

# Real-World Experience with Peanut Oral Immunotherapy: Lessons Learned From 270 Patients



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**What is already known about this topic?** Prospective controlled trials have established the safety and efficacy of peanut oral immunotherapy in a research setting.

**What does this article add to our knowledge?** The experience reported here, from a private allergy practice, demonstrates that peanut oral immunotherapy can be performed in a clinical setting with results comparable to those obtained in a research setting.

**How does this study impact current management guidelines?** Clinical practice guidelines, derived from controlled clinical trials, may be informed by real-world experience in a private allergy practice.

**BACKGROUND:** Peanut allergy (PA) is a significant and increasing problem, interfering with psychological development and family life. The standard recommendation to avoid peanut products and have access to injectable epinephrine is often inadequate. Oral immunotherapy for PA has been formally studied. Clinical observations of allergen immunotherapy have repeatedly enhanced patient care.

**OBJECTIVE:** The purpose of this study was to report observations on the treatment of 270 patients with PA over 8.5 years.

**METHODS:** This is a retrospective record review of patients beginning peanut oral immunotherapy between January 1, 2009, and June 1, 2017, approved by the North Texas Institutional Review Board.

**RESULTS:** A total of 270 patients aged 4 to 18 years comprising 107 girls and 163 boys were treated. A total of 214 of 270 patients (79%) completed immunotherapy escalation. Age ( $P < .001$ ) and peanut IgE ( $P < .001$ ) correlate inversely with completing dose escalation. Epinephrine-treated reactions in

63 and isolated gastrointestinal symptoms in 101 patients, respectively, were the most common adverse reactions to treatment but did not preclude success. Peanut IgE decreased by 65% after 3 years of maintenance treatment and 14 of 214 patients (6.5%) were able to achieve sustained unresponsiveness.

**CONCLUSIONS:** In an allergy office practice setting, 79% of patients are able to complete a peanut desensitization protocol and maintain the desensitized state indefinitely with daily dosing. With appropriate planning and precautions, peanut oral immunotherapy may be performed in an allergy office. Careful observations of clinical treatment can contribute to the development of effective treatment strategies. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:418-26)

**Key words:** Peanut allergy; Food allergy; Oral immunotherapy; Food allergy immunotherapy; Food allergy reactions; Sustained unresponsiveness

## INTRODUCTION

In the 7 years between the publication of an editorial stating that peanut oral immunotherapy (POIT) was not ready for clinical use<sup>1</sup> and a review of immunotherapy for food allergy,<sup>2</sup> there have been at least 200 reports of immunotherapy for allergy to various foods. The conclusions of previous reports<sup>3,4</sup> on the psychosocial impact of food allergy have been supported by additional studies of food allergy bullying<sup>5</sup> and degraded family quality of life.<sup>6</sup> During that period, there were more than 1,000,000 emergency department visits for food allergy reactions.<sup>7</sup> The Food and Drug Administration estimates that there are 150 deaths per year due to food allergy.<sup>8</sup> Clearly, there is a need for an alternative to the standard avoidance management strategy.<sup>2,9</sup>

Although previous reports of prospective, randomized controlled trials of POIT have demonstrated that approximately

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Conflicts of interest: At the time of patient treatment and data collection, R. L. Wasserman, A. R. Hague, D. M. Pence, R. W. Sugerman, S. K. Silvers, and J. G. Rolan were employed by Pediatric Allergy/Immunology Associates, Texas, and then Allergy Partners of North Texas. S. K. Silvers is now employed by Texan Allergy and Asthma Center. M. Herbert is employed by Medical City Hospital. Received for publication March 16, 2018; revised May 13, 2018; accepted for publication May 16, 2018.

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#### Abbreviations used

ELORS- eosinophilic esophagitis–like oral immunotherapy–related syndrome

ETR- epinephrine-treated reaction

OIT- oral immunotherapy

POIT- peanut oral immunotherapy

PP- peanut protein

PSIgE- peanut specific IgE

80% of patients can be desensitized, each report of food allergy immunotherapy details a somewhat different approach: differences in the forms of food, routes of administration, dosing schedules, durations of maintenance dosing, and outcome measures.<sup>10-13</sup> No study has yet demonstrated the ideal or even preferred food allergy immunotherapy algorithm. Subcutaneous aeroallergen immunotherapy was practiced for more than 100 years before broad agreement on best practices was achieved.<sup>14</sup> That agreement was based on information derived from both prospective, controlled trials that included limited numbers of patients and careful clinical observations of patients in treatment that generated important practical information. In an effort to contribute to the knowledge base on POIT, we report observations on 270 peanut-allergic patients treated by oral immunotherapy (OIT).

## METHODS

We report a retrospective medical record review (approved by the North Texas Institutional Review Board) of 270 consecutive patients who received POIT treatment between January 1, 2009, and June 30, 2017, in a single allergy/immunology practice and consented to be included. Six patients declined record review and are not reported.

Each parent and patient was told that the standard of care for peanut allergy was avoidance and preparedness for treating reactions. It was further explained that POIT is not a standard treatment nor research and is not recommended in the Food Allergy Guidelines.<sup>15</sup> Discussions included reference to the unproven nature of the treatment, the limited clinical experience, the rationale for POIT, and the uncertainty of the long-term outcome (desensitization vs tolerance) as well as the risk of anaphylaxis and eosinophilic esophagitis or an eosinophilic esophagitis–like oral immunotherapy–related syndrome (ELORS). Following this discussion, an informed consent document was signed.

A total of 96.7% of patients had a history of an IgE-mediated reaction, 70.7% had experienced anaphylaxis, grades 2-4, and 26 of 270 (9.6%) had a positive peanut challenge within 2 years of beginning POIT. All had a supportive peanut allergy test (*in vitro* or *in vivo*) before starting treatment (Table I). No patient was excluded from treatment because of the severity of their previous reaction(s) or peanut specific IgE (PSIgE) concentration. A total of 268 of 270 patients were older than 5 years. Other atopic diatheses were treated as indicated but no pretreatment was used specifically for POIT (eg, daily antihistamine or omalizumab). Patients with a history of eosinophilic esophagitis or gastroenteritis, but not other atopic disorders, were excluded.

The initial treatment protocol was based on previously used approaches<sup>17-19</sup> and has been reported.<sup>16</sup> Periodically, the protocol was modified on the basis of observations of patient experiences. (For the protocols used at the start and at the end of the observation

TABLE I. Demographic characteristics

| Characteristic                     | Male | Female | Combined |
|------------------------------------|------|--------|----------|
| Age (y), mean                      | 8.2  | 7.9    | 8.1      |
| Sex                                | 163  | 107    | 270      |
| Pretreatment PSiGE* level <14†     | 49   | 32     | 81       |
| Pretreatment PSiGE level 14-100    | 74   | 43     | 117      |
| Pretreatment PSiGE level ≥100      | 38   | 31     | 69       |
| Cutaneous (systemic) reaction only | 33   | 35     | 68       |
| Gastrointestinal reaction only     | 13   | 11     | 24       |
| Respiratory reaction only          | 3    | 1      | 4        |
| Multisystem reaction               | 109  | 56     | 165      |
| No history of reaction             | 5    | 4      | 9        |
| Grade 1 reaction‡                  | 38   | 32     | 70       |
| Grade 2 reaction                   | 61   | 39     | 100      |
| Grade 3 reaction                   | 53   | 28     | 81       |
| Grade 4 reaction                   | 6    | 4      | 10       |
| Positive challenge                 | 17   | 9      | 26       |
| History of intermittent asthma     | 36   | 22     | 58       |
| History of persistent asthma       | 70   | 45     | 115      |

\*Three patients did not have a pretreatment PSiGE level recorded and were excluded from PSiGE-related analyses. Ara H2 determinations for those 3 patients were >100, 11.2, and 0.52 kU/L.

†Commercial laboratories were used for laboratory analyses. The choice of the laboratory was usually determined by the patient's insurance carrier. Although each laboratory claimed that its results were comparable to those of others, the authors did not have the ability to confirm those claims. There may be unidentified variances in the values reported.

‡Reactions were graded according to the Mueller grading system.<sup>16</sup>

period, see Table E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org).) All patients were treated with the same protocol that was in effect at the time of treatment.

Treatment began with a suspension of peanut flour in Kool-Aid containing 2.5 µg of peanut protein (PP) (based on the package label). As the dose of PP increased, alternate forms of peanut providing equivalent doses of PP were used (For equivalent doses of peanut products, see Table E2 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org).) All dose increases were administered under direct observation, initially for 60 minutes and later for 45 minutes (see below), at the treatment site. Patients tolerating an increased dose received the new dose twice a day for a minimum of 1 week (longer if dose increases were delayed by illness or reactions) and then returned to the site for a dose increase. All patients reached a target dose of 3000 mg PP (99% of patients), and then underwent a 6000 mg PP challenge following which they then began a 2000 mg PP maintenance dose that was administered at home once or twice a day for a minimum of 3 years. The treatment team made decisions regarding dose adjustments and discontinuation of therapy on the basis of their collaborative clinical judgment. Scheduled follow-up was 1 month after reaching maintenance and every 6 months thereafter. Patients/parents were instructed to inform the site of any reactions more significant than transient, self-limited oral itch, or abdominal discomfort. Patients were instructed to avoid exercise for 2 hours after ingesting their peanut dose and to contact the treatment site in the event of illness or medical procedure to discuss dose adjustment.

All reported adverse events were captured in the medical record. Patients did not, however, maintain a daily diary of adverse events. Initially, the criteria for epinephrine use were any episode of

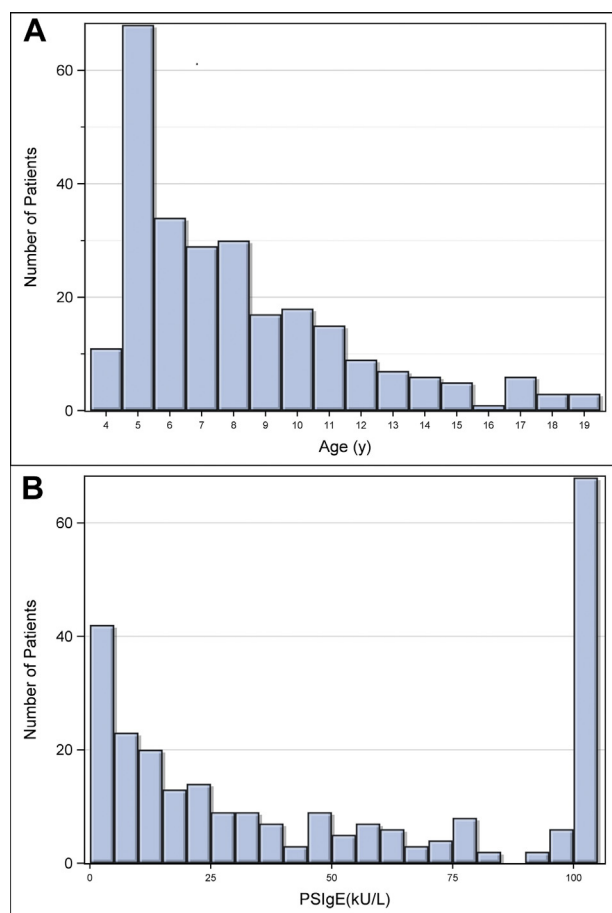


**FIGURE 1.** The distribution by age (A) and PSiGE level (B) at the start of treatment.

vomiting, respiratory symptom, or angioedema with or without urticaria. As we gained more experience, the criteria for epinephrine use evolved to parallel current recommendations for food allergy reactions.<sup>15</sup>

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

## RESULTS

Two hundred seventy patients were treated in a single allergy/immunology practice over 8.5 years. Demographic characteristics, pretreatment IgE levels, and reaction history are presented in Table I.

Most of the treated patients were younger than 10 years (Figure 1, A). The pretreatment PSiGE level showed a bimodal distribution (Figure 1, B), with 69 patients (26%) having a PSiGE level of more than 100 kU/mL.

The disposition of the patients reported herein is shown in Figure 2. At the data collection cutoff date, of the 270 patients who initiated treatment, 40 had discontinued, 8 transferred care to another practice, 8 were lost to follow-up during escalation, and 214 had escalated to the target dose. Twenty-five patients had discontinued and 33 were lost to follow-up while on maintenance therapy.

## Treatment experience

The patient treatment experience is summarized in Table II. One hundred twelve of the 214 patients who reached their target dose did so in 6 months or less and 93% (198 of 214) did so in less than 1 year. Eighty-one percent (214 of 262) of evaluable patients who received an initial dose of peanut reached the planned target dose of PP (3000 mg for 211 of 214 patients). Three patients reached a planned reduced target of 2000 mg. All patients who reached the 3000 mg target dose were challenged with 6000 mg of PP and all but 1 patient passed the challenge (4 on a second attempt). One patient who failed the 6000 mg PP challenge twice continued on to maintenance despite failing the challenge. Most patients who reached the escalation target dose passed a 6000 mg PP challenge, continued on to maintenance therapy, and were permitted to freely incorporate peanut *ad libitum* into their diet although many limited peanut consumption to the required 2000 mg per day because of taste aversion. Three of 270 (1%) patients escalated to a reduced target at parental request and 13 of 211 (6%) reduced their maintenance dose because of taste aversion.

## Adverse events

**Epinephrine-treated reactions.** One hundred epinephrine-treated reactions (ETRs) occurred in 63 of 270 (23%) patients during escalation. Thirty-seven of 100 escalation ETRs occurred in the office. Sixty-five percent of patients experiencing an ETR had only 1 ETR. Five of 100 ETRs required 2 epinephrine doses and 2 required 3 doses. No reaction required more than 3 epinephrine doses or intravenous fluids. Although ETRs were a major reason for discontinuation of therapy, 75% of patients who experienced an ETR went on to reach their target dose. Neither age nor history of anaphylaxis was significantly associated with ETRs ( $P = .904$  and  $.371$ , respectively). In contrast, intermittent asthma and higher PSiGE levels increased the risk of ETRs ( $P = .035$  and  $.019$ , respectively) occurring during escalation. Twenty-eight patients experienced an ETR during maintenance, with 30% (18 of 60) of those occurring during the first 6 months after reaching maintenance. Approximately one-third of maintenance ETRs occurred because patients did not adhere to the postdosing exercise or dose adjustment during illness guidelines. The remainder of maintenance ETRs occurred without an identified cause.

**ELORS.** During the course of this treatment, occasional, transient, mild, self-limited abdominal discomfort was reported. More significantly, during escalation, 37 patients (13.7%) experienced a consistent ELORS<sup>20</sup> characterized by episodic vomiting more than 2 hours after dosing. One patient developed ELORS during maintenance and discontinued therapy. Thirteen of the 16 patients for whom data were available demonstrated an increase in peripheral blood eosinophils (3%–478% of baseline). Treatment was continued in 21 patients with ELORS, with 13 reaching their escalation target. Five of the 8 who discontinued did so because of ELORS. Two discontinued for other reasons and 1 transferred care after successfully resuming escalation. The average time to maintenance for patients with ELORS was  $69.4 \pm 31.8$  weeks in contrast to the group as a whole whose mean time to maintenance was  $31.3 \pm 29.3$  weeks.

ELORS was usually diagnosed clinically (34 of 37 [92%]) after 2 early patients were biopsied and patients were treated on

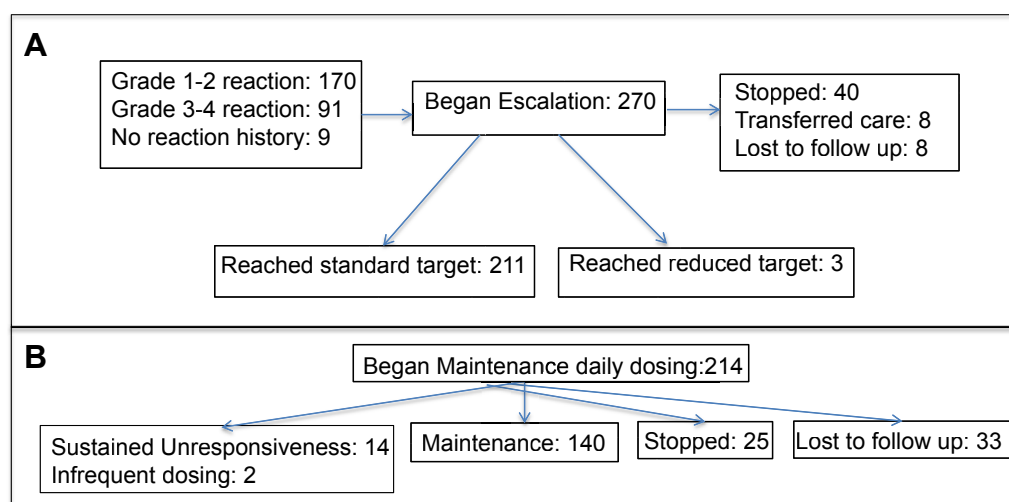


**FIGURE 2. A,** The reaction history and escalation experience of the treated patients. **B,** The outcomes of patients who reached their escalation target and began maintenance therapy. At the data collection cutoff date, 140 patients were taking daily maintenance dosing (Maintenance), 25 had stopped therapy (Stopped), 33 had not been seen in more than 2 years and were considered lost to follow-up (Lost), 14 had demonstrated sustained unresponsiveness (Sustained Unresponsiveness), and 2 were eating peanuts less than twice weekly with no problems.

the basis of their symptoms. Symptoms resolved in most patients following dose reduction. Eighteen of 37 patients with ELORS were treated with short courses (1-4 weeks) of a proton pump inhibitor and 1 patient received an oral corticosteroid for less than 14 days. None of the 35 patients (2 transferred care) with ELORS for whom he have follow-up had persistent symptoms or required prolonged therapy. However, because these patients were not biopsied after they became asymptomatic, we cannot be certain that the presumed eosinophilic infiltrates had resolved.

Most ELORS episodes (21 of 37 [57%]) presented at a PP dose between 2 mg and 10 mg (median, 10.25 mg; range, 0.1-1000 mg), whereas ETRs occurred predominantly at higher doses (Figure 3). Neither age nor history of anaphylaxis was significantly associated with ELORS ( $P = .570$  and  $.546$ , respectively). In contrast, intermittent asthma and higher PSIGe levels increased the risk of ELORS ( $P = .014$  and  $<.001$ , respectively) occurring during escalation.

### Minor adverse events

Adverse events such as intercurrent illness, mild abdominal discomfort, urticaria without additional symptoms, or oral pruritus were not formally captured. A total of 157 patients (58% of the total) reported 330 reactions that did not require epinephrine.

### Escalating to the target dose

The odds ratios for reaching the escalation target were calculated controlling for covariates of age, sex, history of anaphylaxis, pretreatment PSIGe level, development of ELORS, and presence of asthma (persistent and intermittent) (see Table E3 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). For each year increment in patient age (Figure 4), there was a 17% decrease in the odds ratio of reaching the escalation target ( $P < .001$ ). An increase of 1 KU/L in the pretreatment PSIGe level led to a 2% decrease ( $P < .001$ ) in the

likelihood of reaching the target dose (see Figure E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Development of ELORS during escalation significantly reduced the likelihood of reaching maintenance ( $P < .001$ ). Sex ( $P = .730$ ), history of anaphylaxis ( $P = .260$ ), and, in contrast to the observation of Elizur et al<sup>21</sup> during milk OIT, asthma (intermittent,  $P = .291$ , or persistent,  $P = .170$ ) were not statistically significant predictors. The complete multivariate analyses are presented in Table E3.

### Long-term follow-up

Sixty-three ETRs occurred in 28 patients on maintenance POIT, with 18 experiencing more than 1 ETR. Thirteen of 28 (46%) patients who experienced an ETR during maintenance had an ETR during escalation, whereas only 15 of 186 (8%) patients who escalated without an ETR had an ETR during maintenance ( $P < .001$ ). Forty percent (25 of 63) of maintenance ETRs occurred during the first 6 months after reaching maintenance, and 57% (36 of 63) during the first year (see Figure E2 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Approximately 30% of the maintenance ETRs occurred in association with a failure to follow the 2-hour physical activity limit or illness dose adjustment recommendations. Multivariate analysis showed that higher pretreatment PSIGe correlates with the risk of maintenance ETRs ( $P = .003$ ).

Forty-eight patients (18%) discontinued therapy before reaching maintenance and 12% discontinued after reaching maintenance (Table III). The most common reason for stopping escalation was ELORS (44%) followed by reactions (ETRs, 17%; non-ETR reactions, 6%); however, taste aversion and resistance to dosing were also reasons for stopping maintenance (4%). The influence of taste aversion on stopping decisions after ETRs or ELORS was not assessed. Of the 48 patients who dropped out during escalation, 31 (65%) had either an ETR or ELORS during POIT.

**TABLE II.** Treatment experience during escalation and maintenance

| Escalation                                                                         | Value                                               |
|------------------------------------------------------------------------------------|-----------------------------------------------------|
| Reached target of 3000 mg PP, N/total (%)                                          | 211/262* (81)                                       |
| Reached reduced target, N/total (%)                                                | 3/262 (1)                                           |
| Time to target dose (wk), median (range)                                           | 25.8 (15-368)                                       |
| Reached target $\leq$ 6 mo, N/total reaching target (%)                            | 112/214 (52)                                        |
| Reached target $\leq$ 12 mo, N/total reaching target (%)                           | 198/214 (93)                                        |
| No ETRs, N/total (%)                                                               | 207/270 (77)                                        |
| Only 1 ETR, N/total (%)                                                            | 41/270 (15)                                         |
| >1 ETR, N/total (%)                                                                | 22/270 (8)                                          |
| No ETRs, N/total reaching target (%)                                               | 167/214 (78)                                        |
| Only 1 ETR, N/total reaching target (%)                                            | 32/214 (15)                                         |
| >1 ETR, N/total reaching target (%)                                                | 15/214 (7)                                          |
| Non-ETR reactions, N/total (%)                                                     | 157/262 (60)                                        |
| No reactions (ETR/non-ETR), N/total (%)                                            | 92/262 (35)                                         |
| No ETRs, N dropped out/total dropouts (%)                                          | 33/48 (69)                                          |
| Only 1 ETR, N dropped out/total (%)                                                | 8/48 (17)                                           |
| >1 ETR, N dropped out/total (%)                                                    | 7/48 (14)                                           |
| Delayed by ELORS, N/total (%)                                                      | 37/262 (14)                                         |
| ELORS caused discontinuation, N/total with ELORS (%)                               | 21/37 (57)                                          |
| ELORS attempted to reduce dose and continue escalation, N/total with ELORS (%)     | 21/37 (57)                                          |
| ELORS but reached maintenance, N/total with ELORS who attempted to continue (%)    | 13/21 (62)                                          |
| ELORS who reached maintenance/total with ELORS                                     | 13/37 (35)                                          |
| Days with decreased dose among those who reached maintenance                       | Mean, 73.7 $\pm$ 57.9<br>Median, 51 (25-210)        |
| PP dose that first triggered ELORS symptoms (mg)                                   | Mean, 114.5 $\pm$ 241.6<br>Median, 10.25 (0.1-1000) |
| ELORS delay, mean weeks to maintenance/mean weeks to maintenance without ELORS     | 69.4 $\pm$ 31.8/31.3 $\pm$ 29.3                     |
| ELORS delay, median weeks to maintenance/median weeks to maintenance without ELORS | 60.4 (33.7-121.1)/25.1 (14.9-368.3)                 |
| Dropouts (40) + transfers (8) + lost to follow-up (8) during escalation/total (%)  | 56/270 (20.7)                                       |
| Maintenance                                                                        | Value                                               |
| ETRs during maintenance/100 patient-years                                          | 9.9                                                 |
| ELORS during maintenance/100 patient-years                                         | 0.16                                                |
| Dropouts during maintenance/100 patient-years                                      | 3.9                                                 |
| Lost to follow-up N/100 patient-years                                              | 5.2                                                 |

\*270 minus 8 who transferred care.

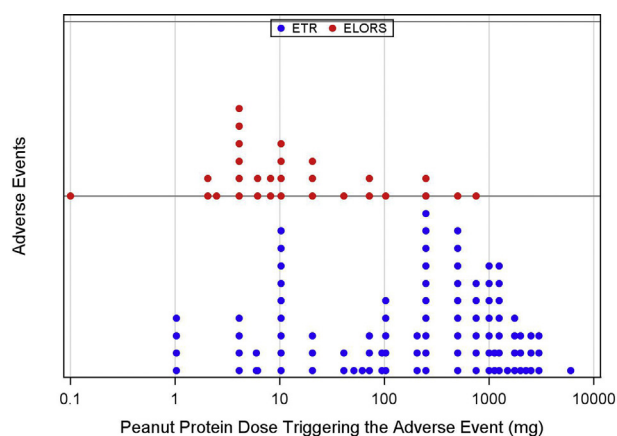
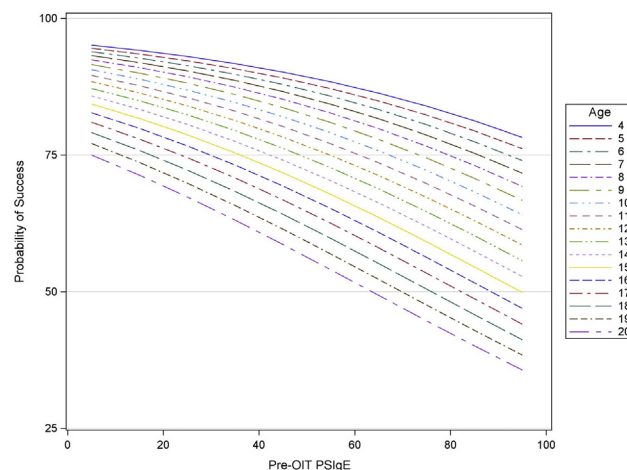
**FIGURE 3.** Each ETR (blue) and diagnosis of ELORS (red) is plotted against the PP dose at which the event occurred. Note that the x-axis (dose) is a log scale.**FIGURE 4.** The probability of reaching the escalation target based on pretreatment PSiGE level and age at the start of therapy.

**TABLE III.** Dropouts

| Primary reason                                               | Escalation   | Maintenance  |
|--------------------------------------------------------------|--------------|--------------|
| Total N/total treated (%)                                    | 48/270 (18%) | 25/214 (12%) |
| Reactions among dropouts                                     | 11/48 (23%)  | 7/25 (28%)   |
| ETRs, N/total dropouts                                       | 8/48 (17%)   | 3/25 (12%)   |
| Non-ETR/non-ELORS reactions, N/N dropouts                    | 3/48 (6%)    | 4/25 (16%)   |
| ELORS, N/N dropouts                                          | 21/48 (44%)  | 1/25 (4%)    |
| Taste aversion/resistance                                    | 2/48 (4%)    | 11/25 (44%)  |
| Burden of care (too many visits, too difficult)              | 1/48 (2%)    | 0            |
| Anxiety with dosing/N dropouts                               | 2/48 (4%)    | 0            |
| Sibling with OIT reaction/N dropouts                         | 2/48 (4%)    | 0            |
| Gastrointestinal complaints (not ELORS)/N dropouts           | 2/48 (4%)    | 0            |
| Perception that OIT causing other health problems/N dropouts | 1/48 (2%)    | 2/25 (8%)    |
| Irregular dosing/N dropouts                                  | 0            | 3/25 (12%)   |
| Failed sustained unresponsiveness challenge/N dropouts       | NA           | 1/25 (4%)    |
| Lost to follow-up*/N total                                   | 6/270 (2%)   | 33/214 (15%) |

\*No contact with the patient for more than 2 y. Lost to follow-up patients are included in the safety (ie, adverse event) but not the efficacy calculations.

Because the minimum duration of maintenance was set at 3 years before beginning treatment, the 105 patients who received daily maintenance dosing for at least 3 years were further analyzed (Table IV). Most of the characteristics of these patients are similar to those of the complete data set. Few patients with ELORS, however, are included in this group. This is, in part, a reflection of our practice, for the first several years, to discontinue therapy whenever there was a suspicion of ELORS.

### Peanut specific antibody

The greatest change in PSiGE level occurs during the first year of maintenance therapy. Approximately 47% of patients experience a greater than or equal to 50% fall in PSiGE level 1 month after completing escalation. Decreases in PSiGE level continued during the maintenance observation period but the changes were modest. Peanut component IgE testing paralleled PSiGE (data not shown) and was only useful in deciding on pretreatment challenges. Forty-four of 167 (26%) had an increase in IgE level after 2 months of maintenance. Seven of the 44 (16%) who had PSiGE repeated demonstrated an increase over baseline 247 to 870 days after reaching maintenance. Peanut specific IgG<sub>4</sub> level was measured in the first 54 patients. In all patients tested, the first peanut specific IgG<sub>4</sub> level after reaching maintenance was more than 80 µg/mL. Because a commercial laboratory was used, the peanut specific IgG<sub>4</sub> level could not be further quantitated and measurement was discontinued.

### Sustained unresponsiveness

The opportunity to demonstrate sustained unresponsiveness, defined as tolerating 6000 mg of PP (24 peanuts) after carefully avoiding peanut for 30 days, was accepted in 19 patients. By the end of the observation period, the criteria for offering patients a sustained unresponsiveness challenge included a minimum of 36 months of maintenance dosing, no ETRs within 2 years of beginning the 30-day avoidance period, a greater than or equal to 90% fall in PSiGE level or a prechallenge PSiGE level of less than 1.0 kU/mL. Eleven of the 19 patients reported here met those criteria. Some challenged patients did not meet these criteria but were challenged at parental request. Eight of the 11 patients who met the criteria tolerated the challenge dose. Six of 8 challenged

patients who did not meet these criteria also passed. The best predictors of passing the challenge were a pretreatment PSiGE level of less than 20 kU/L and a prechallenge PSiGE level of less than 1 kU/L. All 9 patients meeting those PSiGE criteria passed the challenge. Only 5 of 10 patients with pretreatment PSiGE level of more than 20 kU/L and/or a prechallenge PSiGE level of more than 1 kU/L passed the challenge (Table IV). Two patients had discontinued maintenance dosing for more than 30 days before 3 years of therapy and then decided to resume POIT. Both these patients tolerated 6000 mg PP on reintroduction. Although there are very few patients, it appears that pretreatment and prechallenge PSiGE levels may predict the ability to achieve sustained unresponsiveness.

### DISCUSSION

This report is subject to several limitations. As a retrospective study, there are potential biases; however, all treated patients (except those who refused consent) are included. Although a standard treatment protocol was used, clinicians modified patient treatment according to their judgment. Therefore, this report truly reflects an actual clinical practice. Ninety-seven percent (261 of 270) of patients were treated on the basis of a clear and convincing history of an IgE-mediated reaction to peanut or underwent a pretreatment peanut challenge. Three percent (9 of 270) of patients were treated on the basis of testing alone; 6 of 9 patients had a PSiGE level of more than 100 kU/mL. The remaining 3 patients had PSiGE levels of 9.72, 65.7, and 78.5 kU/mL. Seven of these 9 patients experienced reactions, including 3 with ETRs, during escalation, confirming their peanut allergy. Nevertheless, because all patients were not challenged before beginning POIT, we cannot be certain that they were all peanut allergic. Therefore, the reported escalation success rate may be an overestimate. Because PSiGE and peanut specific IgG<sub>4</sub> levels were measured in commercial laboratories, PSiGE levels reported as more than 100 kU/mL were not titrated out and specific IgG<sub>4</sub> levels were not clinically useful. Therefore, a PSiGE level of more than 100 kU/mL could represent a PSiGE value of 105 kU/mL or a PSiGE value of 500 kU/mL. The net result of this limitation, however, would be to underestimate the negative

**TABLE IV.** A total of 105 patients treated for 3 or more years of maintenance

| Patient history and treatment experience                      | Value                                             |                      |
|---------------------------------------------------------------|---------------------------------------------------|----------------------|
| Age at the start of treatment (y), mean                       | 7.6 ± 2.8                                         |                      |
| Pretreatment history of anaphylaxis                           | 69 (66%)                                          |                      |
| History of intermittent asthma                                | 22 (21%)                                          |                      |
| History of persistent asthma                                  | 51 (49%)                                          |                      |
| Discontinued during maintenance                               | 12/105 (11%)                                      |                      |
| Number lost to follow-up                                      | 5/105 (4.7%)                                      |                      |
| Pretreatment PSiGE level (kU/L)*                              | Median, 24.1 (0.25 to 100)<br>Mean, 41.9 ± 38.3   |                      |
| Pretreatment PSiGE level <100 kU/L                            | 81                                                |                      |
| Pretreatment PSiGE level >100 kU/L (no. of patients)          | 24                                                |                      |
| Patients with PSiGE data after 3 y of maintenance             | 53                                                |                      |
| PSiGE level after 3 y on maintenance (kU/L)*                  | Median, 7.16 (0.08 to 100) Mean, 15.4 ± 23.22     |                      |
| Percent decrease in PSiGE level from pretreatment after 3 y*† | Median, 77% (–78% to 100%)<br>Mean, 65% ± 36%     |                      |
| Patients with ≥90% decrease in PSiGE level after 3 y*         | 7/53 (13%)                                        |                      |
| Patients with PSiGE data after 4 y of maintenance             | 34                                                |                      |
| PSiGE level after 4 y on maintenance (kU/L)*                  | Median, 5.78 (0.45 to 100)<br>Mean, 16.55 ± 24.15 |                      |
| Patients with PSiGE data after 5 y of maintenance             | 20                                                |                      |
| PSiGE after 5 y on maintenance (kU/L)*                        | Median, 2.64 (0.1 to 38.1)<br>Mean, 7.23 ± 10.67  |                      |
| Patients experiencing an ETR during escalation                | 31 (30%)                                          |                      |
| No. of escalation ETRs                                        | 50                                                |                      |
| Patients experiencing ETRs during maintenance                 | 18 (17%)                                          |                      |
| No. of maintenance ETRs                                       | 43                                                |                      |
| Patients experiencing ELORS during escalation                 | 3                                                 |                      |
| Patients experiencing ELORS during maintenance                | 1                                                 |                      |
| Sustained unresponsiveness challenges in 19 patients          | Passed                                            | Failed‡              |
| Patients challenged                                           | 14                                                | 5                    |
| Median age (y) at the start of OIT (range)                    | 6.5 (5 to 14)                                     | 8 (7 to 11)          |
| Median duration of maintenance (mo) (range)                   | 44 (16 to 83)                                     | 60 (37 to 67)        |
| History of anaphylaxis before OIT                             | 11/14                                             | 3/5                  |
| Median pre-OIT PSiGE level* (range)                           | 6.92 (0.59 to >100)                               | 28.65 (17.3 to >100) |
| Median prechallenge PSiGE level* (range)                      | 0.81 (0.08 to 8.31)                               | 4.1 (1.34 to 11.5)   |
| Median percent drop in PSiGE level* (range)                   | 88 (–102 to 100)                                  | 89 (70 to 95)        |
| Patients with ≥90% drop in PSiGE level                        | 6/14 (43%)                                        | 2/5 (40%)            |

\*For the purposes of these calculations, PSiGE level of ≥100 kU/L was treated as PSiGE level of 100 kU/L.

†Specific IgE was assayed by more than 1 laboratory and some determinations for a single patient were made by more than 1 laboratory.

‡The patients who failed sustained unresponsiveness challenges tolerated a median (range) of 667 mg (10.5 to 1000 mg) of PP and failed at a median (range) of 1250 mg (105 to 6000 mg) of PP.

effect of PSiGE level on POIT. Although reporting patient experience from a single center is often considered a limitation,<sup>2</sup> it has the advantage that all patients have been treated by the same group of allergists, thereby increasing the likelihood of uniformity of practice as well as in capturing safety and efficacy information. Although the treatment protocol used evolved on the basis of patient experiences (Table E1), the major differences were in the rate of dose escalations. These changes were intended to decrease reactions. Including all patients in the analysis makes the treatment appear to be less safe and effective than it would have if only those patients treated according to the final protocol were included.

Unlike formal clinical studies, patients did not keep daily diaries of adverse events. Patients/parents were, however, encouraged to report all adverse events to their physician. It is likely that almost all ETRs and cases of ELORS have been captured, although it is very possible that milder adverse events have not been reported. Although all patients were treated using the same general algorithm, the absence of a fixed protocol allowed general modifications (see Table E2) and a flexibility in the treatment regimen characteristic of clinical practice but typically not permitted in prospective, controlled clinical trials. This may be considered a limitation or an advantage because it more closely reflects real-world allergy practice.

The apparently high frequency of epinephrine use reflects, in part, the high level of concern about the risk of serious reactions and the well-established principle that early epinephrine use results in favorable outcomes.<sup>22</sup> Nevertheless, 78% (167 of 214) of patients reached maintenance with no ETRs and no reaction required more than 3 doses of epinephrine.

The rate of ELORS is within a range seen in other POIT reports.<sup>23,24</sup> Initially, the occurrence of this clinical picture was considered cause to discontinue therapy. After the report of Levy et al<sup>25</sup> suggesting that POIT could be continued in patients with ELORS by lowering the dose for a period of time, followed by continued escalation, we offered this option to patients/parents. This change during our treatment experience demonstrates the value of a flexible treatment protocol. The relationship of ELORS and persistent eosinophilic esophagitis is unknown because asymptomatic patients (both those who discontinued OIT and those who continued) were not biopsied.

Taste aversion is a major issue in POIT because of the difficulty in masking the taste of peanut despite the use of various peanut products (see Table E3). Because the psychosocial impact and disruption of family life caused by food allergy<sup>26</sup> appears to be more significant for younger children, it is possible that peanut OIT may be an appropriate temporary support used until children reach middle adolescence. Thus, for some families/children, POIT may be beneficial even if the likelihood of achieving sustained unresponsiveness, or continuing maintenance through adolescence, is low. Although an initial attempt to predict patients who had achieved sustained unresponsiveness was made, the current criteria are imperfect because not all patients meeting the criteria passed the challenge and not all patients who failed to meet criteria failed. Further experience will be needed to make more accurate predictions of who will attain sustained unresponsiveness.

## LESSONS LEARNED

- Reaction history does not predict the ability to reach the target POIT dose.
- Age at the initiation of therapy significantly influences the likelihood of reaching the target dose; each year of delay after age 5 years decreases the likelihood of success by 17%.
- Pretreatment PSiGE level correlates inversely with the likelihood of reaching the target. However, a very high pretreatment PSiGE level does not preclude reaching maintenance, especially among younger patients. Forty-eight of 69 (73%) patients with PSiGE levels of more than 100 kU/L reached maintenance.
- Although ELORS prolongs POIT and is an important cause of discontinuation of therapy, the development of this problem does not preclude successful POIT.
- A postdose escalation waiting time of 45 minutes is sufficient.
- The occurrence of ETRs during maintenance therapy demonstrates that even if POIT reduces the risk of significant allergic reactions, the risk is not completely eliminated. Desensitized patients should continue to have epinephrine readily available at all times.
- The source of PP and the use of different forms of peanut (ie, flour, powder, peanut butter, peanut candy, or whole peanuts) for the same patient does not appear to be associated with problems during POIT as long as equal amounts of PP are administered regardless of the form.

POIT desensitizes most patients. Although most of our patients (79%) reached maintenance without the use of epinephrine, POIT requires intense education and close cooperation between the treating allergist and the patient's family. This retrospective analysis did not identify patients for whom POIT will be unsuccessful.

Careful observations of clinical experiences can supplement information derived from controlled clinical trials to improve the treatment of peanut-allergic patients.

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## METHODS

Treatment comprises 3 phases. Phase I is a single day beginning with 1.025  $\mu$ g of PP (The amount of PP in peanut flour is based on the package label.) dissolved in Kool-Aid followed by increasing doses administered every 15 minutes until there is any symptom or until the 6.15 mg dose is reached. PP dissolved in Kool-Aid is made fresh on the day of use. PP in Kool-Aid at the appropriate concentration is provided to patients and stored refrigerated for no more than 7 days. Patients begin phase II by taking the last tolerated dose at home twice a day and return weekly to be challenged with the next dose until they reach 12 peanuts twice a day or the equivalent amount of PP in peanut butter or peanut flour. Peanut flour is provided in capsules (commercial peanut flour is compounded into capsules by a compounding pharmacist) containing different amounts that the patient or parent opens into food or liquid immediately before dosing. Patients receive peanut flour until they have tolerated 205 mg of PP. Although there is significant variation in the

weight of individual peanuts by brand (based on weighing 100 peanuts from several packages of different brands), for the purposes of this treatment, a peanut was defined as weighing 950 mg, 26% of which is protein or 250 mg of protein. In an effort to enhance the safety of the transition from flour to whole peanuts, dose escalation with peanut flour continued until the patient was ingesting about 10% more PP as flour than would be contained in a whole peanut. They are then given the option of using peanut flour, peanut butter, Peanut M&M's, or 1 of 3 brands of whole peanuts. Patients (parents) were permitted to vary the source of PP at their choice. There were no adverse events that could be attributed to changing the source of PP. Dose increases were made with the product that had been used during the previous week. When patients are able to tolerate 12 peanuts per dose (or equivalent), most patients are challenged with 24 peanuts. If they pass the challenge, they continue to phase III, maintenance of 8 peanuts twice a day for 3 months and then once a day for at least 3 years.

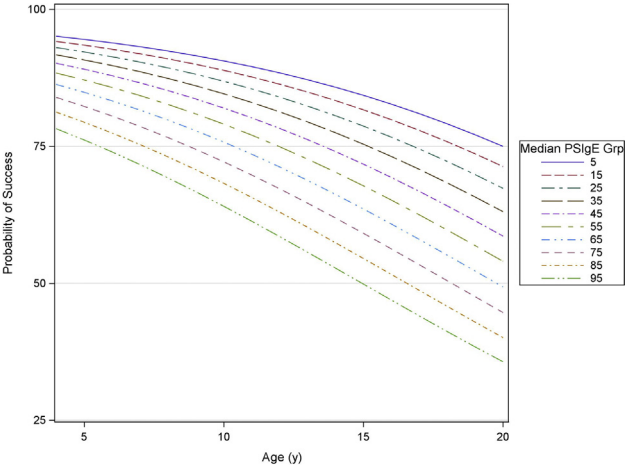


**FIGURE E1.** The probability of reaching the escalation target based on pretreatment PSigE level and age at the start of therapy.

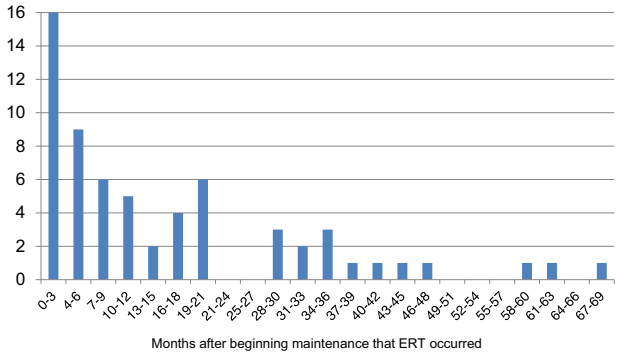


**FIGURE E2.** The frequency and time of occurrence of ETRs while receiving at least 2000 mg of PP per day.

**TABLE E1.** Changes to the treatment protocol during the observation period

| Treatment regimen characteristics        | Protocol January 1, 2009                                  | Protocol June 1, 2016                                     |
|------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|
| Starting dose                            | 1.025 µg PP                                               | 2 µg PP                                                   |
| Doses to reach the day 1 target          | 13 doses all repeated once for a total of 26 doses        | 10 doses                                                  |
| Day 1 target dose                        | 10 mg PP                                                  | 2.05 mg PP                                                |
| Daily dosing frequency during escalation | Twice a day                                               | Twice a day                                               |
| Postdose observation time                | 60 min                                                    | 45 min                                                    |
| Doses to complete escalation             | 14 after day 1                                            | 21 after day 1                                            |
| Target dose                              | 12 peanuts (3 g protein) then pass<br>24-peanut challenge | 12 peanuts (3 g protein) then pass<br>24-peanut challenge |
| Maintenance dosing frequency             | Twice a day for the first year; then once a day           | Once a day                                                |

**TABLE E2.** Peanut products that yield 2000 mg of PP for maintenance dosing

| Peanut product                                                                            | PP content         |
|-------------------------------------------------------------------------------------------|--------------------|
| Shelled whole peanuts                                                                     | 8 peanuts or 7.6 g |
| Honey Line or Seal Salt Peanut                                                            | 8 peanuts          |
| Planters Peanuts                                                                          | 10 peanuts         |
| 28% Byrd Mill Peanut flour                                                                | 4 teaspoons        |
| TruNut Peanut Powder, PB2 Powdered<br>Peanut Butter, Mighty Nut Powdered<br>Peanut Butter | 2½ teaspoons       |
| Peanut Butter & Co Flavored peanut<br>butter or unflavored peanut butter                  | 2 teaspoons        |
| Peanut M&M's                                                                              | 14                 |
| Bamba                                                                                     | 17 g               |
| Peanut Reeses's pieces                                                                    | 43 pieces          |

**TABLE E3.** Multivariate analysis of selected data elements

| Event           | Tested parameter            | Conditional change | Odds ratio (95% CI) | P value |
|-----------------|-----------------------------|--------------------|---------------------|---------|
| ELORS           | Age                         | Per 1-y increase   | 1.03 (0.93-1.14)    | .570    |
|                 | Physician- diagnosed eczema | Yes vs No          | 0.93 (0.41-2.12)    | .872    |
|                 | Sex                         | Female vs Male     | 0.47 (0.20-1.11)    | .086    |
|                 | History of anaphylaxis      | Yes vs No          | 1.30 (0.56-3.04)    | .546    |
|                 | Intermittent asthma         | Yes vs No          | 3.99 (1.33-12.0)    | .014    |
|                 | PSIgE level before OIT      | 1 KU/L increase    | 1.02 (1.01-1.03)    | <.001   |
|                 | Persistent asthma           | Yes vs No          | 1.72 (0.62-4.79)    | .300    |
| ETR             | Age                         | Per 1-y increase   | 1.01 (0.93-1.09)    | .904    |
|                 | Physician- diagnosed eczema | Yes vs No          | 1.21 (0.64- 2.28)   | .555    |
|                 | Sex                         | Female vs Male     | 1.10 (0.60-2.03)    | .756    |
|                 | History of anaphylaxis      | Yes vs No          | 0.75 (0.41-1.40)    | .371    |
|                 | Intermittent asthma         | Yes vs No          | 0.36 (0.14-0.93)    | .035    |
|                 | PSIgE level before OIT      | 1 KU/L increase    | 1.01 (1.00-1.02)    | .019    |
|                 | Persistent asthma           | Yes vs No          | 0.80 (0.41-1.53)    | .493    |
| Maintenance ETR | Age                         | Per 1-y increase   | 1.05 (0.90-1.23)    | .555    |
|                 | Physician- diagnosed eczema | Yes vs No          | 0.35 (0.10-1.18)    | .090    |
|                 | Sex                         | Female vs Male     | 1.28 (0.47-3.45)    | .632    |
|                 | History of anaphylaxis      | Yes vs No          | 1.24 (0.44-3.48)    | .685    |
|                 | Intermittent asthma         | Yes vs No          | 1.50 (0.32-6.98)    | .603    |
|                 | PSIgE before OIT            | 1 KU/L increase    | 1.02 (1.01-1.03)    | .003    |
|                 | Persistent asthma           | Yes vs No          | 1.94 (0.64-5.89)    | .244    |
| Maintenance     | Age                         | Per 1-y increase   | 0.83 (0.75-0.93)    | <.001   |
|                 | Physician- diagnosed eczema | Yes vs No          | 0.45 (0.20-1.01)    | .053    |
|                 | Sex                         | Female vs Male     | 1.01 (0.44-2.28)    | .989    |
|                 | Had ELORS                   | Yes vs No          | 0.09 (0.04-0.24)    | <.001   |
|                 | History of anaphylaxis      | Yes vs No          | 0.89 (0.38-2.05)    | .778    |
|                 | Intermittent asthma         | Yes vs No          | 0.58 (0.21-1.60)    | .291    |
|                 | PSIgE before OIT            | 1 KU/L increase    | 0.98 (0.97-0.99)    | <.001   |
|                 | Persistent asthma           | Yes vs No          | 1.97 (0.75-5.18)    | .170    |