



Letters

Low-dose peanut challenges can facilitate infant peanut introduction regardless of skin prick test size

The Learning Early About Peanut Allergy (LEAP) trial and other studies recommend early peanut introduction to prevent peanut allergy in at-risk infants.^{1,2} In addition, peanut oral immunotherapy (OIT) shows increased rates of sustained unresponsiveness in children younger than 5 years with known peanut allergy,³ suggesting better outcomes with early exposure. The LEAP trial excluded infants with skin prick tests (SPTs) greater than 4 mm.¹ The guidelines recommend peanut introduction or oral food challenge (OFC) only in infants who have SPTs less than or equal to 7 mm and do not specifically address management of infants with SPTs greater than 7 mm (or high peanut IgE levels).⁴ Data suggest that patients with peanut SPT greater than 7 mm are likely to react,^{4,5} but most reference values for SPT and peanut IgE levels are not standardized for infants.^{5,6} It is unknown whether infants with SPT greater than 7 mm may tolerate and benefit from early peanut exposure. Given the potential long-term benefits of tolerating peanut, we sought to offer peanut OFCs to a wider population of sensitized infants.

In our experience, infants developing feeding skills and preferences have difficulty consuming 3.9 g peanut protein (LEAP dose for positive peanut SPT¹) in 1 sitting and, in general, may not eat large quantities of solid foods. In addition, the Enquiring About Tolerance trial demonstrated difficulties in adherence, given the variation in developmental readiness to eat solid food.⁷ Data suggest that lower peanut challenge doses may be considered in selected cases⁸; extrapolation of this strategy to infants could prevent unnecessary avoidance. Therefore, we challenged infants to 1 g peanut and gradually increased the amounts at home to achieve 2 g per serving.

Retrospective chart review was conducted involving peanut OFCs performed in 70 infants aged 6 to 13 months between December 2015 and December 2017 at our pediatric allergy referral center (institutional review board approval in place for the database of OFC outcomes). Infants were referred for evaluation and peanut OFC based on positive peanut IgE test result obtained by an outside clinical provider, moderate to severe eczema, egg allergy, possible reaction after peanut introduction, or a sibling with food allergy. Challenges were offered at clinical providers' discretion to infants whose families declined home introduction, regardless of SPT size.

Peanut SPT size, peanut IgE, and Ara h2 IgE (where available) were compared between infants who tolerated and did not tolerate 1 g peanut OFC. PRACTALL guidelines were used to

determine OFC outcome.⁹ Infants who tolerated 1 g peanut were advised to continue this quantity at home 3 times a week, increasing by 25% per serving every 4 weeks as tolerated up to a goal of 2 g of peanut 3 times a week. After successful OFC, families were advised that true peanut tolerance was unknown given the low challenge dose and that constant epinephrine carriage must continue. We advised close observation of infants after home doses for 1 to 2 hours and that families consider skipping peanut on days when fever or gastrointestinal symptoms were present.

In this study, 54 of 70 infants (77%) aged 6 to 13 months were tolerant of 1 g peanut (Table 1). Of infants with peanut SPT less than or equal to 4 mm, nearly all patients (29 of 30, 97%) tolerated 1 g peanut. Infants with peanut SPT greater than 4 mm mostly tolerated peanut (25 of 40, 63%), including 12 of 22 infants (54.5%) with SPT greater than 7 mm. Nine infants who were not peanut tolerant (9 of 16, 56%; 9 of 70, 13% overall) required epinephrine for mild to moderate symptoms in 2 or more organ systems (based on the European Academy of Allergy and Clinical Immunology grading criteria¹⁰); 4 received 2 doses for incomplete resolution of symptoms (ie, not deterioration in clinical status). Respiratory symptoms were limited to intermittent cough with clear lungs on auscultation. None of the patients had cardiovascular or neurologic signs or symptoms.

Follow-up was achieved in the clinic or by phone at 1- to 3-month intervals up to 1 year. Between 6 and 12 months after peanut OFC, 32 of 54 patients (59%) were eating 2 g or more per serving at least 3 times a week. Nine patients (17%) were eating 1 to 2 g per serving. Nine patients (17%) were eating 0 to 1 g, mostly owing to a lack of regular consumption or patient aversion. Four patients were lost to follow-up. One patient had mild hives after avoiding peanut for 2 weeks but reintroduced peanut without further reactions. A few children initially had contact hives with peanut ingestion; parents were comfortable keeping peanut in the diet and these patients now regularly eat peanut.

There was no statistical difference in age, sex, race, or egg sensitization between peanut-tolerant and nontolerant groups regardless of SPT size. Differences were observed in eczema prevalence and severity in infants with SPT greater than 4 mm. Median peanut SPT size in tolerant infants was 4 mm (range, 0–11 mm) compared with 8 mm (0–16 mm) in nontolerant infants ($P < .01$). Peanut SPT size and peanut IgE levels overlapped between tolerant and nontolerant groups; however, Ara h2 IgE appeared to distinguish reactivity, especially in infants with SPT greater than 4 mm ($P < .05$). Receiver operating characteristic curves showed that Ara h2 greater than or equal to 1.05 kU/L was associated with 75% sensitivity and 72% specificity for peanut reaction, whereas a level of greater than or equal to 6.05

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Table 1
 Demographic and Biomarker Results for Peanut OFC by Tolerance and SPT Size

	SPT ≤ 4 mm		P value	SPT > 4 mm		P value	SPT 5-7 mm		P value	SPT > 7 mm		P value
	(n = 30)			(n = 40)			(n = 18)			(n = 22)		
	Tolerant	Not tolerant		Tolerant ^a	Not tolerant		Tolerant	Not tolerant		Tolerant	Not tolerant	
	(n = 29)	(n = 1)		(n = 25)	(n = 15)		(n = 13)	(n = 5)		(n = 12)	(n = 10)	
Demographics												
Age, mean (range, mo)	9.8 (6-13)	9 (9)	NS+	9.2 (6-13)	9.9 (6-13)	NS	8.9 (6-13)	10.2 (7-13)	NS	9.5 (8-12)	9.8 (6-13)	NS
Sex, male, n (%)	17 (59%)	1 (100%)	NS	15 (60%)	10 (67%)	NS	7 (54%)	4 (80%)	NS	8 (67%)	6 (60%)	NS
Race												
White	15 (52%)	1 (100%)	NS	12 (48%)	6 (40%)	NS	7 (54%)	6 (43%)	NS	5 (42%)	3 (30%)	NS
African American	6 (21%)	0 (0%)		7 (28%)	3 (20%)		3 (23%)	3 (21%)		4 (33%)	3 (30%)	
Hispanic	2 (7%)	0 (0%)		1 (4%)	2 (13%)		0 (0%)	2 (14%)		1 (8%)	1 (10%)	
Asian	0 (0%)	0 (0%)		1 (4%)	0 (0%)		0 (0%)	0 (0%)		1 (8%)	0 (0%)	
Other	6 (21%)	0 (0%)		4 (16%)	3 (20%)		3 (23%)	3 (21%)		1 (8%)	3 (30%)	
Any eczema	22 (76%)	1 (100%)	NS	19 (76%)	13 (87%)	NS	10 (77%)	4 (90%)	.02	9 (75%)	9 (90%)	NS
Moderate-severe eczema	8 (28%)	0 (0%)	NS	6 (24%)	4 (27%)	.04	3 (23%)	2 (40%)	NS	3 (25%)	2 (20%)	.08
Egg sensitization	14 (48%)	1 (100%)	NS	14 (56%)	6 (40%)	NS	6 (46%)	1 (20%)	NS	8 (67%)	5 (50%)	NS
Other food sensitization	7 (24%)	0 (0%)	NS	6 (24%)	8 (53%)	NS	5 (38%)	3 (60%)	NS	1 (8%)	5 (50%)	NS
Sibling with food allergy ^b	0 (0%)	0 (0%)	NS	0 (0%)	2 (13%)	NS	0 (0%)	0 (0%)	NS	0 (0%)	2 (20%)	NS
Suspected peanut allergy	1 (3%)	0 (0%)	NS	4 (16%)	1 (7%)	NS	3 (23%)	0 (0%)	NS	1 (8%)	1 (10%)	NS
Peanut testing at baseline												
SPT wheal, median, mm (range)	0 (0-4)	3 (3)	NS	6.5 (5-11)	10 (5-16)	.10	6 (5-7)	5 (5-7)	NS	9 (8-11)	10 (8-16)	.03
Peanut IgE (kU/L), median (range)	1.50 (<0.10-26.1)	8.65 (8.65)	NS	1.47 (0.16-28.9)	3.97 (0.65-31.2)	.08	2.73 (0.16-28.9)	296 (0.65-11.8)	NS	1.14 (0.3-10.7)	4.56 L (1.2-31.2)	.07
Ara h 2 IgE (kU/L), median (n = 52) (range)	<0.10 (<0.10-3.23)	<0.10 (<0.10)	NS	0.62 (<0.10-13.8)	6.49 (0.47-19.3)	.02	0.58 (0-13.8)	3.76 (0.47-12.5)	NS	1.61 (<0.10-9.57)	6.78 (0.63-19.3)	NS
Peanut IgE / Total IgE-median (n = 48) (range)	1.1 (0-0.12)	0.09 (0.09)	NS	0.02 (0.003-0.31)	0.06 (0.01-0.42)	NS	0.03 (0.003-0.16)	0.04 (0.03-0.42)	NS	0.01 (0.01-0.31)	0.06 (0.01-0.26)	NS

Abbreviations: NS, not significant; OFC, oral food challenge; SPT, skin prick test.

NOTE. Statistical analyses were performed in Stata/SE 13.1. +NS denotes $P > .10$.

^aEight infants deemed tolerant had mild, self-resolving hives during OFC.

^bThese patients also had egg sensitization and atopic dermatitis.

kU/L was associated with 58% sensitivity and 92% specificity (AUC 0.8).

Our study presented data on infants with peanut SPT greater than 4 mm who had not been extensively studied. Ara h2 was a predictor for reaction, notably in infants with SPTs greater than 4 mm. Our population also included a substantial proportion of African American patients, a population that is habitually underrepresented in food allergy research. More than 50% of children with peanut SPT greater than 4 mm tolerated 1 g peanut, including those with peanut SPT greater than 7 mm who would otherwise avoid peanut based on established cutoffs. Most of these infants safely incorporated peanut into their diet. There were no severe reactions, transfers to the emergency department, or admissions. Although risks still exist, this population may benefit considerably from early dietary peanut in a supervised OFC setting. For infants with SPT less than or equal to 4 mm (97%), it is likely safe to introduce peanut at home or in an office setting, consistent with current guidelines.

We did not consider peanut OFC of a 1 g dose to be peanut OIT owing to the significantly higher starting dose of 1000 mg compared with published OIT protocols. We did advise regular ingestion of peanut at home with gradual escalation and epinephrine carriage (similar to OIT), though much less regimented with regard to the form of peanut and pacing of up-dosing. Counseling concerning observation and illness did not differ from what we advise all patients regarding food introduction. Our strategy facilitated the incorporation of peanut into the infant's diet in a developmentally accommodating manner rather than delaying introduction (and missing a potential window for an early introduction) because of the inability to complete a standard peanut OFC dose,^{1,4,9} parental anxiety, or other factors.

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References

1. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(9):803–813.
2. Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med*. 2016;374(18):1733–1743.
3. Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol*. 2017;139(1):173–181.e8.
4. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *J Allergy Clin Immunol*. 2017;139(1):29–44.
5. Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. *J Allergy Clin Immunol*. 2005;115(6):1291–1296.
6. Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. *Pediatr Allergy Immunol*. 2004;15(5):435–441.
7. Perkin MR, Logan K, Marrs T, et al. Enquiring About Tolerance (EAT) study: feasibility of an early allergenic food introduction regimen. *J Allergy Clin Immunol*. 2016;137(5):1477–1486.e8.
8. Garvey AA, O'Sullivan D, Hourihane JO. Home-based induction of sustained unresponsiveness in children with mild reactions to high doses of peanut. *J Allergy Clin Immunol Pract*. 2017;5(6):1757–1759.
9. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130(6):1260–1274.
10. Muraro A, Roberts G, Clark A, et al. The management of anaphylaxis in childhood: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. 2007;62(8):857–871.