

Oral immunotherapy for children with a high-threshold peanut allergy



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ABSTRACT

Background: Between 25% and 30% of children with peanut allergy (PA) have a relatively high-threshold peanut allergy (HTPA), with a single maximal tolerated dose (SMTD) higher than 100 mg of peanut protein (PP). However, this threshold may decrease with time, age, exercise, illness, sleep deprivation, and other covariates.

Objective: To explore the feasibility of a simplified oral immunotherapy (OIT) protocol in a group of children with HTPA.

Methods: Children with PA with an SMTD higher than 100 mg were placed on a 40-week OIT protocol of either 300 mg/d of PP or 100 mg/d for 20 weeks followed by 300 mg/d for 20 weeks. A repeat open peanut food challenge was performed after 40 weeks of treatment and at a 6-month follow-up visit. After the 40-week challenge, all children received a maintenance dosage of 2 g PP 3 times a week.

Results: A total of 28 children with HTPA were enrolled, with 56% boys, 89% younger than 6 years old, and a mean SMTD of 304 mg (95% confidence interval 229–378). All were placed on the described OIT protocol. Overall, 2 children were not compliant and 3 had allergic reactions at home on the dose previously tolerated in clinic, 23 completed the 40-week protocol, and all were able to consume 2 g of PP. The mean tolerated dosage at the 6-month follow-up was 8 g. This enabled most children age-appropriate dietary inclusion of peanut-containing products.

Conclusion: In children with HTPA, a simple, fixed-dose OIT can be both safe and efficacious.

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Introduction

Peanut allergy (PA) continues to be a considerable burden to children and families worldwide.^{1–4} Children with a single maximal tolerated dose (SMTD) equal to or lower than 100 mg of peanut protein, that is, less than one-third of a peanut, can experience accidental reactions even at minute exposures which may be life threatening. In this group, there is an increasing consensus toward treatment with oral immunotherapy (OIT).^{5–10}

Between 20% and 30% of children with PA have a challenge-proven, high-threshold peanut allergy (HTPA), with a SMTD higher

than 100 mg of peanut protein (PP).^{11–15} Because of paucity of research studies addressing this group and the high incidence of adverse events associated with published OIT protocols,^{16–19} there is remarkably less consensus as to the OIT treatment in these children.²⁰ Management of this group of patients is one of the current controversies in allergy.^{20,21}

It is well documented that the reliability of challenge-derived observed thresholds is highly variable and influenced by a plethora of cofactors, such as time,²² age,²³ exercise,²⁴ illness, and medications, such as nonsteroidal anti-inflammatory drugs,²⁵ alcohol,²⁶ sleep deprivation,²⁴ menses,⁶ replication environment, and others. A recent meta-analysis looking at individual threshold levels for PA specifically concluded that in patients who previously reacted to low-level peanut exposures (eg, <50 mg of peanut protein), there can be up to a 10-fold increase in threshold owing to this intrinsic variability.²⁷ In this view, one should ask the question of whether children with “high observed thresholds” today, higher than 100 mg, may react to a low-level exposure tomorrow, when for example, the

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calculated impact of sleep deprivation and exercise may lower allergen reactivity thresholds by up to 45%.²⁴

Increasingly, sophisticated laboratory tests, such as epitope-specific peanut immunoglobulin (Ig)E, IgG4, or basophil activation test (BAT),²⁸ and composite markers based on such tests²⁹ have been used to enable the a priori prediction of the threshold and severity of PA in children. In practical terms, some or all of these tests are not immediately available to the practicing allergist and, conversely, they do not offer insight into the diagnosis or management of the HTPA group.

Therefore, the development of clinical protocols for predicting both HTPA and enabling the safe introduction of PPs into the diet of such children should become a priority.

The aim of this study was to evaluate the feasibility, safety, and efficacy of a simplified OIT protocol in a group of children with HTPA.

Methods

A single-center, cross-sectional, prospective study of children aged 1 to 18 years old, presenting to the pediatric allergy clinic in the Safra Children's Hospital between January 2019 and January 2021 with a challenge-proven (oral food challenge [OFC]) diagnosis of PA, at an emergency department (ED) higher than 100 mg of PP. Before entry into the study, parents and guardians were thoroughly counseled on the potential risks and benefits before they signed informed consent forms approved by the institutional review board of the Sheba Medical Center and the national institutional review board as required for any study involving children in Israel.

Skin Tests

Skin prick testing was performed using single-head lancets on the forearms of children with histamine (1 mg/mL) as positive control, glycerinated saline as negative control, and whole-peanut extract (ALK-Abelló, Hørsholm, Denmark). Wheal and flare sizes were measured after 15 minutes. Patients abstained from antihistamine-containing medications for at least 1 week before the procedure.

Peanut-Specific Immunoglobulin E, Immunoglobulin G4, and Component Resolved Diagnostics

A total of 5 mL of whole blood in ethylenediaminetetraacetic acid tubes was drawn, and plasma was extracted for quantification of peanut sIgE and IgE component resolved diagnostics (Ara h 1, 2, 3, 8, 9) and peanut IgG4 and IgG4 component resolved diagnostics (Ara h1 and Ara h2) by ImmunoCAP (Thermo Fisher Scientific Inc, Waltham, Massachusetts).

Oral Food Challenge

The open-label OFCs to peanut were performed using a commercial preparation of "Bamba" (Osem, Israel) a common snack containing 50% puffed maize and 50% peanut.³⁰ A portion of 21 bamba was deemed equivalent to 2.0 g of PP.³¹ The OFC was performed as an outpatient procedure, starting with a smear of bamba applied to the anterior surface of the tongue. Subsequently, at 20-minute intervals, doses of $\frac{1}{4}$, $\frac{1}{2}$, 1, 2, 6, and 12 snacks were given orally. If no reaction occurred during the entire period, the participant was deemed to have no allergy. If a subjective or transient skin reaction occurred at any dose, a repeat dose was administered before the continuation of the OFC. Those who developed acute allergic reactions, such as urticaria, angioedema, vomiting, persistent complaints of abdominal

pain, wheezing, hypoxia, hypotension, and anaphylaxis during any stage of the challenge, were diagnosed as having PA. Children where the single highest eliciting dose of PP causing an acute allergic reaction was 100 mg or less were labeled as having low-threshold PA (LTPA). Those in whom the single highest eliciting dose of PP causing an acute allergic reaction was higher than 100 mg were labeled as having HTPA.

Protocol of Peanut Oral Immunotherapy in Children With High-Threshold Peanut Allergy

Children for whom the single highest eliciting dosage of PP was greater than 300 mg were placed on a fixed daily dosage of 300 mg for 40 weeks of treatment. At the end of which, a repeat peanut OFC of up to 2 g of PP was performed. Children passing this "exit" challenge were then placed on a maintenance dosage of 2 g PP $\times$ 3 times/wk. The dose was not increased gradually at home but was directly offered in the 40-week exit challenge.

Children for whom the single highest eliciting dosage of PP was between 100 and 300 mg PP were placed on a daily dosage of 100 mg for 20 weeks of treatment, after which, a peanut OFC of 300 mg was performed. If successful, a fixed dosage of 300 mg daily dose was continued at home for the next 20 weeks. At the end of the 40-week treatment period, a repeat peanut OFC up to 2 g of PP was performed. Children passing this "exit" challenge were then placed on a maintenance dosage of 2 g PP $\times$ 3 times/wk.

The families and caregivers were instructed to give a daily fixed dose under adult supervision and the end of daily activities, so patients were at relative rest and awake for 90 minutes at least after the dose.

After 6 months, a repeat OFC was performed, with up to 15 g of PP or age-appropriate peanut doses (ie, up to 1 tablespoon of peanut butter in toddlers or a handful of peanuts in older children), aimed at enabling children the inclusion of age-appropriate dietary peanut-containing products. Notably, during follow-up, there were no complaints suggestive of eosinophilic esophagitis or eosinophilic gastrointestinal disease.

Statistical Analysis

Demographical and clinical data of children with HTPA were compared with those of the group of children with LTPA, diagnosed by the same methodology. Comparison of means of continuous and distribution of categorical variables was performed using analysis of variance. Exploratory Decision Tree Analysis was conducted for the optimization of the a priori risk classification for HTPA as opposed to LTPA. Statistical analyses were performed using SPSS 27.0 (IBM SPSS Statistics, Armonk, New York) and JMP Pro 15.0 (2019; SAS Institute Inc, Cary, North Carolina).

Results

Our cohort included 104 children, with a challenge-confirmed PA, diagnosed in our center between January 2019 and January 2021. Among them, 76 (73%) had LTPA (single maximal eliciting dosage of 100 mg of PP or less) and 28 (27%) had HTPA (single maximal eliciting dosage higher than 100 mg).

Most children with HTPA in our study were young, with more than 80% below 6 years of age. In addition, most were boys (56%) with additional food allergies and other atopy-associated diagnoses (Table 1).

As a group, these children had a mean MTD of 303.57 mg and a mean cumulative tolerated dosage (no observed adverse effect level)

Table 1
Demographics and Clinical Presentation of Participants

Patient details	All (N = 104)	HTPA (N = 28)	LTPA (N = 76)	P value
Age (mo) mean	53	41	57	.05
Age < 6 y old	81%	89%	79%	NS
Sex (% boys)	66%	56%	69%	NS
Atopic dermatitis	68%	70%	66%	NS
Recurrent wheezing or asthma	41%	30%	47%	NS
Other food allergies	66%	54%	73%	NS
Nut allergy	26%	18%	29%	.001
Age at first exposure to peanuts (mo)	12.8	7.7	15.8	NS
First exposure reaction	79%	74%	83%	.04
Initial clinical reaction				
Skin	98%	100%	96%	NS
Respiratory	33%	15%	43%	.01
Gastrointestinal	22%	11%	29%	NS
Anaphylactic	45%	22%	58%	.003
Doses of peanut proteins in (mg) during OFC				
Initial single maximal tolerated dose (mean)	105.99	303.57	33.2	<.001
Initial cumulative tolerated dose (NOAEL) (mean)	181.09	537.5	49.78	<.001
Initial single minimal eliciting dose (mean)	218.16	621.43	69.59	<.001
Initial cumulative adverse effect dose (LOAEL) (mean)	399.46	1158.93	119.66	<.001

Abbreviations: HTPA, high-threshold peanut allergy (maximal tolerated dosage more than 100 mg of peanut protein); LOAEL, lowest observed adverse effect level; LTPA, low-threshold peanut allergy (maximal tolerated dosage of 100 mg of peanut protein or less); NOAEL, no observed adverse effect level; OFC, oral food challenge.

of 537.5 mg, a mean eliciting dosage (ED) of 621.4 mg (95% confidence interval, 512–730), and a mean cumulative adverse effect dosage (lowest observed adverse effect level) of 1158 mg (Table 1).

Parents reported 79% of reactions as occurring during the first exposure to peanut at a mean age of 13 months. The most common reported reactions included skin involvement (>95%), respiratory symptoms (33%), and gastrointestinal symptoms (22%).

When compared with LTPA, children in the HTPA group tended to be younger (average age 41 months vs 57; $P = .05$), less likely to present with a respiratory reaction (15% vs 43%; $P = .01$), or with an anaphylactic reaction (22% vs 58%; $P = .003$).

As a group, compared with patients with LTPA, children with HTPA had significantly smaller results on IgE-based PA tests: peanut skin prick testing was 9.2 vs 11.6 mm ($P = .03$), peanut sIgE 6.4 vs 26.7 ($P = .03$), and Ara h2 sIgE 5.1 vs 22.3 ($P = .03$), respectively. However, on an individual patient basis, there was a considerable overlap between patients with LTPA and those with HTPA (Table 2).

Peanut-specific and Ara h2-specific IgG4 levels did not add to the discriminative capacity of HTPA vs LTPA. However, the ratio of Ara

h2-specific IgE/IgG4 was significantly lower in children with HTPA at 184 vs 579 ($P = .05$).

Using an exploratory decision tree analysis, including an automatic validation algorithm, a series of clinical decision points, such as a previous anaphylactic reaction, the presence or absence of additional food allergies and the occurrence of the first allergic reaction during the first documented exposure to peanut proteins, without the use of data from sophisticated laboratory analyses, such as epitope-specific peanut IgE, IgG4, or basophil activation test, enabled the correct classification of more than 80% of children with high or low PP threshold (Fig 1A and 1B). This algorithm does not replace the oral challenge test, which is still the reference standard method, but it can indicate, using only widely available clinical data, a useful risk stratification.

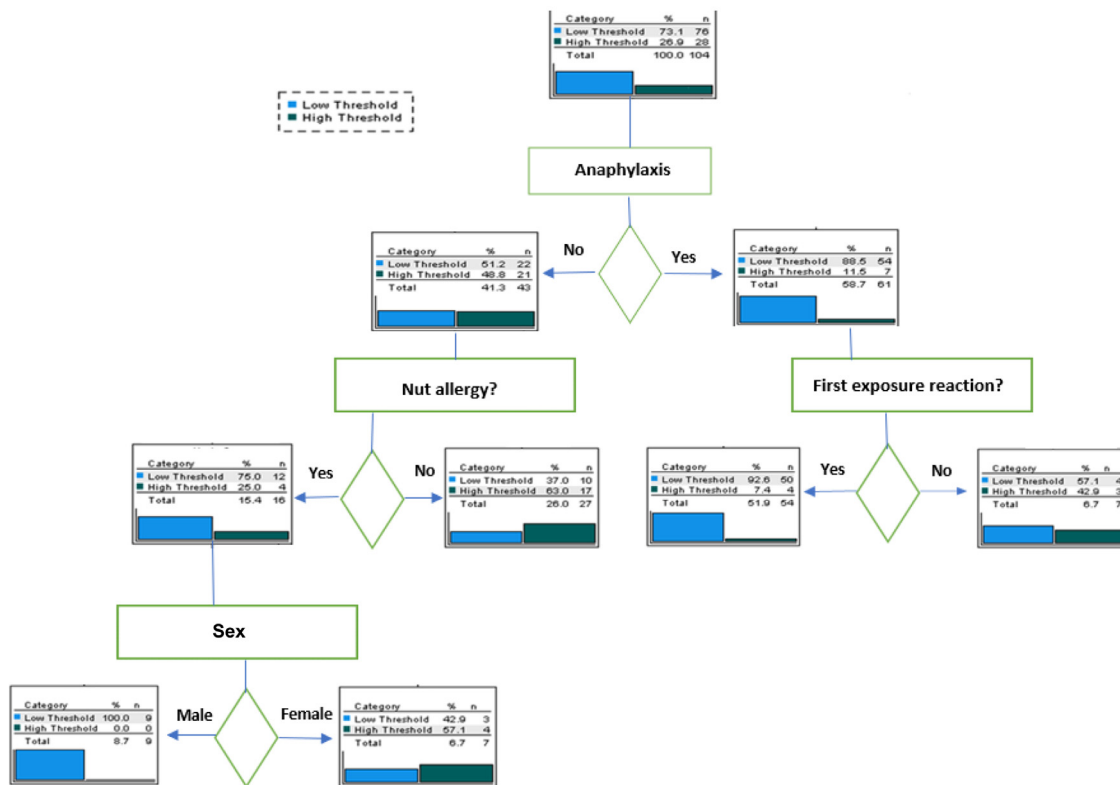
Although available only for a subgroup of patients, immunologic changes over the 40 weeks of OIT treatment revealed decreased skin tests with peanut extracts (from a mean of 9.2 mm to a mean of 2.7 mm; $P < .05$; Fig 2). There was no significant change in levels of specific IgE to peanuts or peanut components; $P = 0.1$, $P = 0.9$ accordingly. There was a tendency for increase in levels of specific IgG4 to peanuts and Ara h2.

Table 2
Skin Tests, Specific IgE, and IgG4 to Peanuts and Peanut Allergenic Proteins, in 28 Children With HTPA, Compared With 76 Children With LTPA

Test	All (N = 104)	HTPA (N = 28)	LTPA (N = 76)	P value
Peanut skin prick test mean mm-wheal (95% CI)	11 (10–12)	9.2 (7.5–10.9)	11.6 (10.4–12.9)	.03
Specific IgE IU/mL mean (95% CI)				
Peanut	22.0 (14.1–30)	6.4 (2.0–10.9)	26.7 (16.7–36.7)	.03
Ara h1	16.6 (6.5–20.7)	1.1 (0.3–2.2)	17.3 (8.3–26.3)	.05
Ara h2	18.4 (11–25.8)	5.1 (0.6–9.7)	22.3 (13.1–31.6)	.03
Specific IgG4 ng/mL mean (95% CI)				
Peanut	0.9 (0.5–1.4)	1.1 (0.7–2.1)	0.9 (0.3–1.4)	NS
Ara h1	0.1 (0.05–0.19)	0.16 (0–0.4)	0.1 (0.04–0.17)	NS
Ara h2	0.4 (0.04–0.74)	0.3 (0–0.7)	0.4 (0–0.9)	NS
Specific IgE over IgG4 ng/mL mean (95% CI)				
Peanut	192 (107–278)	77 (11–142)	226 (118–334)	NS
Ara h2	489 (309–669)	184 (21–347)	579 (356–800)	.05

Abbreviations: CI, confidence interval; HTPA, high-threshold peanut allergy (maximal tolerated dosage in excess of 100 mg of peanut protein); Ig, immunoglobulin; LTPA, low-threshold peanut allergy (maximal tolerated dosage of 100 mg of peanut protein or less); NS, not significant.

a) Decision Tree Analysis



b) Classification

Observed	Predicted		Percent Correct
	Low Threshold	High Threshold	
Low Threshold	63	13	82.9%
High Threshold	7	21	75.0%
Overall	67.3%	32.7%	80.8%
Percentage			

Figure 1. Decision tree analysis for classification of children with PA into HTPA and LTPA. (A) Decision tree analysis. (B) Classification. HTPA, high-threshold PA; LTPA, low-threshold PA; PA, peanut allergy.

Outcomes and Safety of the High-Threshold Peanut Allergy Oral Immunotherapy Protocol

A total of 28 children with HTPA were enrolled in a simplified OIT protocol as detailed previously (Fig 3).

A total of 19 children with HTPA with an initial SMTD of less than 300 mg of PP were started on a daily dosage of 100 mg for 20 weeks. There were 2 children, both under 3 years of age, who discontinued the study owing to compliance issues within the first week of home-based therapy without any adverse events. In addition, 2 children discontinued the study within the first week of treatment, because of an allergic reaction at home, to the same dose previously tolerated in the clinic. The remaining 15 patients continued their 100 mg PP dosage for 20 weeks, passed the

300 mg challenge at that time, and continued to complete the additional 20 weeks of treatment on the higher dose. All children in this group completed the 40-week treatment period, passed an exit challenge with 2 g of PP without mishap, and were put on a maintenance protocol of 2 g $\times$ 3/wk. All children (15 of 15) have already passed the 6-month follow-up challenge and are consuming, in addition to their maintenance dose, age-appropriate doses (3–10 g) of PP-containing foods without issue.

There were 9 children with HTPA with an initial SMTD higher than 300 mg of PP, labeled as very HTPA, who were started on a daily dosage of 300 mg for 40 weeks. One of the children reacted at home after a few days of home treatment with an anaphylactic reaction, including respiratory complaints, and necessitated at-home administration

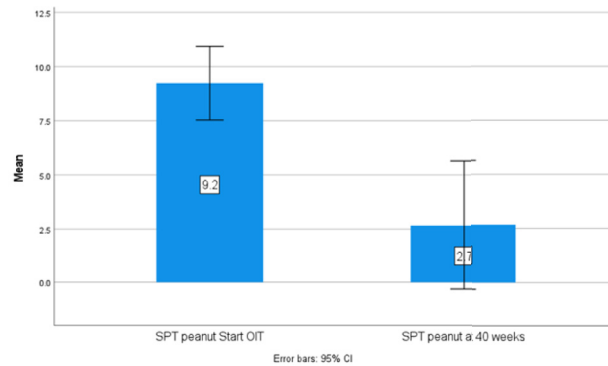
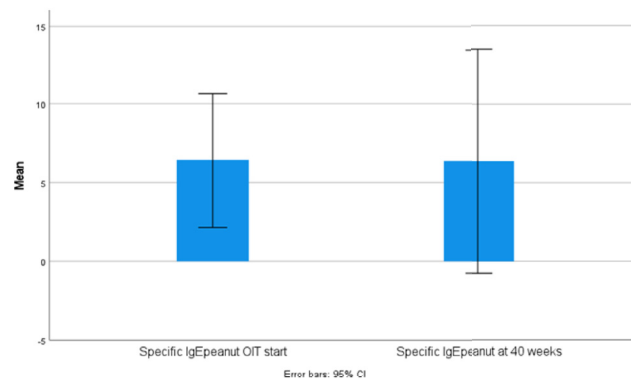
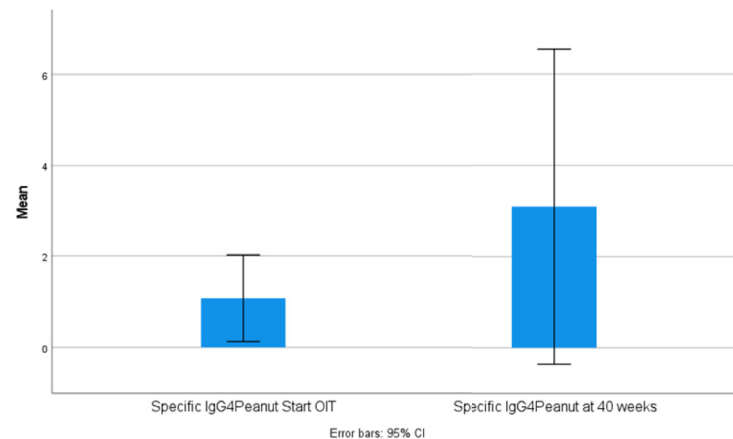
a) Skin Prick Tests (mm wheal size) with commercial peanut extract**b) Specific IgE to peanuts in IU/ml****c) Specific IgG4 to peanuts in ngr/ml**

Figure 2. Immunologic changes over 40 weeks of OIT in children with HTPA. (A) Skin prick tests (mm wheal size) with commercial peanut extract. (B) Specific IgE to peanuts in IU/mL. (C) Specific IgG4 to peanuts in ng/mL. CI, confidence interval; HTPA, high-threshold PA; Ig, immunoglobulin; OIT, oral immunotherapy; PA, peanut allergy; SPT, skin prick testing.

of adrenaline and an ED visit. The other 8 children have completed the 40-week treatment period, passed an exit challenge with 2 g of PP without mishap, and were on a maintenance protocol of 2 g $\times$ 3/wk for 6 months. All children in this group (8 of 8) have already passed the 6-month follow-up challenge and are now consuming, in addition to their maintenance dose, age-appropriate doses (4–15 g) of PP-containing foods without issue.

In an intention-to-treat analysis, 23 of 28 patients (82%), successfully completed the protocol and were on a “LEAP like” maintenance dosage of 2 g of PP 3 times a week similar to LEAP.³² All, 23

of 28 (82%), have successfully incorporated peanut-containing foods into their regular diet in addition to the recommended maintenance dose.

Discussion

In this study, we enrolled young patients with HTPA to a simplified reintroduction protocol, starting with the confirmation of the MTD during an allergy clinic-based open challenge.

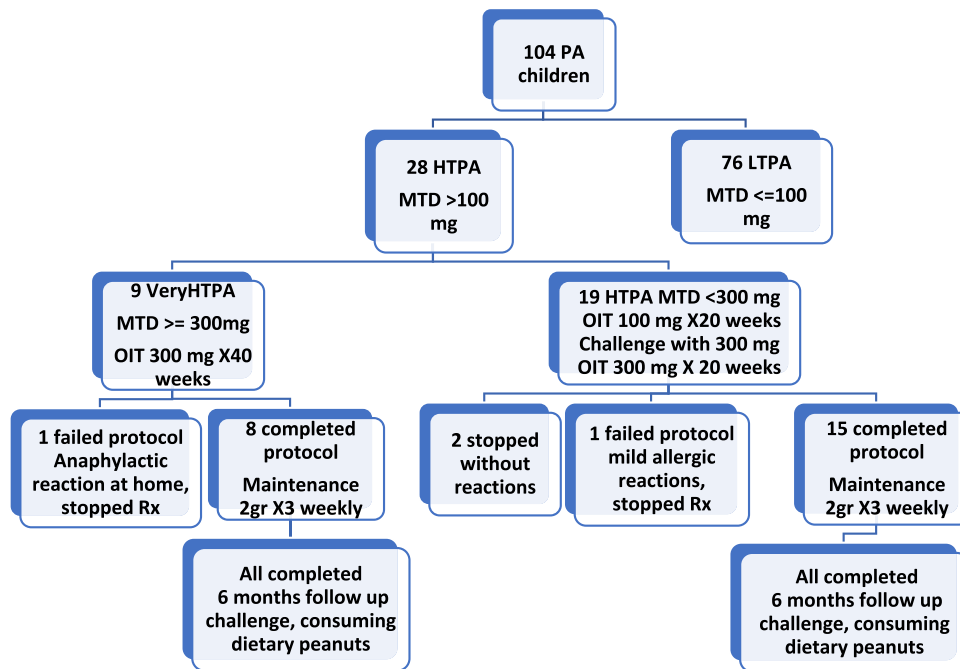


Figure 3. Disposition and outcomes of 28 study patients. Rx, Treatment.

All children had IgE-mediated sensitization to peanut allergens and previously had allergic reactions to peanuts, 70% of them suffered from atopic dermatitis, 30% from episodes of recurrent wheezing or asthma, and 50% had additional food allergies.

A simplified OIT protocol enabled the achievement of a “LEAP like” 2 g PP × 3 times/wk, with maintenance schedule in 23 of 28 (82%) and the safe introduction of PP-containing foods into the diet, that is, all those who have already completed the 6-month follow-up visit. This good acceptance of PP-containing foods into the diet in our study is encouraging and is a strong argument for the adoption of such protocols for children fulfilling the criteria.

The safety of the protocol, with a single anaphylactic reaction at home (3.6%) (which resolved promptly after epinephrine administration) and 2 additional (7.1%) mild allergic reactions (treated with antihistamines) and no gastrointestinal complaints, favorably compares with published peanut OIT protocols,^{33,34} but it needs to be confirmed in larger, blinded studies. Although the protocol is somewhat longer than previously published ones, its safety may be a good argument for its adoption in relatively young patients with a higher threshold PA.^{33,34}

The documented occurrences of allergic reactions, on the same previously tolerated dose, in approximately 10% of children with “HTPA,” within a short period of time after the clinic challenge, emphasize that these children are in fact at risk of anaphylactic reactions and require a personalized and goal-oriented plan, with the aim of reducing the risk and enabling lifestyle choices, all in conjunction with an open discussion with parents and caregivers.

From a clinical point of view, the ability to predict a challenge with LTPA based only on clinical parameters, as revealed in our decision tree analysis (Fig 1), is an important tool for risk stratification of children suspected with having PA.

The single previously published peanut study on children with HTPA by Garvey et al²¹ supports our present findings; however, it did not include a formal rechallenge and a precise PP dosing as reported here.

It is, however, clear that children with HTPA are susceptible to the same low quality of life, anxiety, and social distress, as do children with LTPA, and as documented in our small group of patients, the challenge observed high threshold can change with exercise, time, illness, and so on. Therefore, the needs of this group of children and their families have to be better addressed by the allergist’s community.

The limitations of the study are inherent in its design as an open label, a single center, within a homogenous population, with a small number of children. One might also argue that these children with HTPA may be on their way to resolving their allergy naturally and may be better off not undergoing what effectively is an OIT program, even a very safe one. Nevertheless, given that age and repeated reactions seem to be a major factor in determining high risk,²³ LTPA,²⁰ and in our own data the chances of identifying children with HTPA are substantially better under the age of 48 months,¹¹ it is important to focus more research on this relatively “not so allergic” group, not only in peanuts but all food allergies.

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