaphylaxis. Such patients may never have ingested peanut or have a history of only mild reactions to peanut, which are not always necessarily predictive of subsequent similarly mild reactions (3, 15). Controlled peanut challenges are the 'gold standard' for the diagnosis of peanut allergy and also for determining the severity of reactions and threshold dose in individual patients (16). But even when challenges are performed because it is suspected that peanut allergy may have resolved up to 30% of reactions can be severe (17).

Studies have proposed various cutoffs (decision points) of the peanut skin prick test (SPT) and specific IgE level that are diagnostic of peanut allergy even in the absence of a supportive history or a positive food challenge (18–30). However, with the exception of four studies (3, 6, 13, 17), which have reported weak associations between the test results and the severity of reactions on challenge, most have either not sought or not found such a correlation. Therefore, it is not known whether decision points indicating a significant risk of severe reactions on challenge differ to those indicating probable allergy but providing no information relating to individual threshold dose or severity of reactions. As a result, many patients may be denied a challenge, even though they may not develop a severe reaction and therefore may also be denied information useful for the management of their individual allergy.

This study aimed at determining the usefulness of the peanut SPT and/or specific IgE level for predicting the risk, in peanut-sensitized children, of a severe reaction during a peanut food challenge involving the ingestion of up to 12 g of peanut.

Methods

Study design

A prospective case-control study was conducted at Sydney Children's Hospital, a tertiary referral children's hospital in Sydney, Australia, between

September 2003 and July 2006. The Human Research Ethics Committee (HREC) of our area health service approved the study protocol.

Patients and controls

The study sample was recruited consecutively from children attending Sydney Children's Hospital for peanut food challenges (Food Challenge Clinic). All included children were sensitized to peanut (peanut SPT wheal 3×3 mm larger than a saline control), and all parents agreed to participate after giving written informed consent. Children with a negative peanut SPT, those who had a definite history of anaphylaxis to peanut in the 3 months prior to the study, or who were known to have tolerated peanut regularly in the year prior to the study, were excluded. Although, as these children would not routinely have been referred from the Allergy Clinic to the Challenge Clinic in the first place, there were actually no potential subjects excluded on these grounds. Peanut SPTs were not carried out specifically for inclusion in the study but were always part of the routine clinical investigation into the child. Eighty-nine children were recruited, 56 had a positive peanut challenge and 33 had a negative challenge.

Skin prick testing

Skin prick test was performed using a commercial whole peanut extract 1:10 w/v (Hollister-Stier laboratories LLC, Spokane, WA, USA) with a negative control (glycero-saline) and a positive control (10 mg/ml histamine HCL). In 2 (3.6%) subjects, the SPT was performed on the day of the challenge, in the remainder it was performed prior to the challenge (range 3–326 days; median 81). Usually, the test was performed on the ventral surface of the child's forearm. Antihistamine medication was withheld for at least 72 h prior. The resulting wheal was measured at 15 min. The SPT wheal size was then calculated as the arithmetic mean of the longest diameter and the one orthogonal to it. This value was used to determine the sensitivity and specificity at various sizes of SPT.

Measurement of peanut-specific IgE

Measurement of peanut-specific IgE (Pharmacia UniCAP system FEIA Phadia, Upsala, Sweden) was taken on all subjects. The lower limit of measurement of the test was 0.35 kU/l and the upper limit was 100 kU/l. For analysis, values < 0.35 kU/l were deemed to be 0.35 kU/l, and values > 100 kU/l were deemed to be 101 kU/l. As

the protocol provided that blood could be drawn on the day of the challenge, in 67.3% of cases the test was performed on the day of the challenge, and therefore the results were not available prior to commencing the challenge. Specific IgE was measured prior to the challenge in the remaining 32.7% (range 2–307 days; median 80).

Peanut challenges

The peanut challenges were in-hospital open-label design and were not placebo controlled. No child was excluded from having a peanut challenge because of the size of the SPT alone. All challenges were performed as part of routine clinical assessment of the study subject; none were performed exclusively for enrollment in this study. Overall about 40% of the challenges were carried out because the child was SPT positive to peanut but had no history of peanut ingestion and/or a reaction; in the remaining 60%, most were performed to determine whether tolerance had developed. A few were carried out to also determine the threshold dose and potential severity of reactions. All children undergoing challenges had been on a peanut-free diet prior to the challenge (although information on whether they were specifically avoiding foods labeled 'may contain traces of peanut' was not captured) and were all free of symptoms such as urticaria and wheeze.

For the peanut challenges, finely chopped peanut (containing 26% protein) was used. The peanut was disguised in a food of which the child was known to be tolerant, e.g., ice cream or custard. The children were given 0.02, 0.2, 2.0, 3.8, and 5.7 g (11.7 g cumulative; equivalent to approximately 12 peanuts) at 20 to 30-min intervals under medical supervision. The children were observed in hospital for a period of 2 h after the last ingested dose. Vital signs including pulse, respiratory rate, blood pressure, and percutaneous oxygen saturations were monitored hourly. Intravenous lines were not routinely placed and in fact were never required during the challenges. Challenges were scored and reactions managed as described previously (18). Anaphylaxis was defined as a reaction involving the cardiovascular (e.g., syncope, hypotension, arrhythmia) and/or respiratory system (e.g., deep/persistent cough, stridor, wheeze) and at least one other system. If a mild, non-anaphylactic reaction (usually cutaneous or gastrointestinal symptoms) occurred, and where the parents and the child consented, challenges were not stopped or reactions treated, and further amounts of peanut were given. The challenge was terminated when either all required

peanut was ingested or a moderate to severe reaction occurred. In a few cases, the child refused to ingest further amounts of peanut but did consent to the withholding of medication, e.g., antihistamine or prednisolone, for > 2 h after the last dose of peanut. The cumulative amount of peanut ingested was then calculated by adding all the individual amounts of peanut ingested until the challenge was terminated.

Statistical methods

Non-parametric data was compared using the Mann–Whitney *U*-test and chi-squared test. Parametric data was compared using the Student's *t* Test. Receiver operator curve (ROC) analysis was used to determine cutoffs of the allergy tests for predicting the severity of reactions. This analysis was performed using SPSS for Windows (version 15 SPSS Inc., Chicago, IL, USA). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and 95% confidence intervals for designated cutoffs of the allergy tests were then calculated. GRAPHPAD PRISM version 4.00 for Windows (GraphPad Software, San Diego, CA, USA, <http://www.graphpad.com>) was used for this analysis. A *p* value of < 0.05 was considered statistically significant.

Results

Eighty-nine in-hospital challenges with peanut were performed between September 2003 and July 2006.

Outcome of peanut challenges

Overall, the prevalence of clinical peanut allergy (positive peanut challenge) was 56/89 (62.9%), and the prevalence of anaphylaxis was 21/89 (23.6%). No child had involvement of their respiratory system without involvement of at least one other system. No anaphylactic reactions involved symptoms suggestive of cardiovascular involvement. However, on 34 occasions the challenge was not completed, i.e., the child did not ingest all required peanut and also did not develop anaphylaxis. Usually, the challenge was not completed at the request of a parent (they were concerned about either the risk to the child or the child's level of discomfort or both) or because the child refused to ingest any further doses of peanut. A reaction had not yet occurred in only five of these 34 children when the child or parent refused to complete the challenge, i.e., most refused to continue because of mild to

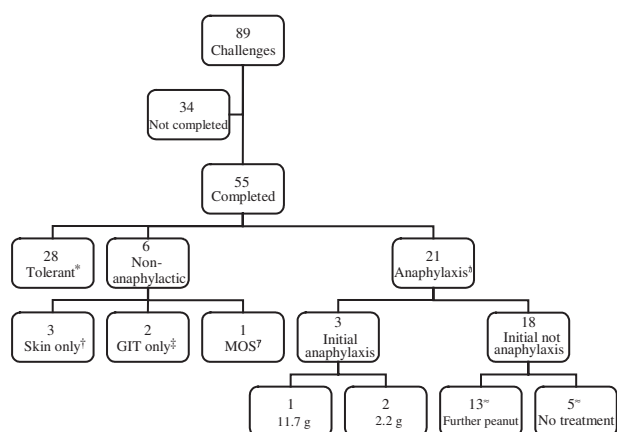


Fig. 1. Outcome of peanut challenges. *No reaction noted within 2 h of challenge. †Facial or generalized urticaria or angioedema only. ‡Abdominal pain, nausea, vomiting, and diarrhea only. §Multi-organ system reaction – involvement of two or more systems without involvement of the cardiovascular or respiratory system. (These children usually had a skin reaction with abdominal pain and/or vomiting.) ¶Involvement of the cardiovascular or respiratory system and at least one other system. *These children all reacted to peanut, initially as a mild reaction which then evolved to include features of anaphylaxis.

moderate symptoms, despite the fact that in 26/34 cases these symptoms resolved without treatment. Because we could not be sure whether the outcome of these challenges would have been different had they been completed, they were excluded from the final analysis. This left 55 challenges that either resulted in anaphylaxis or were completed with or without a reaction (Fig. 1). Sixteen children known to have previously reacted to peanut demonstrated a resolution of their peanut allergy by a negative peanut challenge. Assuming that the entire original cohort was peanut allergic rather than only peanut sensitized on enrollment in the study, this would indicate a resolution rate of 18%, which is similar to other studies. If only children with either a history of a reaction or a reaction on challenge (whether they were included in the final analysis or not) are counted the resolution rate would be $16/72 = 22\%$.

Treatment of reactions

All reactions either resolved spontaneously or with the appropriate treatment. None of the six children who completed the challenge but did not develop anaphylaxis received any medical treatment within 2 h of the last dose of peanut. Of the 21 children who developed anaphylaxis, 20 (95%) were treated with antihistamine, 14 (67%) with oral prednisolone, 13 (62%) with inhaled salbutamol, and 13 (62%) with

intramuscular adrenaline. Five (24%) children who did not receive adrenaline did however receive inhaled salbutamol, and five children who received adrenaline did not require salbutamol. Overall 3 (15%) children in this group, in whom anaphylaxis evolved slowly, received neither adrenaline nor salbutamol and were managed with antihistamine only. The mean time between the last dose of peanut and any treatment in the anaphylactic group was 52.95 ± 42 min. There were no hospitalizations or deaths.

Study groups

The demographics of the included children are shown in Table 1a. In those children who had previously ingested peanut (67.3%), neither a previous reaction nor previous anaphylaxis to peanut was associated with anaphylaxis during a challenge. The demographics of the excluded children compared with included children are shown in Table 1b. Excluded children were more likely to have had an objective initial reaction than included children (χ^2 , $p = 0.03$), and the included children were more likely to be male (χ^2 , $p = 0.04$).

Table 2 shows the number of subjects in each group and the total cumulative dose of peanut consumed during the challenges. Twenty-one children developed features of anaphylaxis during peanut challenges. The cumulative dose ingested by these 21 children ranged from 0.02 to 11.7 g of peanut. More children developed anaphylaxis after a large amount of peanut than a small amount. Twenty-eight did not have any reaction during the challenge after a cumulative dose of 11.7 g of peanut and were considered tolerant of peanut. A further six children developed a non-anaphylactic reaction but also completed the challenge. The types of reactions which these children developed are shown in Fig. 1. For analysis, these children were grouped together with the tolerant children to form the control group because the goal was to determine the risk of anaphylaxis following the ingestion of up to 12 g of peanut. A sensitivity analysis demonstrated that the difference in the mean peanut SPT wheal size between the control and anaphylactic groups remained significant whether these six children were placed in the tolerant or anaphylactic groups (data not shown).

Progression of challenges

Anaphylaxis developed in 21 of the 55 challenges (Fig. 1). However, in most cases anaphylaxis did not occur until either further doses of peanut

Table 1 Demographics of (a) included subjects (n = 55) and (b) included vs. excluded children (n = 89)

	Control group n = 34	Anaphylactic group† n = 21	
(a)			
Age (months)			
Mean ± s.e.m.	56.2 ± 38.7	66.5 ± 44.2	p = 0.37*
Sex (n)			
Boys	25	17	p = 0.53**
Girls	9	4	
History of peanut allergy (n)			
Known previous peanut ingestion	25	12	p = 0.21**
Any previous reaction to peanut†	22	12	p = 0.21
Previous anaphylaxis to peanut‡	5	3	p = 0.73**
Other atopic disease (n)			
Asthma	11	7	p = 0.94**
Eczema	23	13	p = 0.66**
Other food sensitivity/allergy§	11	6	p = 0.77**
Allergic rhinitis	6	7	p = 0.18**
Any atopy¶	29	20	p = 0.25**
	Included n = 55	Excluded n = 34	
(b)			
Age (months)			
Mean ± s.e.m.	60.1 ± 40.8	51.7 ± 24.8	p = 0.28*
Sex (n)			
Boys	42	19	p = 0.04**
Girls	13	15	
History of peanut allergy (n)			
Known previous peanut ingestion	37	28	p = 0.12**
Any previous reaction to peanut†	34	28	p = 0.12
Previous anaphylaxis to peanut‡	8	3	p = 0.22**
Other atopic disease (n)			
Asthma	18	13	p = 0.60**
Eczema	36	24	p = 0.62**
Other food sensitivity/allergy§	17	12	p = 0.67**
Allergic rhinitis	13	3	p = 0.08**
Any atopy¶	49	29	p = 0.60**

*t test; **Chi Square test.

†History of any reaction to peanut in children previously exposed to peanut regardless of severity.

‡History of anaphylaxis to peanut in children previously exposed to peanut.

§Documented allergic reaction and/or positive SPT to foods other than peanut.

¶One or more of asthma, eczema, or food sensitivity/allergy.

Table 2 Outcome of 55 challenges, reaction threshold levels, and cumulative amount of peanut ingested when challenge stopped

Challenge outcome	n (%)	Reaction threshold amount		Cumulative amount	
		<6 g (n)	>6 g (n)	<6 g (n)	>6 g (n)
Anaphylaxis	21 (38)	15	6	10	11
Non-Anaphylactic*	6 (11)	2	4	0	6
Tolerant*	28 (51)	0	0	0	28

*Control Group = Non-anaphylactic + Tolerant.

beyond the threshold dose were ingested or treatment of mild symptoms was delayed allowing the reaction to progress. Table 2 shows the distribution of threshold and total cumulative doses of peanut for the 21 children who developed anaphylaxis. Of these, only 3/21 (14.3%) developed anaphylaxis as their initial reaction. One of these patients reacted (with anaphylaxis) at a cumulative dose of 11.7 g of peanut, and the other two reacted at a cumulative dose of 2.2 g of peanut. The other 18/21 children developed an initial non-anaphylactic reaction, which then progressed to anaphylaxis. Thirteen (72.2%) consumed further peanut before developing anaphylaxis, and the difference between the initial and final amounts of peanut ingested before anaphylaxis occurred was 2 g or less in 7/13. While 5/18 did not ingest further amounts of peanut, in the absence of any medical intervention, their reactions progressed spontaneously to anaphylaxis within the 2- h observation period.

Similarly, two of the six children who completed the challenges and developed non-anaphylactic reactions reacted to the last required dose of peanut, and so no further peanut was ingested. The remaining four in this group developed a threshold reaction at a lower dose before completing the challenges.

In terms of the severity of threshold reactions before challenges were continued (excluding the three children whose initial reactions were anaphylactic), the initial reactions were subjective in 11/24 and objective in 13/24. Subjective reactions included oral itch (seven cases), abdominal pain (three cases), and nausea (one case). Objective reactions included mild urticaria and/or erythema (six cases), vomiting which resolved (three cases), mild cough only (one case) or a combination of vomiting, diarrhea, urticaria, and/or cough (three cases) all of which spontaneously resolved or almost completely resolved in less than 30 min prior to continuation of the challenges. Thus, 20/24 children who developed an initial non-anaphylactic reaction and then completed the challenge, with or without developing anaphylaxis, either developed a subjective reaction only or at worst developed vomiting as their objective reaction. If challenges had been stopped and treated when the initial milder reactions occurred, it is possible that only 3/21 children would have developed anaphylaxis.

Relationship of peanut SPT and specific IgE with challenge outcome

We considered that the 18 children who had milder threshold reactions and later developed

Table 3 Comparison of the peanut SPT and *in vitro* test outcomes for anaphylactic children with mild initial reactions and controls

	Anaphylactic subgroup (n = 18) [†]	Control group (n = 34)	
Mean SPT wheal size (mm)	10.1 (6.5–15.5)	6.7 (3–11.5)	p < 0.0001*
Median peanut-specific IgE (kU/l)	20.5 (0.86–>100)	0.68 (<0.37–8.5)	p < 0.0001*

*p < 0.05.

[†]Initial reaction non-anaphylactic. SPT, skin prick test.

anaphylaxis would have been misclassified if the challenges had been stopped before anaphylaxis developed. We compared the mean peanut SPT wheal size and peanut-specific IgE level for those children who developed anaphylaxis with the control group and found that they did indeed have a significantly larger mean SPT wheal size and higher median peanut-specific IgE level. Table 3 shows the mean and range of the peanut SPT wheal size and peanut-specific IgE level for the two groups.

The mean SPT wheal size and median peanut-specific IgE level were each tested for an association with the occurrence of anaphylaxis. The mean SPT wheal size for the anaphylactic group was 10.2 mm compared with 6.7 mm in the control group (*t* test p < 0.0001). The median peanut-specific IgE level in the anaphylactic group was 19 kU/l compared with 0.68 kU/l in the control group (Mann–Whitney p < 0.0001).

Cutoffs of the peanut SPT and specific IgE level for predicting whether anaphylaxis was likely to be the outcome of a challenge were calculated. Receiver operator curve analysis revealed an area under the curve of 0.845 (95% C.I 0.744–0.945) for SPT and 0.951 (95% C.I 0.898–1.005) for peanut-specific IgE for diagnosing anaphylaxis, suggesting that they are of equal value (Fig. 2). A peanut SPT wheal size of 6.75 mm was 95% sensitive and 56% specific for predicting anaphylaxis, while a wheal of 11.25 mm was 33% sensitive and 97% specific. A peanut-specific IgE level of 2.08 kU/l was 95% sensitive and 85% specific, while a level of 7.7 kU/l was 70% sensitive and 97% specific (Table 4).

Discussion

This study included a group of children with sensitization to peanut as demonstrated by a positive test for peanut-specific IgE. We found a significant difference in the peanut SPT wheal size and specific IgE level between peanut-sensitized children who on peanut challenge developed

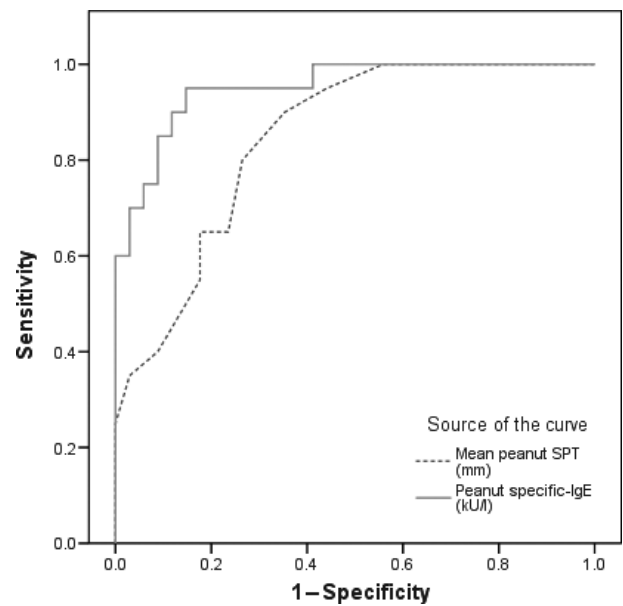


Fig. 2. Receiver operator curve of peanut skin prick test wheal size and specific IgE level for predicting anaphylaxis.

anaphylaxis (after ingesting up to 12 g of peanut) compared to those who did not do so. We achieved this firstly by excluding only peanut-sensitive children with a clear history of anaphylaxis to peanut in the preceding 3 months and including all others regardless of the size of their peanut SPT or peanut-specific IgE level. This meant that our study included children with a broad range of peanut SPT and peanut-specific IgE results (Table 3) compared with other studies which excluded children with test results above various cutoffs or with any history of severe reactions (25–27).

Secondly, many previous studies have stopped challenges and administered treatment to the child at the first sign of a mild reaction because the aim was to diagnose peanut allergy rather than to determine severity (23). These and other retrospective studies often report no correlation between the severity of a reaction to peanut and either the size of the peanut SPT or the level of peanut-specific IgE (19, 23, 27). We considered that some reactions classified in these studies as mild may have become more severe if further doses had been given or treatment had been delayed. Any difference in the mean SPT wheal size or specific IgE level between children who did develop anaphylaxis and those that did not may have been obscured by the results from such a group of children incorrectly classified as non-anaphylaxis prone. This prospective study allowed us to monitor the progression of reactions because challenges were not routinely

Table 4 Utility of tests for predicting severity outcome of challenge

	Sensitivity (%)	95% C.I	Specificity (%)	95% C.I	PPV (%)	NPV (%)	LR
SPT $\geq$ 6.75 mm	95	76–100	56	38–73	57	95	2.2
SPT $\geq$ 11.25 mm	33	15–57	97	85–100	88	70	11.3
CAP $\geq$ 2.08 kU/l	95	75–100	85	69–95	79	97	6.5
CAP $\geq$ 7.7 kU/l	70	46–88	97	85–100	93	85	23.8

SPT, skin prick test; CAP, peanut-specific IgE level (Pharmacia UniCAP); PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

stopped at the first sign of a reaction, and milder reactions were not immediately treated. We identified a subgroup of 18 children within the anaphylactic group who developed mild reactions initially but progressed to anaphylaxis when the challenges were continued. These children did indeed have allergy test results significantly different from controls (Table 3). A criticism of this analysis may be that the majority of the comparison group (controls) did not *have* mild to moderate reactions but were in fact tolerant of peanut (28/34). And of course, one would expect to find a difference between children with and without peanut allergy (18). As a result, we also compared these 18 children with two other small groups. Firstly compared with the three who developed anaphylaxis, initially there was no apparent difference in the mean SPT wheal size or peanut-specific IgE level (data not shown). Secondly when the data on the six control children who were not tolerant but also did not develop anaphylaxis was compared with those from the 18 with mild reactions progressing to anaphylaxis, we found that there was a significant difference in the mean SPT wheal size and peanut-specific IgE levels (data not shown). Although the numbers are too small to draw any absolute conclusions, we believe that these results suggest the differences between these 18 children and the control group as a whole are valid.

The time interval between testing, i.e., SPT or measurement of specific IgE ranged from 0 to 326 days. For practical reasons, it was not possible to repeat the SPT on the day of the challenge in most cases; however, the median time between the SPT and the challenge was <3 months, and $2/3$ of specific IgE levels were performed on the day of the challenge. Therefore, although it is possible that the results may have been different if more of the tests had been performed closer to the challenge, it seems unlikely that our results would have differed significantly.

There were 12 tolerant children who, despite having detectable peanut-specific IgE on SPT or serum specific-IgE measurement, had never knowingly ingested or had not previously reacted to peanut, and we were concerned that some of them may not have been allergic to peanut at

study entry. We performed a sensitivity analysis (data not presented) of the study data excluding these 12 children to leave 22 (peanut sensitive) controls (16 tolerant and six non-anaphylactic) and 21 children who had anaphylactic reactions. Excluding these 12 children did not change the significance of any demographic or test results or predictive value for the study. Also as a history of a reaction to peanut was not an *a priori* requirement for inclusion in the study, and as all children were sensitized to peanut, these children were included in the final analysis.

In this study, the utility of SPT and specific IgE cutoffs (decision points) for predicting anaphylaxis on challenge were similar to those found in a previous study at our hospital to be predictive of any peanut allergy (18). Therefore, provided that the decision points are known to be valid at the location where they are being used this study suggests that it is unnecessary to challenge children with results above these decision points even if the purpose of the challenge is to determine severity. However, a clinically useful finding of this study was to identify cutoffs of the peanut SPT and peanut-specific IgE level that were >95% sensitive for predicting that anaphylaxis would be unlikely to develop during challenges. These were found to differ significantly from cutoffs that have been reported to be >95% sensitive for excluding peanut allergy of any severity, usually <3 mm for the SPT (21, 27). As such, there would seem to be significant benefit in challenging children with positive peanut-specific IgE tests whose results lie below a relevant decision point to determine whether clinical peanut allergy is present, the threshold dose and the potential severity of reactions.

Contrary to other studies which suggest that anaphylaxis tends to occur in children who have lower reaction thresholds (17), in this study almost as many developed anaphylaxis after a cumulative dose of >6 g (11/21) as <6 g (10/21). Once again this is presumably because when challenges are stopped at the first sign of a reaction, only those children who have low anaphylaxis thresholds will be allowed to develop anaphylaxis. This study suggests that anaphylaxis without preceding milder symptoms

is the exception (3/21), but when challenges are continued anaphylaxis may be triggered by larger amounts of peanut. This may be because further amounts of peanut cause the child to exceed both the reaction threshold and subsequently the anaphylaxis threshold or because treatment is delayed. Therefore, by aborting the challenge when any reaction occurs many cases of anaphylaxis may be avoided, and the margin of safety for food challenges increased. If one assumes that most accidental ingestion of peanut involves only small amounts, our data may indicate that in most cases milder symptoms will serve as a 'warning' of the risk of impending anaphylaxis allowing the appropriate actions to be taken, e.g., seeking medical attention. In this study, 62% of children who developed anaphylaxis were treated with adrenaline. However, a further 24% did receive inhaled salbutamol as wheeze was the chief manifestation of anaphylaxis. The remainder (three children) received only antihistamine, but in these children anaphylaxis evolved more slowly, and close monitoring showed improvement in their clinical symptoms before adrenaline was given. The decision as to how to treat each individual patient was left to the discretion of the clinician attending the clinic which may explain some variability in the treatments used. However, all of these patients were closely monitored in a relatively controlled situation in hospital, and there were no cardiovascular symptoms among our patients. Adrenaline should still be recommended as first line treatment for anaphylaxis in the community or in the emergency department.

The way in which most anaphylactic reactions progressed suggests that any peanut-sensitized patient (a person with detectable peanut-specific IgE) who is tolerant of a predetermined amount or does not develop anaphylaxis during a peanut challenge could possibly react or develop anaphylaxis if larger amounts of peanut were ingested or treatment delayed. Therefore, we suggest that children for whom the peanut challenge is negative be asked to ingest larger amounts of peanut at home over a day or two following the challenge before they are deemed truly tolerant of peanut.

There are a number of aspects of peanut allergy that are thought to be variable or unpredictable and therefore may influence the conclusions that can be drawn from any study including this study. The data on whether previous reactions or previous severe reactions are associated with subsequent severe reactions are conflicting. In this study, a history of either any previous reaction to peanut and/or anaphylaxis to peanut was not

associated with the development of anaphylaxis during peanut challenge (Table 1).

In conclusion, we have shown that in children sensitized to peanut the results of peanut-specific IgE tests can be used to identify those at risk of anaphylaxis on challenge compared with those who will turn out to be tolerant or develop non-anaphylactic reactions. Children with larger SPT wheal sizes or high peanut-specific IgE levels (above defined but not necessarily universally applicable (18) cutoffs or decision points) seem likely to develop anaphylaxis on challenge, and therefore there does not seem to be any benefit in performing peanut challenges in these children even if anaphylaxis has not occurred previously. Furthermore, excluding these children would improve the safety of oral peanut challenges. Children with positive peanut allergy tests whose results lie below these decision points are most likely to benefit from a challenge not only to determine whether clinical peanut allergy is present but also to determine the risk of anaphylaxis and the threshold dose.

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