Original Article

Community Private Practice Clinical Experience with Peanut Oral Immunotherapy

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What is already known about this topic? Food allergies, including peanut allergy, are increasing in the United States, and peanut oral immunotherapy has been used in several centers as an effective treatment.

What does this article add to our knowledge? The safety of peanut oral immunotherapy has been debated. This article examines the rates of adverse events in patients on peanut oral immunotherapy and proposes patient and immunologic factors that may be associated with adverse reactions.

How does this study impact current management guidelines? This study aims to provide clinicians with data from private practice clinical experience using peanut oral immunotherapy to help anticipate and prepare for possible adverse events and develop strategies for more individualized treatments.

BACKGROUND: Peanut oral immunotherapy is an effective treatment for desensitizing peanut-allergic patients, but the frequency of adverse reactions has limited its widespread use.
OBJECTIVE: To review the frequency of adverse reactions that patients on peanut oral immunotherapy experience during build-up and maintenance phases and explore factors that may contribute to adverse events.
METHODS: A retrospective chart review of children and adults with peanut allergy undergoing peanut oral immunotherapy at the New England Food Allergy Treatment Center in West Hartford, Conn was performed. Data on patient demographics, allergic profile, peanut allergy testing, and details of reactions in build-up and maintenance phases were collected. A systemic reaction was defined as one of the following: (1) severe reaction involving 1 system, such as generalized hives and/or angioedema; (2) 2 or more of the following symptoms: cutaneous or oral, respiratory, or gastrointestinal symptoms; (3) drop in blood pressure; or (4) need for epinephrine.
RESULTS: Data were available on 783 patients aged 3.5 to 48.3 years. During buildup, 78 patients (10%) experienced at least 1 systemic reaction, 660 (84%) at least 1 gastrointestinal adverse event, 369 (47%) at least 1 cutaneous adverse event, and 157 (20%) at least 1 respiratory adverse event. Thirty-four patients (4%) required epinephrine during buildup. Six hundred ninety-seven patients (89%) completed buildup and progressed to maintenance. During maintenance, 131 patients (19%) experienced at least 1 systemic reaction, 190 (27%) at least 1 gastrointestinal adverse event, 104 (15%) at least 1 cutaneous adverse event, and 50 (7%) at least 1 respiratory adverse event. Seventy-four patients (11%) required epinephrine during maintenance. None of the adverse events required hospitalizations, and there were no mortalities. Nine patients (1%) were diagnosed with eosinophilic esophagitis during buildup or maintenance. Increasing pretreatment peanut specific IgE levels were associated with increased odds of a systemic reaction during buildup. Increasing age, pretreatment peanut specific IgE level, and a systemic reaction in buildup were associated with increased odds of a systemic reaction during maintenance.
CONCLUSIONS: Peanut oral immunotherapy may be an effective and safe treatment for carefully selected peanut-allergic patients under the guidance of experienced providers. Specific patient characteristics and immunologic factors may help predict adverse events. **(J Allergy Clin Immunol Pract 2020;8:2727-35)**

Key words: *Food allergy; Peanut oral immunotherapy; Systemic reactions; Epinephrine use*

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INTRODUCTION

Food allergies increased in prevalence in recent years and may affect approximately 8% of the population in the United States,

Abbreviations used
NEFATC- New England Food Allergy Treatment Center
OIT- Oral immunotherapy
OR- Odds ratio
PN-OIT- Peanut oral immunotherapy

with peanut and tree nut allergy affecting approximately 2%.[1-3] Peanut allergy is a major health concern due to the risk for anaphylaxis and adverse effects on the quality of life.[4-9] Recommended treatment for food allergies has traditionally been strict dietary avoidance and the use of epinephrine autoinjectors for systemic reactions. Although this has been a fairly effective strategy, it is difficult for many patients and their families to implement and follow strict avoidance.[10-12] Furthermore, accidental ingestions are not uncommon, with an annual incidence of 12% to 14%.[13,14]

There is an emerging need in the community for alternative approaches to managing peanut allergy. Peanut oral immunotherapy (PN-OIT) has been demonstrated, in both research and private practice settings, to be a safe and effective treatment.[15-21] In addition, PN-OIT may have a positive impact on the quality of life.[22]

Although an increasing number of allergy specialists have incorporated PN-OIT into their clinical practice, there is reluctance of many to offer this treatment to their patients. The concern is that more research is needed to evaluate the safety and long-term efficacy of PN-OIT. Currently, there is also a paucity of data that allows us to evaluate which patients may be at the highest risk of adverse events from PN-OIT.

Our center has extensive clinical experience, with 783 children and adults with peanut allergy treated to date. This study aimed to characterize clinical reactions that patients have experienced during build-up and maintenance phases of PN-OIT. We also aimed to explore clinical and immunologic factors, such as age, sex, pre-OIT peanut specific serum IgE, presence of atopy, and severity of peanut reactions before PN-OIT, that may be associated with adverse events.

METHODS

Patients

We studied 783 patients who underwent PN-OIT at the New England Food Allergy Treatment Center (NEFATC) in West Hartford, Conn. Some patients were self-referred, whereas others were referred by physicians in the community. Patients initiated PN-OIT between November 2010 and August 2016. Patients were diagnosed with peanut allergy on the basis of a positive clinical history, an elevated immunoCAP level (peanut IgE $\geq$ 15 kU/L), and/or peanut skin test size (wheal $\geq$ 8 mm diameter). Serum and skin peanut allergy testing was done within 1 year before starting PN-OIT. In a minority of patients, lower immunoCAP levels or smaller peanut skin test wheals were deemed diagnostic if the clinical history indicated a recent or significant allergic reaction. In patients who failed to meet entry criteria, an oral challenge was performed. Written informed consent was obtained from patients or their parents before the start of desensitization. Patients younger than 2 years, those with uncontrolled asthma, history of eosinophilic esophagitis, history of previous reactions requiring intensive care admission or intubation, and inability to comply with regular dosing regimen were excluded. Pregnant women and women who were planning to become pregnant were excluded.

Procedures

NEFATC is a private community-based center established to exclusively perform food allergen desensitization therapy. Patients received PN-OIT as part of treatment for their allergies and not as part of a research protocol. The goal of this treatment was to protect patients from accidental exposures to peanuts. Patients were desensitized to peanut protein through daily ingestion of peanut flour and then transitioned to other peanut products as shown in Figure 1. Byrd Mill 12% light roast peanut flour was used for all doses 400 mg and lower and was provided by NEFATC. Patients were transitioned to peanuts, peanut M&M's, or peanut butter M&M's. At higher doses, PB2 dehydrated peanut butter and regular peanut butter were additional options. The peanut dose was increased every 2 weeks as tolerated until a maintenance dose was reached and was continued daily thereafter. Minimal maintenance dose was 2.5 peanuts per day, but some patients did go up to 15 peanuts per day. Patients were asked to come in to switch dosing forms in maintenance. In case of missed doses, if fewer than 3 doses were missed, patients were instructed to resume home dosing. If greater than 3 doses were missed, patients were instructed to call the center. Beyond 3 days of missed doses, the dose would typically be reduced, and patients would be instructed to come in to the clinic for redosing. Patients were seen every 2 weeks during build-up. Patients on maintenance were asked to return for follow-up every 6 months. Most patients continued follow-up in maintenance for about 2 years.

Patients and their parents were asked to record their side effects using a daily diary, which was reviewed with center staff at each visit before increasing, continuing, or decreasing the dose. Patients were instructed to avoid exertion for 2 hours after dosing and to hold a dose in an event of a febrile illness and poorly controlled asthma. Patients who experienced adverse events during their menstrual cycle were asked to hold the dose during menses. In addition, patients were advised to consume their dose with food, preferably a high-carbohydrate meal.

For daily diaries, patients were asked to record instances of cutaneous, gastrointestinal, respiratory, and systemic symptoms. Cutaneous symptoms that were considered significant included urticaria, angioedema, erythema, worsening atopic dermatitis, other rashes, pruritis, or itchy eyes. Gastrointestinal complaints included abdominal pain or oropharyngeal itching that did not resolve without treatment in 15 minutes, abdominal pain described as moderate/severe, nausea/emesis, reflux, or difficulty swallowing. Respiratory symptoms included throat or chest tightness, chest pain, wheezing, shortness of breath, or significant nasal congestion. A systemic reaction was defined as 1 of the following: (1) severe reaction involving 1 system, such as generalized hives and/or angioedema; (2) 2 or more of the following symptoms: cutaneous or oral symptoms, respiratory symptoms, or gastrointestinal symptoms; (3) drop in blood pressure after taking a peanut dose; or (4) need for epinephrine.

Data collection

A retrospective analysis of the patients' charts who have undergone PN-OIT at NEFATC was approved by the Yale institutional review board. OnCore, a Yale protected database, was used for data collection and storage.

The charts of 783 patients who have undergone PN-OIT were reviewed, and data were collected on patients' demographics, history

		Peanut OIT Protocol		Adjustments to protocol used		
Visit 1#		0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 1.5 mg, 3 mg		**Target dose:** -320 patients were updosed to 2.5 peanuts or 3 peanut M&M's (visit 16) -423 patients were updosed to 6 peanuts or 8 peanut M&M's (visit 19) -40 patients were updosed to target dose of 10-15 peanuts or 12-20 peanut M&M's** *doses added about halfway through the protocol **when patients were uptitrated to 15 peanuts, the following additional titrations were used 8 peanuts ->10 peanuts -> 12 peanuts -> 15 peanuts # Byrd Mill flour was used for all doses 400 mg and lower		
Visit 2#		6 mg				
Visit 3#		9 mg*				
Visit 4#		12 mg				
Visit 5#		18 mg*				
Visit 6#		25 mg				
Visit 7#		35 mg*				
Visit 8#		50 mg				
Visit 9#		75 mg				
Visit 10#		100 mg				
Visit 11#		125 mg				
Visit 12#		165 mg				
Visit 13#		225 mg				
Visit 14#		300 mg				
Visit 15#		400 mg				
Visit 16	2.5 peanuts	3 peanut M&M's	4 PN butter M&M's	-	-	-
Visit 17	3 peanuts	4 peanut M&M's	5 PN butter M&M's	¾ tsp PB2 dehydrated peanut butter	1 miniature Reese's peanut butter cup	½ tsp Peanut butter
Visit 18	4 peanuts	5 peanut M&M's	6 PN butter M&M's	1 tsp PB2 dehydrated peanut butter	-	-
Visit 19	6 peanuts	8 peanut M&M's	9 PN butter M&M's	1 ½ tsp PB2 dehydrated peanut butter	2 miniature Reese's peanut butter cup	1 tsp Peanut butter

FIGURE 1. Details of the PN-OIT protocol used by the NEFATC.

of peanut allergy, confirmatory testing for peanut allergy (including pre-OIT peanut ImmunoCAP, total IgE, peanut component testing, peanut skin testing, and oral challenge results, if available), presence of other atopic and allergic conditions, date of the start of PN-OIT, date of transition to maintenance, discontinuation of treatment, and reasons for discontinuation.

For build-up and maintenance phases, data were collected on cutaneous, respiratory, gastrointestinal, and systemic reactions. Any new gastrointestinal medications that were started during buildup were included. New diagnoses of eosinophilic esophagitis were included. Epinephrine use and need for physician, urgent care, or emergency room visit for treatment of systemic reactions were recorded. If present, any associated patient-reported potential triggers for systemic reactions were recorded.

Data analysis

Clinical histories were summarized using mean, SD, frequencies, and proportions. Unadjusted associations between outcomes of interest (systemic, gastrointestinal, respiratory reactions in build-up and systemic reactions in maintenance) and demographic and immunologic parameters were examined using binary logistic regression. The following predictors were considered: age, sex, pre-OIT peanut IgE, need for epinephrine for reactions to peanuts before starting oral immunotherapy (OIT), presence of eczema, and presence of asthma. Systemic reaction during buildup was explored as predictor of systemic reaction in maintenance. Multivariable logistic regression was used for adjusted analyses. We checked for potential multicollinearity by examining all bivariable associations among predictors using either the χ^2 test, student t test, or Spearman correlation coefficient. Variables were retained in the model at alpha of 0.10, as well as on the basis of their clinical meaningfulness. Results were summarized using odds ratios (ORs) and 95% CI. Analysis was done using SPSS Statistics version 24 (IBM Corp, Armonk, NY).

RESULTS

Patient characteristics

Table I presents patient characteristics. Mean age at OIT initiation was 9.7 ± 4.8 years (3.5-48.3). Ninety-seven percent of patients were younger than 18 years. Thirty-eight percent of patients were female. Average age at peanut allergy onset was 2.6 ± 2.8 years (0.2-26). Eighty-six percent of patients reported previous clinical reaction to peanuts, with 25% previously needing epinephrine and 30% requiring emergency room visits. Patients in the study also had significant comorbid atopy: 65% had additional food allergies, 55% had allergic rhinitis, 53% had asthma, and 42% had atopic dermatitis. Mean size of pre-OIT skin test was 13.1 ± 5.2 mm (range, 0-40 mm) for wheal and 28.1 ± 10.4 mm (range, 0-70 mm) for flare. Very few patients (0.6%) had pre-OIT skin test wheal less than or equal to 3 mm. Mean value for pre-OIT serum peanut IgE was 53.1 ± 41.2 kU/L (range, 0->100 kU/L). Six and a half percent of patients had a pre-OIT peanut IgE level of less than or equal to 0.35 kU/L. Pre-OIT component testing is included in Table I.

Adverse events during the build-up phase

Mean duration that patients spent in buildup was 230.5 ± 83.2 (1-697) days. A few patients (2.6%) spent less than 30 days in buildup; 6.1% of patients spent less than 90 days in buildup. As shown in Figure 2, *A*, during the build-up phase, 660 patients

TABLE I. Patient characteristics

Characteristic	Sample size	Value
No. of patients		783
Age (y)	776	9.7 ± 4.8 (3.5-48.3)
Sex	783	Female: 38% Male: 62%
Characteristics of peanut allergy before OIT initiation		
Patient's age at peanut allergy onset (y)	568	2.6 ± 2.8 (0.2-26)
% of patients with previous clinical allergic reaction to peanut	780	86%
% of patients requiring epinephrine for previous peanut reaction	734	25%
% of patients requiring ER visit for previous peanut reaction	749	30%
Associated atopic conditions		
% of patients with other food allergies	782	65%
% of patients with allergic rhinitis	782	55%
% of patients with asthma	780	53%
% of patients with atopic dermatitis	783	42%
Pre-OIT testing		
SPT (wheal/flare) (mm/mm)	346	13.1 ± 5.2/28.1 ± 10.4
Peanut specific IgE (kU/L)	718	53.1 ± 41.2 (0-100)
Arah1 (kU/L)	386	27.5 ± 33.4
Arah2 (kU/L)	386	42.6 ± 38.7
Arah3 (kU/L)	386	11.6 ± 22.1
Arah8 (kU/L)	386	4.7 ± 13.2

ER, Emergency room; *SPT*, skin prick test.
Values recorded as mean ± SD (minimum-maximum).

(84%) experienced at least 1 gastrointestinal adverse event. Three hundred sixty-nine patients (47%) experienced at least 1 cutaneous adverse event. One hundred fifty-seven patients (20%) experienced at least 1 respiratory adverse event. Seventy-eight patients (10%) experienced a total of 110 systemic reactions. Table II presents frequencies of multiple systemic reactions during buildup. Thirty-four patients (4%) required epinephrine for at least 1 of their systemic reactions. Characteristics of systemic and single-system adverse reactions during buildup are presented in Tables III and IV.

As presented in Table V, increasing pre-OIT peanut IgE levels were associated with increased odds of having at least 1 systemic reaction during buildup (OR per increase in 1 SD of pre-OIT peanut IgE, 1.65; 95% CI, 1.24-2.20; $P = .001$), controlling for age, sex, need for epinephrine for peanut allergy before OIT, presence of asthma and eczema, and duration of buildup. When patients who dropped out during the build-up phase were excluded from the analysis, increasing pre-OIT peanut IgE levels remained significantly associated with increased odds of having at least 1 systemic reaction during buildup (OR per increase in 1 SD of pre-OIT peanut IgE, 1.63; 95% CI, 1.20-2.21; $P = .002$), controlling for above factors (data not shown). Increasing pre-OIT peanut IgE level was associated with increased odds of having at least 1 gastrointestinal reaction during buildup (OR per increase in 1 SD of pre-OIT peanut IgE, 1.65; 95% CI, 1.29-2.11; $P < .001$), controlling for age, sex, need for epinephrine for peanut allergy before OIT, presence of asthma and eczema, and duration of buildup (data not shown).

Systemic reactions during the build-up phase

Mean number of days from the start of therapy to an episode of systemic reaction was 151.7 ± 98.1 (0-382 days). As shown in Table III, of 110 systemic reactions, 47 (43%) required treatment with epinephrine. Fifty-three (48%) required a visit to a medical professional. Forty-four of the episodes required a visit to the emergency department, 7 required a visit to a physician in a medical office or urgent care, 1 was seen in our center, and 1 patient was seen by a family member who is a physician assistant. None required hospitalizations. No fatalities occurred.

No clearly associated factors to explain systemic reactions were self-reported by patients in most cases. Thirteen percent of the episodes cited association with exercise within 2 hours of taking a peanut dose. Additional 3.6% of the episodes cited association with exercise within 3 hours of taking a peanut dose. In additional 5.4% of the episodes, patients reported vigorous exercise on the same day as the peanut dose (one-half reported exercise before the dose; one-half did not specify the time frame between the dose and exercise). Other patient self-reported factors associated with systemic reactions included unrelated illness (5% of episodes), possible cross-contamination (1.8% of episodes), alcohol use (1% of episodes), menses (1% of episodes), and stress (1% of episodes). There was no association between systemic reaction rates and the month of the year (data not shown). In 6.3% of systemic reactions, based on patient report of the reaction, reactions were thought to be unrelated or unlikely related to peanut ingestion.

Gastrointestinal reactions during the build-up phase

As shown in Table IV, of 783 patients, 533 patients (68%) reported at least 1 episode of abdominal pain, 375 (48%) at least 1 episode of oral itch, 218 (28%) at least 1 episode of vomiting, 123 (16%) at least 1 episode of nausea, 101 (13%) at least 1 episode of reflux, and 82 (10%) at least 1 episode of difficulty swallowing. Ninety-four patients (12%) started a medication for gastrointestinal symptoms during the build-up phase. Eight (1%) started proton pump inhibitors. Seventy-eight (10%) started H2

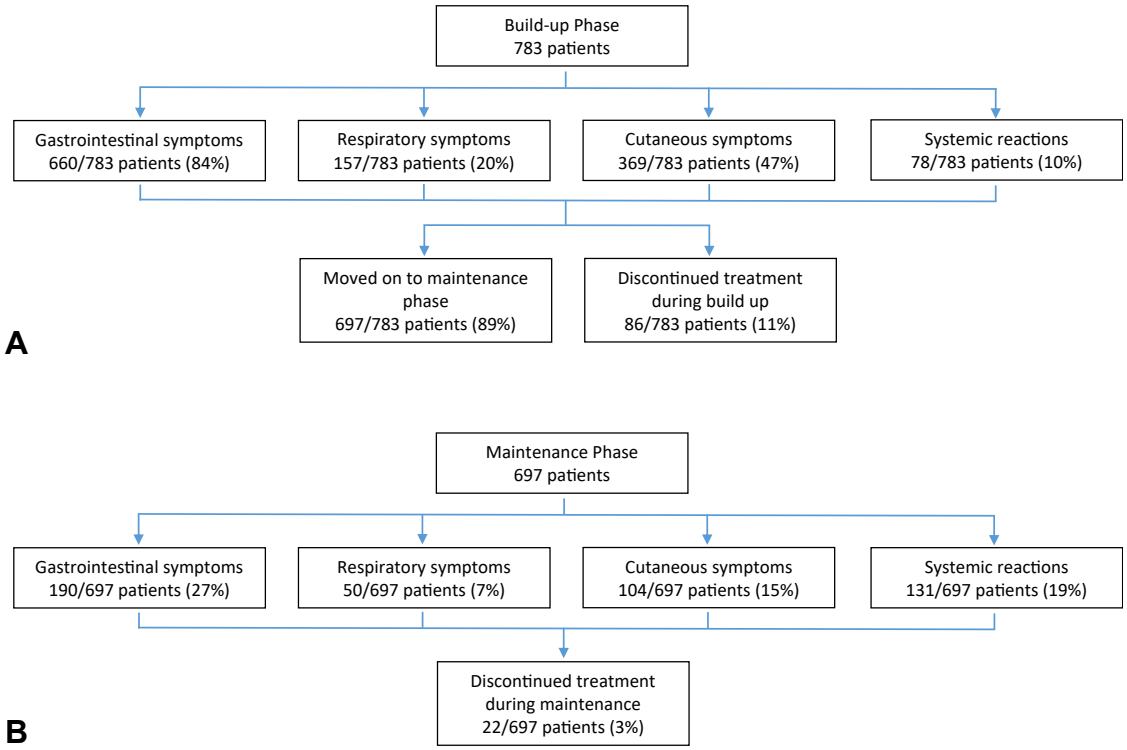

FIGURE 2. (**A**) Adverse reactions during the build-up phase. A flow diagram demonstrating the number of patients who started in the build-up phase and distribution of adverse reactions experienced. Number of patients who moved on to maintenance and number of patients who discontinued treatment during the build-up phase are also shown. (**B**) Adverse reactions during the maintenance phase. A flow diagram demonstrating the number of patients who started in the maintenance phase and distribution of adverse reactions experienced. Number of patients who discontinued treatment during the maintenance phase is shown.

TABLE II. Multiple systemic reactions during build-up and maintenance phases

	No. of patients (%)	
No. of reactions	Build-up phase	Maintenance phase
1+ systemic reactions/patient	78 (10.0)	131 (18.8)
2+ systemic reactions/patient	20 (2.6)	39 (5.6)
3+ systemic reactions/patient	9 (1.1)	14 (2.0)
4+ systemic reactions/patient	2 (0.3)	7 (1.0)
5 systemic reactions/patient	1 (0.1)	—

TABLE III. Characteristics of systemic reactions during the build-up phase

Characteristics of systemic reactions	n (%)
No. of systemic reactions reported	110
No. of reactions requiring epinephrine (% of total systemic reactions)	47 (43)
No. of reactions requiring antihistamine (% of total systemic reactions)	60 (55)
No. of reactions requiring a visit to a medical professional (% of total systemic reactions)	53 (48)
Patients seen in the emergency department (% of patients seen by medical professional)	44 (83)

blockers. Four patients (0.5%) were diagnosed with eosinophilic esophagitis.

Cutaneous reactions during the build-up phase

As shown in Table IV, of the 783 patients, 216 (28%) developed at least 1 episode of hives, 79 (10%) at least 1 episode of angioedema, 21 (3%) at least 1 episode of atopic dermatitis, 52 (7%) at least 1 episode of other rashes, 135 (17%) at least 1 episode of skin itching, and 48 (6%) at least 1 episode of itchy eyes.

Respiratory reactions during the build-up phase

As shown in Table IV, of 783 patients, 26 (3%) experienced at least 1 episode of shortness of breath, 22 (3%) at least 1 episode of chest tightness, 33 (4%) at least 1 episode of wheezing, 17 (2%) reported at least 1 episode of chest pain, and 58 (7%) at least 1 episode of rhinorrhea or nasal congestion.

TABLE IV. Characteristics of single-system adverse events during the build-up phase

Characteristic	Patients with at least 1 episode, n (%)	Mean number of episodes reported per patient, mean ± SD
Gastrointestinal symptoms		
Abdominal pain	533 (68)	7.1 ± 11.7
Oral itch	375 (48)	6.0 ± 10.8
Vomiting	218 (28)	2.8 ± 2.8
Nausea	123 (16)	3.1 ± 4.4
Reflux	101 (13)	3.4 ± 4.6
Difficulty swallowing	82 (10)	3.8 ± 11.6
Cutaneous symptoms		
Hives	216 (28)	2.9 ± 3.8
Angioedema	79 (10)	1.9 ± 1.5
Atopic dermatitis	21 (3)	2.6 ± 2.2
Other rash	52 (7)	2.2 ± 3.0
Skin itching	135 (17)	2.5 ± 3.4
Itchy eyes	48 (6)	2.0 ± 2.6
Respiratory symptoms		
Shortness of breath	26 (3)	1.6 ± 1.2
Chest tightness	22 (3)	3.0 ± 4.0
Wheezing	33 (4)	1.5 ± 0.9
Chest pain	17 (2)	3.0 ± 3.6
Rhinorrhea/nasal congestion	58 (7)	1.8 ± 2.4

TABLE V. Multivariable regressions for systemic reactions in build-up and maintenance phases

Parameter	n (%)	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Systemic reactions during the build-up phase					
Age (per increase in 1 SD of age)	—	1.23 (1.00-1.51)	.05	1.20 (0.93-1.53)	.16
Sex (male vs female)	Male 45 (9.3%) Female 33 (11.1%)	0.82 (0.51-1.3)	.42	0.85 (0.51-1.45)	.56
Pre-OIT peanut IgE (per increase in 1 SD of pre-OIT peanut IgE)	—	1.66 (1.27-2.16)	<.0001	1.65 (1.24-2.20)	.001
Has patient required epinephrine for peanut allergy before OIT (yes vs no)	Yes 24 (13.1) No 52 (9.4)	1.45 (0.87-2.43)	.16	1.05 (0.58-1.91)	.88
Presence of eczema (yes vs no)	Yes 29 (8.9) No 49 (10.7)	0.82 (0.51-1.33)	.41	0.93 (0.54-1.59)	.78
Presence of asthma (yes vs no)	Yes 43 (10.4) No 34 (9.2)	1.15 (0.71-1.84)	.58	0.85 (0.51-1.45)	.56
Duration of buildup (per increase in 1 SD of duration of buildup)	—			1.32 (1.05-1.65)	.016
Systemic reactions during the maintenance phase					
Age (per increase in 1 SD of age)	—	1.28 (1.07-1.54)	.007	1.24 (1.01-1.54)	.04
Sex (male vs female)	Male 70 (16.2) Female 61 (22.9)	0.65 (0.44-0.96)	.03	0.62 (0.40-0.96)	.03
Pre-OIT IgE (per increase in 1 SD of pre-OIT IgE)	—	1.81 (1.46-2.24)	<.0001	1.64 (1.31-2.07)	<.0001
Has patient required epinephrine for peanut allergy before OIT (yes vs no)	Yes 39 (24.4) No 79 (16.2)	1.67 (1.08-2.58)	.02	1.51 (0.93-2.46)	.09
Presence of eczema (yes vs no)	Yes 49 (17.3) No 82 (19.8)	0.85 (0.57-1.25)	.41	—	—
Presence of asthma (yes vs no)	Yes 75 (20.9) No 56 (16.7)	1.32 (0.90-1.93)	.16	—	—
Presence of systemic reaction during buildup (yes vs no)	Yes 31 (34.9%) No 100 (15.9%)	4.01 (2.56-7.25)	<.0001	3.09 (1.73-5.53)	<.0001

Adverse events during the maintenance phase

As shown in Figure 2, *B*, during maintenance follow-up, 190 (27%) patients experienced at least 1 gastrointestinal adverse event. One hundred four (15%) experienced at least 1 cutaneous adverse event. Fifty (7%) experienced at least 1 respiratory adverse event. One hundred thirty-one (19%) experienced at

TABLE VI. Characteristics of systemic reactions during the maintenance phase

Characteristics of systemic reactions	n (%)
No. of systemic reactions	191
No. of reactions requiring epinephrine (% of total systemic reactions)	94 (49)
No. of reactions requiring antihistamine (% of total systemic reactions)	101 (53)
No. of reactions requiring a visit to a medical professional (% of total systemic reactions)	120 (63)
Patients seen in the emergency department (% of patients seen by medical professional)	106 (88)

least 1 systemic reaction, with a total number of 191 reported systemic reaction episodes. Table II presents frequencies of multiple systemic reactions during maintenance. Seventy-four patients (11%) required treatment with epinephrine. Characteristics of systemic and single-system adverse reactions during maintenance are presented in Tables VI and VII.

As shown in Table V, increasing age (OR per increase in 1 SD of age, 1.24; 95% CI, 1.01-1.54; $P = .04$), pre-OIT peanut IgE (OR per increase in 1 SD of pre-OIT peanut IgE, 1.64; 95% CI, 1.31-2.07; $P < .0001$), as well as sex (OR male vs female, 0.62; 95% CI, 0.40-0.96; $P = .03$) and presence of systemic reaction during buildup (OR yes vs no, 3.09; 95% CI, 1.73-5.53; $P < .0001$) were associated with increased odds of having at least 1 systemic reaction during maintenance, controlling for need for epinephrine for peanut allergy before starting OIT. When patients who dropped out during the maintenance phase were excluded, increasing age (OR per increase in 1 SD of age, 1.24; 95% CI, 1.01-1.53; $P = .04$), pre-OIT peanut IgE (OR per increase in 1 SD of pre-OIT peanut IgE, 1.63; 95% CI, 1.30-2.06; $P < .0001$), and presence of systemic reaction during buildup (OR yes vs no, 3.14; 95% CI, 1.73-5.72; $P < .0001$) remained significantly associated with increased odds of having at least 1 systemic reaction during maintenance, controlling for rest of the above factors.

Systemic reactions during the maintenance phase

Mean number of days to first systemic reaction since starting maintenance was 357.7 ± 378.3 (range, 2-2038 days). As shown in Table VI, 94 (49%) episodes required epinephrine. One hundred twenty episodes (63%) resulted in a visit to a medical professional. Of these, 106 resulted in a visit to the emergency department, 2 required a call to the emergency medical services but did not require a visit to the hospital, 8 required a visit to a physician in medical office or urgent care, 2 were treated in our center, and 2 required a visit to the nurses' office. None required hospitalization. No fatalities occurred.

No associated patient-reported factors to explain systemic reactions were reported in most cases. Fourteen percent of the systemic reactions were reported to be associated with exercise within 2 hours of taking a peanut dose. An additional 8% of the episodes were reported to be associated with vigorous exercise on the same day as the peanut dose. Other patient-reported factors associated with systemic reactions included concurrent illness (3.5% of episodes), combination of illness and exercise (0.5% of episodes), possible cross-contamination or accidental ingestion of larger amount of peanut (3.6% of episodes), missed doses on previous days (3.6% of episodes), switch to a different peanut product (1.5% of episodes), hot bath or shower right after the dose (2.6% of episodes), or stressful life event (0.5% of episodes). In 6% of cases, based on patient's report of the reaction, it was thought to be unrelated or unlikely related to peanut ingestion.

Gastrointestinal reactions during the maintenance phase

As shown in Table VII, of 697 patients, 94 (13%) patients reported at least 1 episode of abdominal pain, 90 (13%) at least 1 episode of oral itch, 51 (7%) at least 1 episode of vomiting, 22 (3%) at least 1 episode of nausea, 15 (2%) at least 1 episode of reflux, and 18 (3%) at least 1 episode of difficulty swallowing. Five (0.7%) patients were diagnosed with eosinophilic esophagitis during the maintenance phase.

Cutaneous reactions during the maintenance phase

As shown in Table VII, of 697 patients, 59 (8%) developed at least 1 episode of hives, 28 (4%) at least 1 episode of swelling/angioedema, 2 (0.3%) at least 1 episode of atopic dermatitis, 15 (2%) at least 1 episode of other rashes, 20 (3%) at least 1 episode of skin itching, and 12 (2%) at least 1 episode of itchy eyes.

Respiratory reactions during the maintenance phase

As shown in Table VII, of 697 patients, 10 (1%) developed at least 1 episode of shortness of breath, 5 (1%) at least 1 episode of chest tightness, 16 (2%) at least 1 episode of wheezing, 4 (1%) reported at least 1 episode of chest pain, and 10 (1%) at least 1 episode of rhinorrhea or nasal congestion.

Discontinuation of treatment

Eighty-six of 783 (11%) patients stopped treatment during the build-up phase. Twenty-two of 697 patients (3%) stopped treatment during the maintenance phase. Of 108 patients who stopped treatment, 43 (40%) reported their gastrointestinal symptoms as a primary reason for discontinuation, 20 (19%) reported quality-of-life issues such as inconvenience, time constraint, travel, study abroad, dislike of the peanut taste, and expense, 10 (9%) reported systemic reactions, 5 (5%) had unrelated illness for which they discontinued treatment and never restarted, 4 (4%) reported worsening respiratory symptoms, 1 (1%) became pregnant, and 1 (1%) experienced persistent tongue itching. Twenty-four (22%) patients did not identify their reason for discontinuation.

DISCUSSION

To our knowledge, this is the largest study examining the safety of private practice experience with PN-OIT in children and adults with peanut allergy. It confirms previous experiences that PN-OIT carries risks, but can be practiced as an effective treatment for carefully selected peanut-allergic patients in centers equipped to manage adverse events associated with this therapy. Our study also explores clinical and immunologic factors that may be associated with increased adverse events from PN-OIT.

Eighty-nine percent of patients in our study were able to progress from buildup to maintenance. This finding is similar to those previously reported in the 2014 study by Wasserman et al,[18] looking at the multiple practices experience with PN-OIT, where 85% of patients achieved a target maintenance dose.

The side-effect profile demonstrated in our study is also similar to those previously reported.[16,18] Although most patients experienced skin, respiratory, or gastrointestinal reactions, the

TABLE VII. Characteristics of single-system adverse events during the maintenance phase

Characteristic	Patients with at least 1 episode, n (%)	Mean number of episodes reported per patient, mean ± SD
Gastrointestinal symptoms		
Abdominal pain	94 (13)	3.1 ± 3.8
Oral itch	90 (13)	4.5 ± 8.5
Vomiting	51 (7)	2.3 ± 3.3
Nausea	22 (3)	1.4 ± 0.7
Reflux	15 (2)	2.0 ± 1.6
Difficulty swallowing	18 (3)	1.6 ± 1.1
Cutaneous symptoms		
Hives	59 (8)	2.0 ± 2.3
Angioedema	28 (4)	1.7 ± 1.5
Atopic dermatitis	2 (0.3)	1.0 ± 0.0
Other rash	15 (2)	1.5 ± 1.2
Skin itching	20 (3)	1.6 ± 1.0
Itchy eyes	12 (2)	1.3 ± 0.9
Respiratory symptoms		
Shortness of breath	10 (1)	3.1 ± 3.9
Chest tightness	5 (1)	1.4 ± 0.9
Wheezing	16 (2)	3.1 ± 4.5
Chest pain	4 (1)	1.0 ± 0.0
Rhinorrhea/nasal congestion	10 (1)	1.3 ± 0.7

number of reactions necessitating epinephrine use, visits to the emergency room, new medications, and cessation of therapy was relatively low. Gastrointestinal reactions were the most common during buildup, with 84% of patients reporting at least 1 gastrointestinal symptom, but only 11% started either H2 blockers or proton pump inhibitors and 0.5% were diagnosed with eosinophilic esophagitis during buildup.

Systemic reaction rate during buildup was 0.6 systemic reactions per 1000 peanut doses, and systemic reaction rate during the first year of maintenance was 0.5 systemic reactions per 1000 peanut doses. A 2019 meta-analysis of the existing peanut immunotherapy studies estimated predicted rate of anaphylactic reactions of 222 per 1000 individuals (on the basis of baseline risk of 71 reactions per 1000 individuals and risk ratio of 3.12).[23] In our study, 99 per 1000 individuals experienced at least 1 systemic reaction during buildup and 110 per 1000 individuals experienced at least 1 systemic reaction during the first year of maintenance. Per 1000 patients, 140 total reactions (assuming some patients may have had greater than 1 systemic reaction) would be predicted during buildup and 179 reactions would be predicted during the first year of maintenance. Although these numbers are higher than the baseline risk that would be expected with allergen avoidance, it should be noted that epinephrine was used in 47% of the reactions, and 57% required a visit to a medical professional. None of the reactions resulted in hospitalization, intensive care unit admission, or fatality. Our study confirms that PN-OIT is associated with a higher risk of systemic reactions compared with avoidance strategy, but avoids the element of complete unpredictability as would be expected with accidental ingestions.

It is interesting to note that systemic reaction rates did not decrease significantly in maintenance compared with buildup. One explanation for this observation may stem from more frequent follow-up during buildup as well as improved adherence to the dosing regimen and the 2-hour rest period after dosing during buildup. Although relatively few patients self-reported suspected reasons for systemic reactions in both buildup and maintenance, it is interesting to note that although exercise and concurrent illness play a role in both, patients reported missed doses and switch to a different peanut product as reasons for systemic reaction during the maintenance phase. Persistence of systemic reactions into the maintenance phase may suggest that once PN-OIT therapy gains more widespread use, we will need to be particularly careful in patient selection and will need to continue frequent follow-up during maintenance. Whether systemic reactions in the maintenance phase have different etiology compared with those in the build-up phase will need to be explored.

Our study also explored associations of patient demographic and immunologic profiles with odds of having an adverse reaction during buildup and maintenance. Increased pre-OIT peanut specific IgE was associated with increased odds of systemic reactions during buildup. Increased pre-OIT peanut IgE was associated with increased odds of gastrointestinal reactions during buildup. Increased age, pre-OIT peanut specific IgE, and presence of a systemic reaction during buildup were associated with increased odds of systemic reactions in maintenance. As a future of this therapy, it would be ideal to be able to risk stratify patients before starting PN-OIT and adjust patients' treatment protocols on the basis of their risk.

This study is subject to several limitations. This was a retrospective review, subject to potential biases, including patient selection bias. There was no entrance peanut oral challenge requirement; however, this is similar to real-world practice where initiation of PN-OIT would be dependent on clinical judgment, taking patient history and skin and/or immunoCap testing into account. Certain data were missing for certain patients. Data are based on questionnaires and recall of symptoms experienced.

Recall of reasons for systemic reactions is also prone to recall bias because patients were asked to list any and all factors they thought may have been associated with their reactions. It is particularly interesting that many patients chose not to use epinephrine or present to the emergency room for their systemic reactions—again, this is based on real-life experience, and it is quite possible that more patients should have used epinephrine or have been assessed by a medical professional for their symptoms. It is also important to note that patients remained in buildup and maintenance for varying lengths of time with variable follow-up, and we did not collect the information regarding the true duration of maintenance follow-up for each patient.

CONCLUSIONS

This large single-center study of private practice experience with PN-OIT adds to the body of literature confirming that PN-OIT may be safe and can be implemented in a clinical practice setting. Many questions remain regarding the true risk of eosinophilic esophagitis, reasons for persistence of systemic events during the maintenance phase, determination whether PN-OIT can be disease modifying, and identification of risk factors for adverse events during PN-OIT. It would also be interesting to reassess changes to patients' quality of life as a result of PN-OIT in larger studies. As PN-OIT gains more widespread use in clinical practice, it is important that we continue evaluating these questions in both randomized controlled trials and retrospective cohorts to continue to provide the most efficacious and safe therapies for our patients.

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