Original Article

First Real-World Safety Analysis of Preschool Peanut Oral Immunotherapy

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What is already known about this topic? A clinical trial of peanut oral immunotherapy (P-OIT) in 37 preschoolers was found to be effective (78% achieved sustained unresponsiveness after discontinuing therapy for 4 weeks) and safe, with mild/moderate reactions and 1 patient receiving epinephrine.

What does this article add to our knowledge? P-OIT in 270 preschoolers in the real-world setting appears safe for the vast majority of patients, with 71.2% of reactions during buildup being mild, 2.23% of reactions requiring epinephrine, and low dropout rate (10%).

How does this study impact current management guidelines? P-OIT could be considered for preschoolers in the real-world allergy clinic setting, due to its favorable safety profile in the vast majority of patients and high completion rate in this age group.

BACKGROUND: In 2017, a clinical trial of 37 subjects demonstrated that preschool peanut oral immunotherapy (P-OIT) was safe, with predominantly mild symptoms reported and only 1 moderate reaction requiring epinephrine.

OBJECTIVES: We sought to examine whether these findings would be applicable in a real-world setting.

METHODS: As part of a Canada-wide quality improvement project, community and academic allergists administered P-OIT to preschool-age children who had (1) skin prick test wheal diameter greater than or equal to 3 mm or specific IgE level greater than or equal to 0.35 kU/L and history of reaction and/or positive baseline oral food challenge, or (2) no ingestion history and specific IgE level greater than or equal to 5 kU/L. Over 16 to

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Abbreviations used
AE- Adverse event
CPP-OIT- Canadian preschool peanut oral immunotherapy
EoE- Eosinophilic esophagitis
IQR- Interquartile range
OFC- Oral food challenge
OIT- Oral immunotherapy
OR- Odds ratio
P-OIT- Peanut oral immunotherapy
ps-IgE- Peanut specific IgE
QI- Quality improvement
SPT- Skin prick test

22 weeks, patients had biweekly clinic visits for updosing, and consumed the dose daily at home between visits. Target maintenance dose was 300 mg peanut protein. Symptoms were classified using a modified World Allergy Organization Subcutaneous Immunotherapy Reaction Grading System (1 mildest, 5 fatal).
RESULTS: Of 270 patients who started P-OIT in the period 2017 to 2018, 243 reached maintenance, and 27 dropped out (10.0%); 67.8% of patients experienced reactions during buildup: 36.3% grade 1, 31.1% grade 2, and 0.40% grade 4. Eleven patients (4.10%) received epinephrine (10 patients received 1 dose, 1 patient received epinephrine on 2 separate days), representing 2.23% of reactions (12 of 538) and 0.029% of doses (12 of 41,020).
CONCLUSIONS: We are the first group to describe preschool P-OIT in a real-world multicenter setting. The treatment appears to be safe for the vast majority of patients because symptoms were generally mild and very few reactions received epinephrine; however, life-threatening reactions in a minority of patients (0.4%) can still occur. **© 2019 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2019;7:2759-67)**

Key words: *Peanut allergy; Peanut oral immunotherapy; Oral immunotherapy; Safety; Allergic reactions; Adverse events; Preschool children; Preschoolers; Real-world*

INTRODUCTION

Peanut oral immunotherapy (P-OIT) is a promising therapy for children with peanut allergy, and there is a growing body of evidence from clinical trials suggesting its safety and efficacy.[1-5] Outside of a research setting, some allergists have been offering P-OIT for many years to school-age children.[6-8] Although desensitization data appear promising, there is a high rate of reactions requiring epinephrine (14.5%-27.0%).[6-8] This high rate is in contrast to avoidance, where the annual incidence rate of accidental exposure to peanut is approximately 12.4%, with 1% to 2% of patients requiring epinephrine per year.[9] As a consequence, many allergists do not believe that oral immunotherapy (OIT) should be offered outside of a research setting, and have not routinely offered it in their clinics because of safety concerns.[10-13] Although controversy about OIT outside of the research setting will persist, at least 1 academic OIT research group has stated recently that "the time has come to stop placebo-controlled trials of [milk] oral immunotherapy and focus on real-life studies."[14] In addition, although many allergists consider tolerance to be the long-term goal, many parents have a much stronger desire for desensitization.[15,16]

In early 2017, a seminal article published by Vickery et al[3] demonstrated for the first time that P-OIT was very effective (78% achieved sustained unresponsiveness after discontinuation of therapy for 4 weeks) and safe in preschool-age children (aged 9-36 months), with only mild to moderate reactions and one moderate reaction requiring epinephrine. In addition, there is evidence that infants may be less fearful than older children of their food allergens and their immune systems may be more easily altered.[3,17] This has led some allergists, who had reservations about offering P-OIT outside of a research setting, to consider it as a treatment option for preschool children in their clinics.

Following publication of the Vickery et al[3] preschool P-OIT trial, a group of community and academic allergists from across Canada initiated a quality improvement (QI) project titled Canadian Preschool Peanut Oral Immunotherapy (CPP-OIT) to determine the safety of preschool P-OIT outside of a research setting and provide practitioners with guidance more relevant to their clinical practices. This article describes the first real-world safety data on 270 preschool-age children as part of CPP-OIT.

METHODS

Study design

CPP-OIT is a QI project, with the primary aim of improving the health care services and outcomes of children with peanut allergy. It involves a collaboration between community and academic allergists in British Columbia, Alberta, Manitoba, and Nova Scotia. Enrollment of preschoolers in community-based and hospital-based allergy clinics across Canada began in April 2017. The current safety analysis includes data from the first 270 children enrolled in CPP-OIT.

Patient selection

Children were included if they were aged 9 to 71 months ("preschool" aged), and had either (1) a history of an allergic reaction to peanut (at home or during optional baseline oral food challenge [OFC]) and either a positive skin prick test (SPT) wheal diameter of greater than or equal to 3 mm, or peanut specific IgE (ps-IgE) level of greater than or equal to 0.35 kU/L, or (2) no peanut ingestion history and a ps-IgE level of greater than or equal to 5 kU/L.

Children were not included in the current safety analysis if they had a previous life-threatening episode of anaphylaxis (including hypotension, respiratory distress, profound lethargy) including at the optional baseline OFC, allergy to a dilution agent/vehicle used in the peanut capsules (eg, oat), severe atopic dermatitis requiring systemic therapy, or asthma requiring more than medium-dose inhaled corticosteroid therapy. Contraindications at the discretion of the allergist were language barriers, asthma exacerbation requiring an emergency room visit or hospitalization, or oral corticosteroid therapy in the last 6 months.

Procedures

In contrast to previous P-OIT studies in children, this project allowed participating allergists to select from 3 different protocol options. One protocol used Bamba (Osem Group, Holon, Israel) peanut butter puffs, a second used peanut flour or powdered peanut butter (eg, powdered peanut butter powder, PB2 Foods, Tifton, Ga) compounded at local pharmacies into capsules with inert filler and

opened into a food product for the child to ingest, and the third protocol was a hybrid of the previous 2, starting with peanut flour or powdered peanut butter, and moving to Bamba at the fourth updose (Table I).

Optional open-label OFCs were conducted according to each clinic's protocol. Patients who reacted to an eliciting dose of 300 mg during the baseline OFC were still started on OIT because they still needed to be desensitized. If they were not started on OIT, they would have been deemed allergic (defaulting to standard of care, which is avoidance). For updosing visits, pediatric allergists saw children every 2 weeks over 8 to 11 clinic visits (16-22 weeks), with a target maintenance dose of 300 to 320 mg peanut protein based on the chosen protocol (Table I). Between clinic visits, patients ingested peanut on a daily basis at home. Symptoms and treatment/management of allergic reactions, including epinephrine use, during clinic buildups were recorded in the patient's medical chart. Caregivers were recommended to note symptoms at home and report them to the allergist at the next visit. Symptoms were graded according to a modified World Allergy Organization Subcutaneous Immunotherapy Reaction Grading System,[18] with adaptations specific to allergic reactions in infants (see Figure 1). We also adopted mild (grade 1), moderate (grades 2 and 3), or severe, including death (grades 4 and 5), categories from the Consortium of Food Allergy Research[3,19] in an effort to make our real-world data comparable to previously published results that used these grading systems for adverse events (AEs).

Patients were provided with a standardized flow sheet containing instructions on how to manage at-home reactions, when to hold P-OIT doses (eg, during a viral illness), and when to administer epinephrine (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Allergists received a similar flow sheet (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

We received a waiver for ethics from the Research Ethics Board at The University of British Columbia/British Columbia Children's Hospital because CPP-OIT is a QI project.

Statistical analysis

Means, percentages, and 95% CIs were calculated for categorical variables (eg, symptoms at initial reaction and sex). The median and interquartile range (IQR) were calculated for continuous variables (eg, age, ps-IgE, and SPT). Multivariable logistic regression was performed to identify characteristics associated with (1) dropping out of P-OIT during buildup (yes/no) and (2) receiving epinephrine during P-OIT build-up (yes/no). Data were analyzed using Stata 15.

RESULTS

Baseline characteristics of P-OIT patients

From April 2017 to November 2018, 270 preschoolers (243 from community clinics and 27 from hospital-based clinics) with a median age of 23.0 months (IQR, 15.0-33.0 months) started P-OIT (see Table II). Of these, 94.5% had experienced a previous reaction to peanut: 68.9% grade 1 and 24.1% grade 2. The median baseline ps-IgE level was 5.03 kU/L (IQR, 1.50-18.7 kU/L) and SPT wheal diameter was 7.00 mm (IQR, 5.00-9.00 mm). Fifteen patients (5.50%) were never exposed to peanut before entry into P-OIT, and their median baseline ps-IgE level was 18.6 kU/L (IQR, 7.49-59.6 kU/L). All these had either a baseline ps-IgE level of greater than or equal to 5.0 kU/L (7 patients), a positive baseline OFC (2 patients), or both (6 patients). Most patients had eczema (71.9%), and 51.9% had other food allergies.

Tolerability of P-OIT

Of the 270 patients enrolled into CPP-OIT, 243 reached maintenance and 27 dropped out (10.0% dropout rate). Reasons

TABLE I. Protocol options for CPP-OIT

Week no.	Hybrid (PB2* then Bamba†)	PB2*-Only	Bamba†-Only
0	28.8 mg PB2 (12 mg PP)	First-day escalation (every 15-30 min)	1/8 Bamba stick (∼10 mg PP)
		0.24 mg PB2 (0.1 mg PP)	
		0.48 mg PB2 (0.2 mg PP)	
		0.96 mg PB2 (0.4 mg PP)	
		1.92 mg PB2 (0.8 mg PP)	
		3.6 mg PB2 (1.5 mg PP)	
		7.2 mg PB2 (3 mg PP)	
		14.4 mg PB2 (6 mg PP)	
2	60 mg PB2 (25 mg PP)	28.8 mg PB2 (12 mg PP)	1/4 Bamba stick (∼20 mg PP)
4	120 mg PB2 (50 mg PP)	60 mg PB2 (25 mg PP)	1/2 Bamba stick (∼40 mg PP)
6	1 Bamba stick (∼80 mg PP)	120 mg PB2 (50 mg PP)	1 Bamba stick (∼80 mg PP)
8	1.5 Bamba sticks (∼120 mg PP)	180 mg PB2 (75 mg PP)	1.5 Bamba sticks (∼120 mg PP)
10	2 Bamba sticks (∼160 mg PP)	240 mg PB2 (100 mg PP)	2 Bamba sticks (∼160 mg PP)
12	3 Bamba sticks (∼240 mg PP)	300 mg PB2 (125 mg PP)	3 Bamba sticks (∼240 mg PP)
14	4 Bamba sticks (∼320 mg PP = maintenance dosing)	374.4 mg PB2 (156 mg PP)	4 Bamba sticks (∼320 mg PP = maintenance dosing)
16	Maintenance dosing	468 mg PB2 (195 mg PP)	Maintenance dosing
18	Maintenance dosing	588 mg PB2 (245 mg PP)	Maintenance dosing
20	Maintenance dosing	720 mg PB2 (300 mg PP = maintenance dosing)	Maintenance dosing

PB2, Powdered peanut butter; *PP*, peanut protein.

*Allergists who chose to use peanut flour instead of PB2 adjusted for protein content.

†There are different types of Bamba packages with different protein content. The calculations in this table for the number of Bamba sticks are based on the package with 5 g protein/28 g Bamba.

World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (see text)

Grade 1 Mild	Grade 2 Moderate	Grade 3 Moderate	Grade 4 Severe	Grade 5 Severe
Symptom(s)/ sign(s) of one organ system present[i] **Cutaneous** Generalized pruritus, urticaria, flushing or sensation of heat or warmth[ii] **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper respiratory** Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) **or** Throat-clearing (itchy throat) , drooling **or** Cough perceived to come from the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Conjunctival erythema, pruritus or tearing **or** **Neurological:** Very quiet/sleepy Irritable Cranky (in an infant or child) **Other** Nausea, metallic taste, or headache	***Symptom(s)/ sign(s) of more than one organ system present*** **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea **or** **Other** Uterine cramps	**Lower respiratory** Asthma (e.g., 40% PEF or FEV1 drop, NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula or tongue edema with or without stridor	**Lower or Upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness **or** **Neurological:** Profound lethargy (in an infant or child)	Death

Drooling is a symptom associated with throat clearing and itchy throat, which younger children may not express verbally

All of these grade 4 symptoms were contraindications to starting the treatment based on our inclusion/exclusion criteria.

We can justify profound lethargy as an indicator of an altered level of consciousness (LOC) due to significant hypotension in infants and children

Wanted to ensure that we erred on the side of caution and treated behavior changes as an effect on another organ system, since small infants and children are poor at verbalizing additional symptoms that are occurring but may be difficult to objectively observe

Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4.

Note: children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis, e.g., becoming very quiet or irritable and cranky.

Revisions in red Justifications for revisions in blue

FIGURE 1. Modified World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System.[18] *PEF*, Peak expiratory flow.

for the dropouts included repeated allergic reactions, symptoms suggestive of eosinophilic esophagitis (EoE) (see below), child refusing to consume the daily dose, and parental anxiety. The median duration of buildup for those reaching maintenance was 22.0 weeks (IQR, 16.0-29.0 weeks), for those who dropped out was 5.00 weeks (IQR, 2.00-14.0 weeks), and overall was 20.0 weeks (IQR, 14.0-29.0 weeks).

Baseline OFCs

Baseline OFCs were completed in 30.7% (n = 83) of patients, with the most common symptoms being urticaria (75.9%), pruritis (36.1%), and vomiting (22.9%). There were 3 OFCs that were not completed because the child refused to consume the dose. The median eliciting dose for the OFC was 240 mg peanut protein (IQR, 80.0-880 mg). Of note, the eliciting dose for the OFC was greater than 300 mg peanut protein for 38 of 83 (45.7%) patients; these patients were started on OIT at a higher dose (eg, closer to 300 mg) and their buildup time was reduced. In some cases, the patient was started on the 300-mg maintenance dose. Epinephrine was administered, alone or with other medications (antihistamine, bronchodilator, steroids), in 18.0% of OFCs, and antihistamines were given alone in 56.6% of OFCs (Table III).

Safety of P-OIT

We found that 67.8% (183 of 270) of preschoolers experienced at least 1 allergic reaction during the buildup phase in the clinic or at home (Table IV). According to our modified World Allergy Organization grading system,[18] 36.3% of patients experienced grade 1 (mild) symptoms, 31.1% grade 2 (moderate), and 0.40% grade 4 (severe). In total, there were 538 allergic reactions experienced in 270 patients, for a rate of 1.99 allergic reactions per patient. Eleven patients (4.10%) received epinephrine (10 patients received 1 dose, 1 patient received epinephrine on 2 separate days) during buildup. Of these, 6 doses were given during clinic updosing visits, and 6 were given at home; 11 doses were given for grade 2 reactions and 1 for a grade 4 reaction. We include baseline and reaction characteristics for those patients who received epinephrine in Table E1 in this article's Online Repository at www.jaci-inpractice.org. Thirty-two (11.9%) patients received antihistamines for symptoms, 1 (0.37%) received a bronchodilator (at home), and 3 (1.11%) patients visited the emergency department for an allergic reaction, all of which were grade 2.

Three patients experienced symptoms suggestive of EoE, one of which underwent a biopsy, which ruled out EoE; an additional case of EoE was identified as an incidental finding during a biopsy to rule out celiac disease (the EoE persisted despite stopping P-OIT). We include CPP-OIT protocol deviations

TABLE II. Baseline characteristics of patients included in CPP-OIT

Characteristic	Overall	Reached maintenance	Dropped out
Total	N = 270	N = 243	N = 27
Age (mo) at entry into OIT, median (IQR)	23.0 (15.0-33.0)	23.0 (15.0-32.0)	22.0 (16.0-34.0)
Age (mo) at initial reaction, median (IQR)	10.0 (7.00-12.0)	10.0 (7.00-13.0)	9.00 (7.00-12.0)
No. of months between peanut reaction and first OIT dose, median (IQR)	9.00 (4.00-20.0)	9.50 (4.00-19.0)	7.50 (6.0-28.5)
Sex: male, n (%)	159 (58.9)	137 (56.4)	22 (81.5)
Initial allergic reaction, n (%)	255 (94.5)	230 (94.6)	25 (92.6)
Grade of initial reaction, n (%)			
Grade 1	186 (68.9)	166 (68.3)	20 (74.1)
Grade 2	69 (24.1)	64 (26.3)	5 (18.5)
Grade 3	None	None	None
Grade 4	None	None	None
Never exposed, n (%)	15 (5.50)	13 (5.40)	2 (7.40)
Baseline peanut SPT, median (IQR)	7.00 (5.00-9.00)	7.00 (5.00-9.00)	6.00 (5.50-9.50)
Baseline peanut specific IgE level, median (IQR)	5.03 (1.50-18.7)	4.99 (1.51-16.0)	50.7 (1.40-100)
Baseline OFC, n (%)			
Completed	83 (30.7)	72 (29.6)	11 (40.7)
Incomplete	3 (1.10)	3 (1.20)	0 (0.00)
Not done	184 (68.2)	168 (69.1)	16 (59.3)
Other atopic conditions, n (%)			
Eczema	194 (71.9)	170 (70.0)	24 (88.9)
Asthma	44 (16.3)	40 (16.5)	4 (14.8)
Allergic rhinitis	21 (7.78)	17 (7.00)	4 (14.8)
Other food allergies, n (%)	140 (51.9)	125 (51.4)	15 (55.6)
Egg	88 (32.6)	77 (31.7)	11 (40.7)
Tree nut	41 (15.2)	37 (15.2)	4 (14.8)
Milk	44 (14.9)	42 (17.3)	2 (7.41)
Protocol chosen, n (%)			
Bamba-only	68 (25.2)	56 (23.0)	12 (44.4)
Peanut flour-only	127 (47.0)	116 (47.7)	11 (40.7)
Hybrid	75 (27.8)	71 (29.3)	4 (14.9)

(Table E2 in this article's Online Repository at www.jaci-inpractice.org) and characteristics of patients with EoE-like symptoms in Table E3 in this article's Online Repository at www.jaci-inpractice.org.

The overall rate of epinephrine use during P-OIT buildup was found to be 2.93 doses per 10,000 total days on P-OIT (0.029%), with 25.9 per 10,000 clinic doses (0.26%) and 1.55 per 10,000 home doses (0.016%) (Table V). Similarly, the rate of grade 4 (severe) reactions was very low, with 0.24 per 10,000 total doses (0.002%), 4.31 per 10,000 clinic doses (0.04%), and none at home.

In a multivariable logistic regression model of patient characteristics associated with dropping out of P-OIT, those with a higher baseline IgE (odds ratio [OR], 1.03; 95% CI, 1.01-1.05) were more likely to drop out during P-OIT buildup (Table VI). In a multivariable logistic regression model of patient characteristics associated with epinephrine use during P-OIT buildup, patients with a higher baseline SPT (OR, 1.35; 95% CI, 1.05-1.75) and a higher baseline ps-IgE (OR, 1.03; 95% CI, 1.01-1.06) were more likely to receive epinephrine (Table VII). See Figure 2 for a visual representation of epinephrine use and dropouts within different baseline ps-IgE categories.

DISCUSSION

We are the first group to describe the safety of preschool P-OIT in a real-world, multicenter setting of community and academic allergy clinics. We confirm with a large sample of 270 patients that the treatment is safe for the vast majority of patients; only 0.4% of patients experienced a severe reaction and 11 patients (4.07%) received epinephrine during buildup. The treatment was well tolerated, with only 10% of patients dropping out during buildup. The collaboration between a large group of community and academic allergists for CPP-OIT demonstrates that getting past the controversy of offering P-OIT by analyzing outcomes of real-world data is both healthy for our specialty and a possible means for reducing confusion among parents about the role of P-OIT.[20]

One patient (0.40%) in our data set experienced a grade 4 (severe) AE. Although Vickery et al's preschool study did not report any severe AEs, our sample size (n = 270) was more than 7 times larger than that of Vickery et al's study (n = 37); hence, the latter study may have been too small to enable detection of a grade 4 reaction.[3] The largest phase III randomized controlled trial of 496 children aged 4 to 17 years comparing AR101 P-OIT with placebo, titled PALISADE (Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults), which was recently published, found a 4.3% rate of severe AEs in the P-OIT group, which is higher than ours.[5] This could be due to higher rates of anaphylaxis in older children than in younger children.[21,22] A study of P-OIT with probiotic by Tang et al[23] reported an extremely high rate of severe AEs (45.2%). Of note

TABLE III. Characteristics of patients completing baseline OFC

Characteristic	N = 83*
Symptoms at entry OFC, n (%)	Urticaria: 63 (75.9)
	Angioedema: 6 (7.23)
	Pruritus: 30 (36.1)
	Cough: 13 (15.7)
	Wheeze: 5 (6.02)
	Rhinitis: 13 (15.7)
	Conjunctivitis: 8 (9.64)
	Abdominal pain: 8 (9.64)
	Vomiting: 19 (22.9)
	Diarrhea: 1 (1.20)
	Sleepy: 0 (0.00)
	Profound lethargy: 0 (0.00)
	Hypotension: 0 (0.00)
	Respiratory distress: 0 (0.00)
	Other: 15 (18.1)
	Redness: 3 (3.61)
Grade of reaction, n (%)	
Grade 1	33 (39.8)
Grade 2	50 (60.2)
Eliciting dose in mg protein, median (IQR)	240 (80-880)
Treatment of reaction	
Antihistamine alone	47 (56.6)
Epinephrine (total)	15 (18.0)
Alone	6 (7.20)
With antihistamine	6 (7.20)
With antihistamine, bronchodilator	1 (1.20)
With antihistamine, steroids	2 (2.40)

*Three patients started an OFC but refused to eat peanut so the OFC was terminated and the patient was started on OIT.

TABLE IV. Grading of allergic reactions and treatment/management of allergic reactions in CPP-OIT

	Patients, n (%)	Allergic reactions, n (%)
Grade/treatment	N = 270	N = 538
Highest grade of reaction, n (%)		
No reactions	87 (32.2)	—
1 (Mild)	98 (36.3)	383 (71.2)
2 (Moderate)	84 (31.1)	154 (28.6)
3 (Moderate)	None	None
4 (Severe)	1 (0.40)	1 (0.20)
5 (Death)	None	None
Treatment/management of reaction		
Epinephrine administered	11 (4.07)	12* (2.23)
Delayed next dose	19 (7.04)	23 (4.28)
Antihistamine given	32 (11.9)	65 (12.1)
Bronchodilator given†	1 (0.37)	1 (0.19)
Emergency department visit	3 (1.11)	3 (0.56)

*One patient received 2 doses of epinephrine (once at the first buildup visit in clinic, and the other a few days after the first buildup visit, at home) and subsequently dropped out of OIT. The other 10 patients each received 1 dose of epinephrine, 5 in the clinic during a buildup visit, and 5 at home.
†Parent administered at home without administering epinephrine.

is that 32.3% of placebo patients in their study also experienced severe AEs, which the authors attributed to anxiety. In addition, the high rate of reported severe AEs in their study could also be because these were defined as "any symptom that prevents daily activities and might require therapeutic intervention," which could lead to misclassification. For the 3 published real-world studies of P-OIT,[6-8] there are no data on the grading of AEs based on specific symptoms, limiting the ability to compare our real-world data on severity of AEs with others.

During buildup, 4.07% of CPP-OIT patients received epinephrine for allergic reactions. This was higher than the 2.5% reported in Vickery et al's preschool study,[3] but lower than the 14.0% reported in PALISADE[5] and the 14.5% to 27.0% from the 3 published chart reviews of patients who received P-OIT outside of a research setting.[6-8] The goal of our group was to be as safe as possible, because this was not a clinical trial and allergists were not always available if an allergic reaction occurred at home. Therefore, we encouraged parents to give epinephrine if there was a possibility that anaphylaxis was occurring. Direct evidence of this approach in CPP-OIT comes from 11 of 12 epinephrine doses being given for grade 2 reactions, whereas only 1 of 12 doses was given for grade 4 reactions. Most reactions that occurred at home would meet clinical criteria for anaphylaxis, and in general epinephrine use at home was congruent with its use in clinic.

The potential benefit of our real-world preschool P-OIT data on families cannot be emphasized enough. The recent study by Greenhawt et al[15] noted that parents "specifically sought a therapy that would protect their child, through a process involving minimal risk to the child." In fact, this theme was expressed in all their parent interviews. Our data indicate that the risk of having reactions requiring epinephrine either in the clinic or at home is extremely low, with only 12 reactions requiring epinephrine out of more than 41,000 patient days on P-OIT. Our data suggest that preschool P-OIT may be able to meet the needs of most families who seek a safety margin for accidental exposures to small amounts of peanut (≤300 mg) as a desired outcome through a protocol involving low risk.

Although not a primary focus for this safety analysis, we found that among our 270 CPP-OIT patients, 3 experienced symptoms consistent with possible EoE, one of whom had a subsequent biopsy, which ruled out EoE, and an additional patient who had an incidental finding of EoE during a biopsy to rule out celiac disease. P-OIT was discontinued in this patient after the EoE diagnosis (but the EoE persisted despite discontinuation). This indicates that our biopsy-proven rate of EoE of 1 of 270 (0.37%) is in line with that in the PALISADE trial,[5] but considerably less than the range reported in a 2014 meta-analysis, which found that 2.7% (range, 0.99%-5.33%) of patients on OIT have EoE.[24] The authors of the meta-analysis speculated the actual occurrence might be lower than 2.7% due to a funnel plot analysis showing significant publication bias in favor of reporting EoE after OIT. However, many patients with suspicious symptoms do not undergo endoscopy, and so the true prevalence of EoE could also be underrepresented in OIT studies.

Previous publications noted asthma to be a risk factor for reactions during OIT,[25] or failure to reach maintenance for OIT,[26] but our data did not confirm this finding. Similarly, neither Nachshon et al[8] nor Wasserman et al[7] found asthma to be a risk factor for OIT withdrawal. The PALISADE trial did find that 3% of P-OIT patients, and 2.4% of placebo patients,

TABLE V. Rates of allergic reactions and epinephrine use in-office, at home, and overall

	In-office buildup visits	Home doses*	Total days on P-OIT
Total no. of doses	N = 2,321	N = 38,699	N = 41,020
Grade 1 reactions			
No.	193	190	383
Rate	832 per 10,000 doses (8.32%)	49.1 per 10,000 doses (0.49%)	93.1 per 10,000 doses (0.93%)
Grade 2 reactions			
No.	46	108	154
Rate	198 per 10,000 doses (1.98%)	27.9 per 10,000 doses (0.28%)	37.5 per 10,000 doses (0.38%)
Grade 3 reactions			
No.	None	None	None
Rate	—	—	—
Grade 4 reactions			
No.	1	None	1
Rate	4.31 per 10,000 doses (0.04%)	—	0.24 per 10,000 doses (0.002%)
Epinephrine use			
No.	6	6	12
Rate	25.9 per 10,000 doses (0.26%)	1.55 per 10,000 doses (0.016%)	2.93 per 10,000 doses (0.029%)

*Home doses calculated as the difference between the total number of buildup days and the total number of in-office buildup visits.

TABLE VI. Multivariable logistic regression analysis of characteristics associated with patients dropping out of P-OIT

Characteristic	OR (95% CI)
Age at entry	1.00 (0.93-1.07)
Sex: male	8.24 (0.87-78.0)
Moderate/severe* initial reaction	1.05 (0.24-4.63)
Other food allergies	1.26 (0.26-6.09)
Asthma	1.18 (0.23-6.12)
Baseline SPT	0.96 (0.78-1.18)
Baseline ps-IgE	**1.03 (1.01-1.05)**
Moderate/severe* reaction during buildup	4.20 (0.88-20.1)

Odds ratios in bold indicate a statistically significant result (i.e., the 95% CI does not cross 1.0).
*Moderate/severe reaction defined as grade 2, 3, 4 reactions.

TABLE VII. Multivariable logistic regression analysis of baseline characteristics associated with patients receiving epinephrine during P-OIT buildup

Characteristic	OR (95% CI)
Age at entry	0.95 (0.88-1.03)
Sex: male	2.02 (0.30-13.5)
Moderate/severe* initial reaction	4.31 (0.69-26.9)
Other food allergies	0.18 (0.03-1.29)
Asthma	0.67 (0.09-4.79)
Baseline SPT	**1.35 (1.05-1.75)**
Baseline ps-IgE	**1.03 (1.01-1.06)**

Odds ratios in bold indicate a statistically significant result (i.e., the 95% CI does not cross 1.0).
*Moderate/severe reaction defined as grade 2, 3, 4 reactions.

withdrew from the study because of AEs related to the respiratory system, but there are no further details regarding the symptoms experienced.[5] Similarly, asthma did not predict receiving epinephrine during P-OIT in our study. These data suggest that there is no need to hesitate to offer P-OIT to preschoolers with a history of mild or moderate asthma that is well controlled.

Study limitations

The key limitations of our data stem mainly from the fact that this was a real-world QI study and not a clinical trial. The lack of rigorous protocol adherence reflects real-life clinical practice, and was expected among participating clinicians.

A recent criticism of using P-OIT products not approved by the Food and Drug Administration is high variability in peanut allergen levels between different commercial products based on laboratory assays,[27] which our protocol is susceptible to. However, the degree to which this variability affects clinical outcomes has not been studied. Our data suggest that, at least in preschoolers, allergen variability in different peanut products has little impact on safety, as only 0.4% of patients experienced a severe reaction, and this did not differ according to the OIT protocol chosen. We hypothesize that in preschoolers, factors such as viral illnesses play a greater role in augmenting risk of reactions than does allergen variability of peanut products. To address this theoretical potential risk, we suggest parents sign consent indicating acceptance of allergen variability when OIT is performed with products that have not had allergen content specifically measured.

In contrast to published P-OIT clinical trials, our patients were not required to undergo a baseline OFC to confirm peanut allergy. Making the OFC optional is more reflective of the real world; it is unlikely that every clinician or parent would agree to a baseline OFC for patients with a relatively high likelihood of peanut allergy. In addition, this enrollment requirement can create added resource burden for clinical practices unable to accommodate a baseline OFC for every single patient they wish to start on P-OIT. Moreover, 97.4% of patients in our study had either a convincing history or a reaction at their optional baseline OFC. Only 5.50% of patients had no peanut ingestion history.

It was expected, on the basis of a previous study,[7] that higher specific IgE levels might correlate with a higher dropout rate due to allergic reactions. Although this was seen in our descriptive data, the effect size of ps-IgE was clinically insignificant

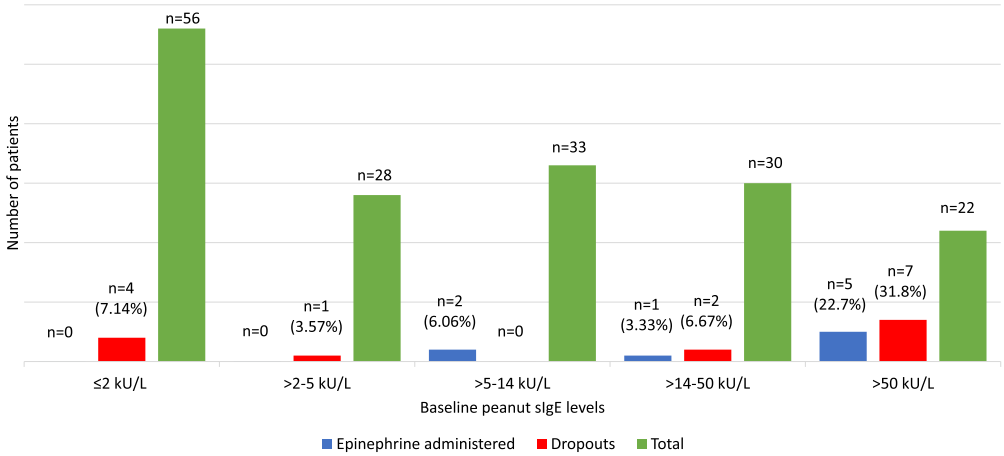

FIGURE 2. Baseline peanut specific IgE (sIgE) levels, and number of patients receiving epinephrine, dropping out, and total number of patients within each category of baseline ps-IgE. This figure is a visual representation of the number and proportion of patients receiving epinephrine and dropping out during P-OIT buildup, according to their baseline ps-IgE. Data on baseline ps-IgE were available for 169 of the 270 patients.

(OR, 1.03) and our sample size was too small to allow statistically significant comparisons of different ps-IgE ranges.

Parents were not asked to record timing of AEs in a diary because there is often poor adherence to such collection methods,[28] and they are impractical in a real-world setting. This creates uncertainty as to whether mild symptoms were caused by the peanut dose or by viral illnesses common in this age group. As a result, our study has likely overestimated the reaction rate, though in a safety analysis this overestimation is preferable to its converse. Additional bias may have been introduced because of lack of reporting of adherence and possible missed doses, although our safety outcomes would still be impressive based on an assumption of low adherence.

Finally, it should be stated that these results are not necessarily generalizable to higher-risk patients with poorly controlled asthma (for which OIT is typically contraindicated), or those with grade 4 symptoms from history or at baseline OFC, which we did not include in our analysis.

In conclusion, we are the first group to describe preschool peanut OIT in a real-world, multicenter setting. We confirm with a large sample of 270 preschool children that the treatment is safe for the vast majority of patients, and well tolerated, and could be offered outside of the research setting to families that desire it. However, there is still the potential for a life-threatening allergic reaction in a minority of patients (0.4%), though this was well managed with epinephrine administration. Our future work within the CPP-OIT project will be to report on long-term safety and efficacy outcomes with P-OIT desensitization, and sustained unresponsiveness for patients who elect to stop daily P-OIT.

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ONLINE REPOSITORY

RESULTS

Protocols chosen and protocol deviations

Of the 270 patients, 68 (25.2%) were placed on the Bamba-only protocol, 127 (47.0%) on the powdered peanut butter (PB2)-only protocol, and 75 (27.8%) on the hybrid protocol.

There were frequent protocol deviations, with 212 of 270 (78.5%) not rigidly following their chosen protocol (Table E2). The top 3 protocol deviations were additional doses (predominantly a 50-mg PB2 dose), longer time interval between buildup visits, and starting P-OIT at a higher dose. The protocol chosen varied considerably by region. As an example, all allergists in Alberta chose the Bamba-only protocol, whereas in Manitoba, all allergists chose the hybrid approach.

Allergists were surveyed about the reasons for their choice of protocol. Responses in favor of PB2 included wider availability across the country, more control, and dosing precision (as the PB2 was encapsulated by a pharmacist), and made the protocol less likely to be replicated by nonphysicians. Involving the pharmacy also afforded the ability to discontinue P-OIT by canceling a prescription at the pharmacy if there were issues with a family's adherence or inappropriate treatment of adverse reactions. Some allergists noted familial hesitancy to introduce Bamba due to concerns of less precise dosing, tolerability, or lack of nutritional value, but indicated they would consider switching a patient to Bamba if PB2 had been tolerated for several months on maintenance.

The Bamba protocol was chosen because of cost (pharmacy compounded PB2 cost varied widely across the country from $30 to $70 CAD per month), convenience (eg, if the child required a longer than typical duration of therapy at a given dose, use of Bamba negated the need to send refills to the pharmacy), and the sense that feeding was less "medicalized." It was preferred in younger children as well. The hybrid approach was chosen for precision early on when small differences in peanut dosing were potentially more consequential. At higher doses, the switch to Bamba allowed more flexibility in rebooking appointments and increased ease of administration.

Some allergists reported that participants experienced an increased frequency of perioral erythema with doses of Bamba after switching from PB2. In addition, 2 allergists noted systemic reactions with the switch to Bamba at 80 mg peanut protein that did not occur when the child was then switched back to PB2.

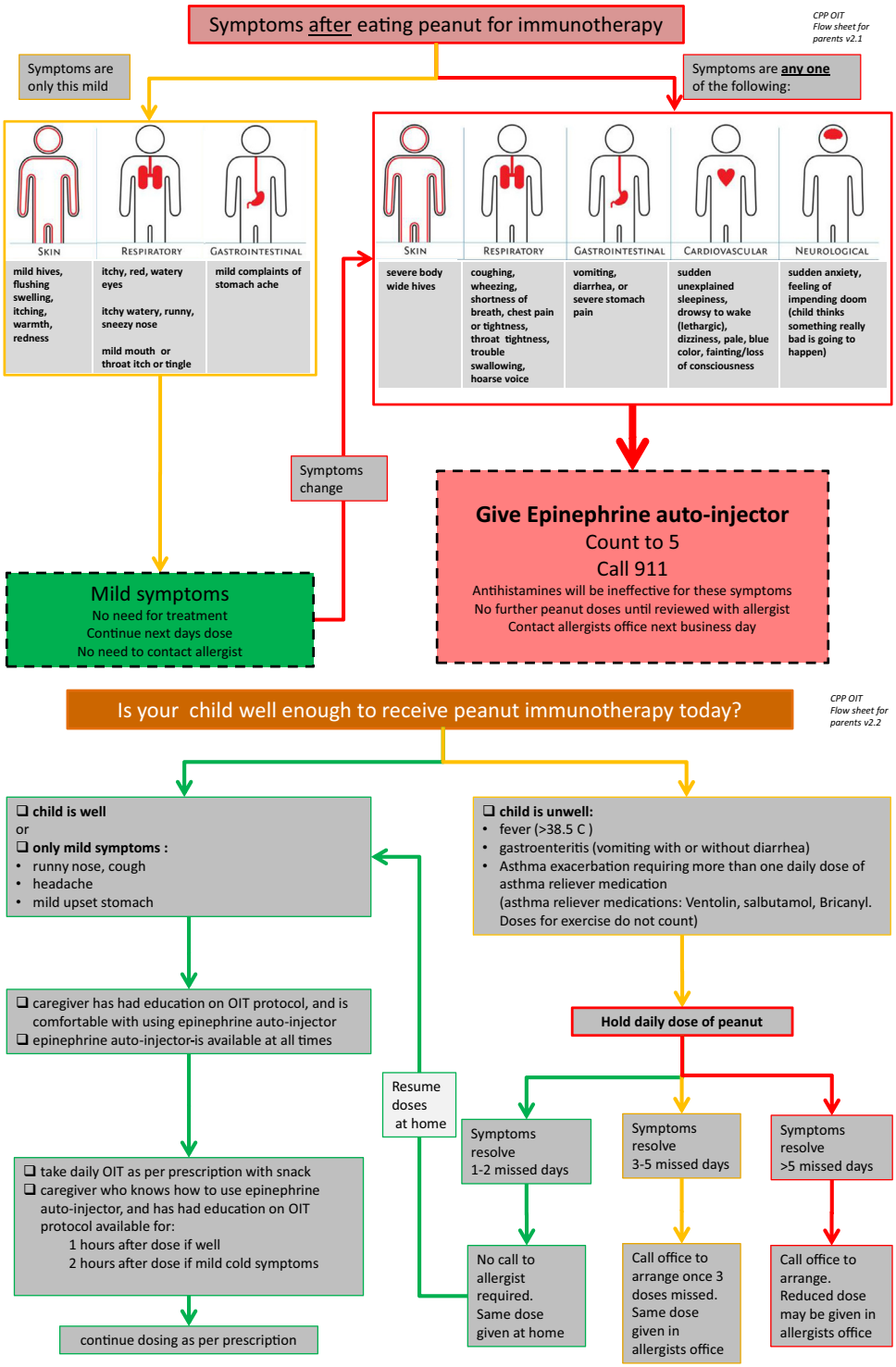

FIGURE E1. Flow sheet for parents—daily dose instructions and side effect management.

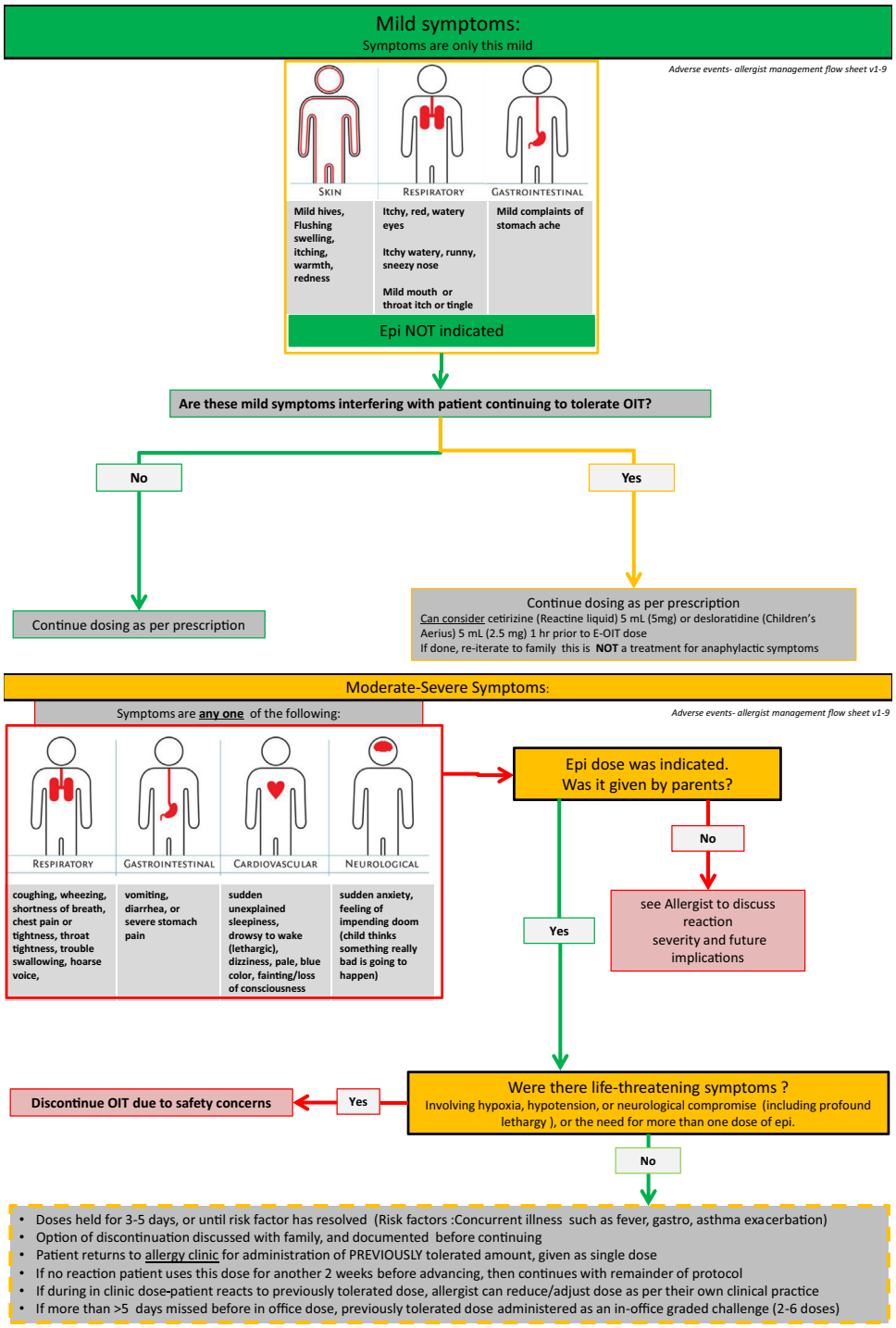

FIGURE E2. AEs—allergist management flow sheet. *Epi*, Epinephrine.

TABLE E1. Baseline and reaction characteristics of patients who received epinephrine during P-OIT buildup

Patient no.	Sex (M/F)	Baseline SPT/IgE	Symptoms during baseline OFC	Age at reaction (mo)	Dose (mg)	Where did the reaction take place?	Symptoms experienced	Grade of reaction	Other treatment/ management	Outcome
Patient 1	M	15.0 mm	OFC not done	27	12 mg	In clinic	Pruritis, conjunctivitis, vomiting	2	None	Continued OIT, reduced dose
		>100 kU/L		27	6 mg	At home	Pruritis, cough, rhinitis, conjunctivitis, vomiting	2	Second- generation antihistamine, steroids, ED visit	Dropped out
Patient 2	M	8.00 mm	Vomiting; epinephrine given	31	10	In clinic	Vomiting, redness	2	None	Dropped out
Patient 3	M	6.50 mm	Cough, rhinitis, vomiting; epinephrine, antihistamine, prednisolone given	17	40	In clinic	Cough, rhinitis, vomiting	2	Second- generation antihistamine, prenisolone	Continued OIT buildup; eventually dropped out because of poor adherence
Patient 4	M	10.0 mm	OFC not done	26	6	At home	Vomiting	2	Second- generation antihistamine	Continued OIT buildup
		60.3 k U/L								
Patient 5	F	8.00 mm	OFC not done	30	6	At home	Abdominal pain, vomiting	2	None	Continued OIT, reduced dose
		>100 kU/L								
Patient 6	M	11.0 mm	OFC not done	46	320	At home	Urticaria, angioedema, pruritis, cough, wheeze	2	None	Continued OIT, reduced dose
		12.3 kU/L								
Patient 7	F	9.00 mm	OFC not done	12	25	At home	Urticaria, angioedema, wheeze	2	Second- generation antihistamine, ED visit	Continued OIT, reduced dose
		17.4 kU/L								
Patient 8	M	15.0 mm	OFC not done	33	80	At home	Cough, wheeze, rhinitis	2	ED visit	Continued OIT, reduced dose
		5.60 kU/L								
Patient 9	F	18.0 mm	OFC not done	66	25	In clinic	Abdominal pain, vomiting, sleepy	2	None	Continued OIT, reduced dose
		>100 kU/L								
Patient 10	M	13.0 mm	OFC not done	33	12	In clinic	Abdominal pain, sleepy	2	None	Dropped out
Patient 11	M	11.0 mm	OFC not done	22	25	In clinic	Abdominal pain, vomiting, sleepy, hypotension	4	None	Dropped out
		58.1 kU/L								

F, Female; *M*, male.

TABLE E2. CPP-OIT protocol deviations

Protocol deviations	All patients	Reached maintenance	Dropouts
Any deviation from protocol	212	197	15
Additional dose(s)	126 (59.4)	124 (62.9)	2 (13.3)
Longer time interval between buildup visits	101 (47.6)	95 (48.2)	6 (40.0)
Started at a higher dose	52 (24.5)	48 (24.4)	4 (26.7)
Switched form of peanut protein	18 (8.49)	18 (9.14)	0 (0.00)
Switched protocol	15 (7.08)	14 (7.11)	1 (6.67)
Skipped dose(s)	10 (4.72)	9 (4.57)	1 (6.67)
Repeated dose(s)	11 (5.19)	9 (4.57)	2 (13.3)
Reduced dose(s)	8 (3.77)	6 (3.05)	2 (13.3)
Started at a lower dose	6 (2.83)	4 (2.03)	2 (13.3)
Shorter time intervals between buildup visits	1 (0.47)	1 (0.51)	0 (0.00)

Values are n (%).

TABLE E3. Characteristics of patients with EoE-like symptoms or diagnosis of EoE during P-OIT buildup

Patient no.	Sex	Age	Symptoms experienced	Endoscopy?	Results?	Treatment received	Outcome
Patient 1	M	39 mo	Small stature, mild anemia; incidental finding during endoscopy to rule out celiac disease	Yes	EoE diagnosed	PPI	Discontinued P-OIT for now, but EoE persisted after discontinuation; being investigated for immunodeficiency
Patient 2	M	44 mo	Upper chest pain, abdominal pain	Not performed			EoE symptoms disappeared 1 wk after treatment cessation
Patient 3	M	34 mo	Gagging, vomiting	Yes	Negative for EoE	PPI	Gastrointestinal symptoms did not change after treatment cessation
Patient 4	M	14 mo	Abdominal pain and vomiting	Pending			EoE symptoms did not change after treatment cessation