Original Article

Dosing Reactions and Missed Doses Affect Peanut Oral Immunotherapy Outcomes

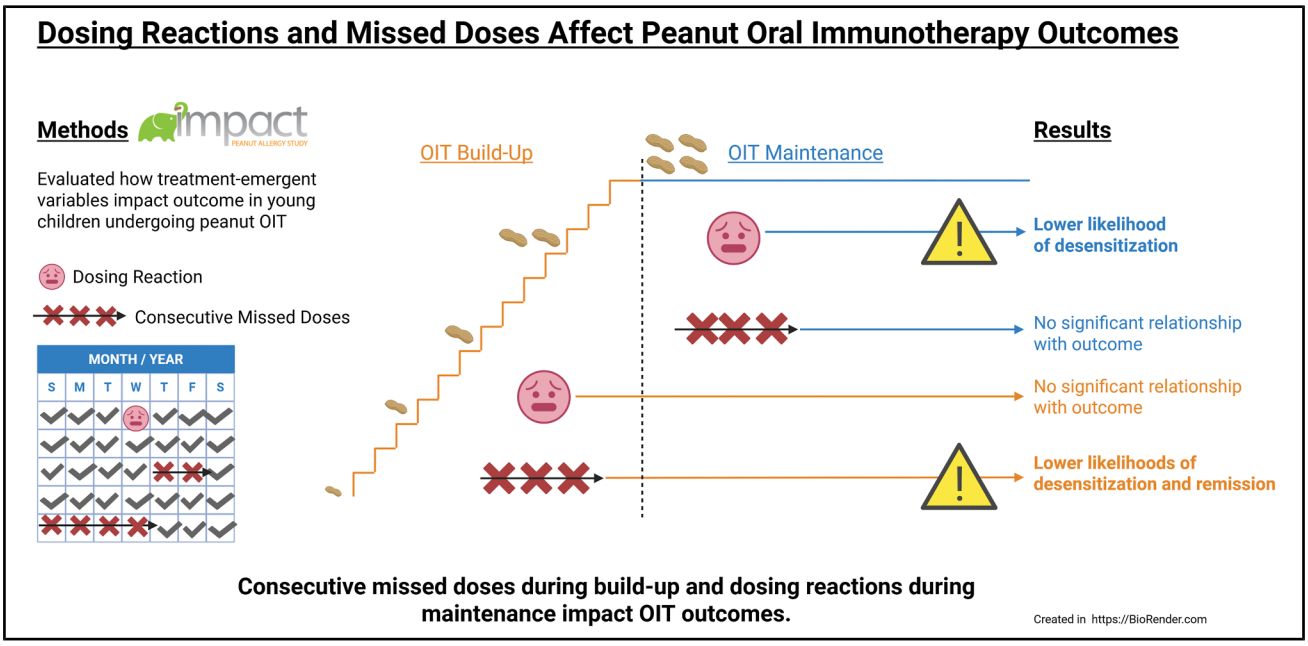
Oluwatobi Olayiwola, MD[a], Lauren Mudd, PhD[b], Lars Dunaway, PhD[b], Tanya M. Laidlaw, MD[a,c], Stacie M. Jones, MD[d], Patricia C. Fulkerson, MD, PhD[e], Srinath Sanda, MD[f], and Michelle F. Huffaker, MD[g] *Boston, Mass; Durham, NC; San Francisco and Stanford, Calif; Little Rock, Ark; and Bethesda, Md*

What is already known about this topic? Most who undergo peanut oral immunotherapy achieve desensitization while some achieve remission after discontinuation. A younger age at screening and lower baseline peanut-specific IgE are associated with desensitization and remission.

What does this article add to our knowledge? This work identifies consecutive missed doses during build-up and dosing reactions during maintenance as predictors of poor outcomes with peanut oral immunotherapy, and supports shared decision making about treatment modification during oral immunotherapy.

How does this study impact current management guidelines? By identifying and quantifying clinical correlates associated with successful peanut oral immunotherapy, these findings offer clinicians variables to consider during phases of peanut oral immunotherapy.

VISUAL SUMMARY



[a]Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Boston, Mass
[b]Rho Federal Systems Division, Durham, NC
[c]Immune Tolerance Network, Department of Medicine, University of California San Francisco, San Francisco, Calif
[d]Department of Pediatrics, Division of Allergy and Immunology, University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, Ark
[e]National Institute of Allergy and Infectious Diseases, Bethesda, Md
[f]Immune Tolerance Network, Department of Pediatrics, University of California San Francisco, San Francisco, Calif
[g]Immune Tolerance Network, Department of Medicine, Division of Pulmonary, Allergy, Critical Care Medicine, Stanford University, Stanford, Calif

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Abbreviations used
DBPCFC- double-blind, placebo-controlled food challenge
IMPACT- Oral Immunotherapy for Induction of Tolerance in Peanut Allergic Children trial
IQR- interquartile range
OIT- oral immunotherapy
OR- odds ratio
pOIT- peanut oral immunotherapy
SPT- skin prick test

BACKGROUND: Peanut oral immunotherapy (pOIT) is a recognized treatment for patients with peanut allergy, though not all patients who undergo this therapy achieve desensitization or remission.
OBJECTIVE: To determine whether missed doses or dosing reactions predict clinical outcomes with pOIT.
METHODS: Data from IMPACT (Oral Immunotherapy for Induction of Tolerance in Peanut Allergic Children trial), a randomized, double-blind, placebo-controlled trial of pOIT in children aged 1 to 4 years with peanut allergy, were analyzed to determine whether treatment-emergent variables influence desensitization (ability to consume 5000 mg of peanut protein without reaction during a blinded oral food challenge after 134 weeks of pOIT) and remission (6 months after discontinuation of pOIT). Logistic regression models, controlling for age and Ara h2–specific IgE, were performed to assess the relationship between dosing reactions, missed doses, and outcomes.
RESULTS: Consecutive missed doses during build-up significantly correlated with reduced likelihood of desensitization ($P = .03$; odds ratio [OR], 0.69; 95% CI, 0.49-0.96), whereas consecutive missed doses during maintenance did not ($P = .10$; OR, 0.79; 95% CI, 0.59-1.05). Furthermore, the total individual missed doses did not significantly correlate with desensitization or remission in either phase of pOIT. Conversely, dosing reactions during maintenance did significantly correlate with reduced likelihood of desensitization ($P = .01$; OR, 0.71; 95% CI, 0.54-0.93), whereas dosing reactions during build-up did not significantly correlate with desensitization ($P = .57$; OR, 0.95; 95% CI, 0.79-1.14). Fewer than 10% of missed doses were attributed to dosing reactions.
CONCLUSIONS: Missed doses during therapy and dosing reactions during maintenance associated with poorer pOIT outcomes. Clinicians should support adherence during build-up and consider dose adjustments for patients having dosing reactions during maintenance therapy. **(J Allergy Clin Immunol Pract 2026;14:453-63)**

Key words: *Food allergy; Oral immunotherapy; Peanut allergy; Efficacy; Safety*

INTRODUCTION

Peanut allergy is a common and often severe food allergy in children. The prevalence of peanut allergy has been increasing in recent decades, with studies showing that it affects approximately 2% of children in Western countries, although rates can vary by region and ethnicity.[1-4] Peanut allergy is lifelong for most affected individuals.[5,6] Despite advancements in our understanding of peanut allergy, there is no cure for peanut allergy, and the focus remains on prevention, early diagnosis, and treatment to reduce the risk of allergic reactions.[7-10] In recent years, treatments for peanut allergy have moved away from strict avoidance to include therapeutic interventions such as peanut oral immunotherapy (pOIT), which provides desensitization to peanut and an increased protection in case of accidental ingestion.[11-14] Furthermore, a subset of children who undergo pOIT achieve remission, a state of nonresponsiveness after discontinuation of immunotherapy.[11,13,15,16] pOIT is also associated with an improvement in quality of life in peanut-allergic patients and their caregivers.[17,18]

Oral immunotherapy is not without risks.[11,16,19-21] Given the inherent risks and burden of pOIT, it is crucial to identify which patients are most likely to benefit from pOIT and who will achieve desensitization or remission after pOIT. Multiple studies have shown that younger age, a higher baseline peanut-specific IgG_4 to peanut-specific IgE ratio, and lower baseline Ara h2–specific IgE and peanut-specific IgE are associated with positive clinical outcomes following pOIT.[12,16,20,22,23] The most commonly described clinical predictor of successful pOIT is younger age.[13,22] However, Lloyd et al[15] also found that a low reaction-eliciting dose at the initiation of pOIT, and comorbid allergic diseases, such as multiple food allergies and self-reported history of wheeze and asthma, reduced the likelihood of achieving remission after pOIT. Although factors such as older baseline age, higher baseline peanut-specific IgE, comorbid allergic rhinitis, and pre-OIT initial grade 2+ reactions are associated with an increased risk of adverse reactions during pOIT, data describing the impact of treatment-emergent variables such as dosing compliance and dosing reactions on the outcome of pOIT are lacking.[21,22]

To date, there are no validated biomarkers that predict which patients will achieve desensitization or remission. In the Oral Immunotherapy for Induction of Tolerance in Peanut Allergic Children trial (IMPACT, ITN050AD, NCT01867671), pOIT administered to children aged 12 months to 48 months was safe and efficacious. A younger age at screening and lower baseline peanut-specific IgE predicted remission, suggesting a therapeutic window of opportunity for early intervention.[13] Here, we assessed the association of treatment-emergent variables,

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Conflicts of interest: All the authors declare that they have no relevant conflicts of interest.
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Corresponding author: Oluwatobi Olayiwola, MD, 60 Fenwood Rd, BTM, Rm 5002U, Boston, MA 02115. E-mail: oolayiwola1@bwh.harvard.edu.
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including missed doses and adverse dosing reactions on the outcomes of desensitization and remission in the IMPACT participants.

METHODS

Study population, design, and procedures

IMPACT was a randomized, double-blind, placebo-controlled, multicenter study that compared pOIT to placebo in peanut-allergic pre–school-age children.[13] The study enrolled participants between August 13, 2013, and October 1, 2015. Eligible participants aged 12 years to less than 48 months with a history of peanut allergy or avoidance, elevated peanut-specific IgE (≥5 kUA/L), a positive peanut skin prick test (SPT) result (wheal ≥3 mm to peanut compared with placebo), and proven clinical reactivity to less than 500 mg peanut protein at the time of study entry were randomized to receive either pOIT at a target maintenance dose of 2000 mg of peanut protein or a placebo (oat flour) for 134 weeks. Double-blind, placebo-controlled food challenges (DBPCFCs) to 5000 mg of peanut protein were conducted at baseline and at the end of the dosing phase (week 134). Participants who tolerated the 5000 mg of peanut protein at the week 134 challenge were categorized as desensitized. All participants then discontinued pOIT and avoided peanut for 26 weeks. Regardless of their week 134 DBPCFC outcome, a follow-up DBPCFC at week 160 to 5000 mg of peanut protein was conducted. Participants who tolerated the week 160 challenge were considered to have achieved remission. The intention-to-treat population (all randomized participants) were the focus of the initial efficacy report.[13] Here, we focus on the per-protocol population: participants with an oral food challenge at week 134 or week 160. Written informed consent was obtained from guardians of the participants. Institutional review boards at each of the 5 academic medical centers approved the study protocol. The study was conducted under a Food and Drug Administration investigational new drug application and monitored by a National Institutes of Health - National Institute of Allergy and Infectious Diseases Data and Safety Monitoring Board. The trial is registered on ClinicalTrials.gov (NCT03345160), and the protocol has been previously published.[13]

DEFINITION OF BUILD-UP AND MAINTENANCE-DOSING PHASES

Participants underwent an initial dose escalation at the start of the study, which was a single day during which participants received multiple doses of peanut flour or placebo with incremental increases every 15 to 30 minutes until a dose of 6 mg peanut protein or placebo was consumed. A minimum tolerated dose of 1.5 mg peanut protein (3 mg of peanut flour) or placebo flour was required to remain in the study. Participants then returned the following morning for an observed single-dose administration of their highest tolerated dose from the preceding day. Daily dosing of pOIT was then continued at home, with an observed dose escalation every 2 weeks during the build-up phase until the target maintenance dose of 2000 mg of peanut protein was reached. The expected build-up phase was 30 weeks. Participants who did not reach the target dose could still enter the maintenance phase at their highest tolerated dose, defined as a minimum of 250 mg of peanut protein or placebo flour. Participants then continued on daily maintenance pOIT for 104 weeks (total 134 weeks) before avoidance (through week 160).

Assessment of dosing compliance and dosing reactions

Home dose-related symptoms and adherence were tracked through daily study diaries, via contact with the study team, and drug accountability logs that were reported in the electronic data capture system. Oral immunotherapy dosing-induced reactions were defined as related to dosing if they occurred within 2 hours of dose administration. Dosing reactions were scored as mild, moderate, or severe using an adapted grading system from the Consortium of Food Allergy Research 3 (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).[24]

SPT and immunoglobulin measurements

Serum biomarkers and SPT results were collected at baseline and at weeks 30, 82, 134, and 160 of the study. SPT was performed with peanut extract, saline, and histamine (Greer Laboratories, Lenoir, NC). Serum immunoglobulin levels were measured by ImmunoCAP 1000 system (Viracor Eurofins, Lee's Summit, Mo), and plasma IgE and IgG_4 to peanut components (Ara h1, 2, 3, 6) were measured using the ImmunoCAP 250 system (Phadia-Thermo Fisher Scientific, Waltham, Mass) as previously described.[13]

Statistical analysis

All assessments for this analysis were performed on the per-protocol population. The sample size consisted of all participants in the per-protocol population with nonmissing values of all variables considered in the analysis. Imputation of desensitization and remission was not done.

Demographic and baseline characteristics were assessed by participants' combined DBPCFC status at week 134 and week 160. Participants who did not tolerate the 5000-mg dose at week 134 challenge were categorized as not desensitized. Participants who tolerated the 5000-mg dose at the week 134 challenge and did not tolerate the 5000-mg dose at the week 160 challenge were categorized as desensitized, and participants who tolerated the 5000-mg dose at the week 160 challenge were categorized as achieving remission. Median and interquartile range were calculated for continuous variables within each overall DBPCFC status, and groups were compared using the Kruskal-Wallis test. Frequencies and percentages were calculated for categorical variables within each overall DBPCFC status, and groups were compared using the χ^2 test (or Fisher exact test when necessary).

Treatment-emergent variables during pOIT, including the number of missed daily pOIT doses, the maximum number of consecutive missed doses (considering all occurrences of consecutive missed daily pOIT doses), the number of dosing reactions (the number of days with at least 1 dosing reaction to daily pOIT), and the severity of dosing reactions (considering the maximum graded severity each day a dosing reaction occurred) were calculated within each study phase (build-up, maintenance, and combined build-up and maintenance).

Multivariable logistic regression analyses were used to assess the effect of each pOIT dose-related metric on desensitization and remission. All regression analyses included 1 pOIT dose-related metric and adjusted for the baseline age of the participant (in months) and baseline Ara h2–specific IgE. Adjusted odds ratios (ORs) (and associated 95% CIs) of tolerating the 5000-mg dose at the DBPCFC for desensitization at week 134 and remission at week 160 were calculated for each dose-related

TABLE I. Demographics and baseline characteristics

Characteristics	Not desensitized (N = 12)	Desensitized (N = 49)	Remission (N = 20)	*P* value*
Baseline characteristics				
Age at screening (mo)	40 (39-42)	39 (33-45)	31 (24-40)	.01†
Weight at screening (kg)	14.40 (13.88-15.48)	14.90 (13.80-16.10)	13.35 (12.28-14.78)	.07†
Sex				.49‡
F	5 (42)	13 (27)	7 (35)	
M	7 (58)	36 (73)	13 (65)	
Race				.87‡
Asian	2 (17)	7 (14)	4 (20)	
Black or African American	0 (0)	1 (2.0)	0 (0)	
Mixed race	3 (25)	10 (20)	2 (10)	
White/Caucasian	7 (58)	31 (63)	14 (70)	
Atopic dermatitis history				>.99‡
Yes	10 (83)	40 (82)	17 (85)	
No	2 (17)	9 (18)	3 (15)	
Peanut allergy history				.13‡
History of peanut allergy symptoms	8 (67)	35 (71)	9 (45)	
Never exposed to peanut	4 (33)	14 (29)	11 (55)	
History of other food allergies				.46§
No	5 (42)	25 (51)	7 (35)	
Yes	7 (58)	24 (49)	13 (65)	
History of anaphylaxis to peanut				>.99‡
Yes	0 (0)	0 (0)	0 (0)	
No	12 (100)	49 (100)	20 (100)	
Wheal size for SPT to peanut at baseline (mm)	15.5 (13.9-20.6)	14.5 (12.0-17.0)	14.0 (11.5-18.0)	.57†
Cumulative tolerated dose of masked DBPCFC to peanut at baseline (mg)	50 (20-75)	25 (5-75)	75 (25-300)	.045†
Baseline biomarkers				
Ara h2−specific IgE at baseline (kUA/L)	107 (56-163)	64 (35-87)	13 (8-39)	<.01†
Ara h2−specific IgE/peanut-specific IgE ratio at baseline, ratio	0.53 (0.44-0.88)	0.70 (0.42-1.05)	0.87 (0.67-1.11)	.22†
Peanut-specific IgE at baseline (kU/L)	243 (62-359)	67 (39-195)	18 (12-50)	<.01†
Peanut-specific IgE/total IgE ratio at baseline, ratio	33 (22-61)	24 (15-43)	8 (3-19)	<.01†
Ara h2−specific IgG_4 at baseline (mg/L)	0.27 (0.09-0.36)	0.24 (0.14-0.41)	0.29 (0.04-0.52)	.98†
Peanut-specific IgG_4 at baseline (μg/mL)	0.84 (0.29-1.37)	0.56 (0.32-1.56)	0.73 (0.08-2.16)	.86†
Peanut-specific IgG_4/IgE ratio at baseline, ratio	0.002 (0.001-0.005)	0.003 (0.001-0.010)	0.006 (0.002-0.047)	.03†
Total IgE at baseline (IU/mL)	452 (302-726)	383 (180-618)	491 (193-730)	.53†

F, Female; *M*, male.
Unless indicated otherwise, n (%) is presented for categorical variables and median (IQR) is presented for continuous variables.
*Comparison of each outcome groups' mean or median.
†Kruskal-Wallis rank-sum test.
‡Fisher exact test.
§Pearson χ^2 test.

metric. A *P* value was obtained to quantify the statistical significance of the relationship between each pOIT dose-related metric and each outcome (desensitization or remission). Lastly, to determine whether there was an interaction between age, baseline Ara h2 IgE, and the maximum cumulative missed doses, a Pearson correlation coefficient was calculated. All

TABLE II. Participant treatment-emergent metrics

Treatment-emergent metrics	Not desensitized (N = 12)	Desensitized (N = 49)	Remission (N = 20)	*P* value*
Dosing metrics				
Time to reach first 2000-mg dose (d)				.34†
Mean ± SD	199 ± 16	196 ± 18	190 ± 16	
Median (IQR)	202 (183-205)	193 (182- 211)	186 (178- 202)	
Range	181-232	167-230	169-224	
Maximum maintenance dose (mg)				.02†
Mean ± SD	1663 ± 580	1935 ± 149	2000 ± 0	
Median (IQR)	2000 (1500-2000)	2000 (2000 -2000)	2000 (2000- 2000)	
Range	250-2000	1600-2000	2000-2000	
Maximum maintenance dose (mg), n (%)				.01‡
250	1 (8.3)	0 (0)	0 (0)	
900	1 (8.3)	0 (0)	0 (0)	
1200	1 (8.3)	0 (0)	0 (0)	
1600	1 (8.3)	8 (16)	0 (0)	
2000	8 (67)	41 (84)	20 (100)	
Average daily maintenance dose (mg/d)				.02†
Mean ± SD	1499 ± 538	1831 ± 175	1899 ± 132	
Median (IQR)	1641 (1374-1934)	1896 (1739-1971)	1934 (1915-1976)	
Range	249-1992	1341-2003	1482-2003	
Duration of build-up phase (d)				.94†
Mean ± SD	230 ± 16	230 ± 16	228 ± 13	
Median (IQR)	223 (220-236)	225 (217-239)	225 (218-236)	
Range	215-257	207-273	210-265	
Duration of maintenance phase (d)				.51†
Mean ± SD	728.1 ± 6.3	729.5 ± 5.4	730.1 ± 5.8	
Median (IQR)	727.0 (724.0-731.3)	728.0 (726.0-734.0)	728.0 (727.0-730.8)	
Range	721.0-740.0	719.0-741.0	725.0-748.0	

Unless indicated otherwise, n (%) is presented for categorical variables and median (IQR) is presented for continuous variables.
*Comparison of the outcome groups' mean or median.
†Kruskal-Wallis rank-sum test.
‡Fisher exact test.

analyses are exploratory, and no adjustments for multiple comparisons were performed.

RESULTS

Participant overview

Of the 209 participants enrolled in the trial, 146 were randomly assigned to pOIT (96 participants) or placebo (50 participants). Eighty-one of those randomized to pOIT met per-protocol criteria and completed the week 134 DBPCFC to peanut. A total of 70 participants randomized to pOIT completed the avoidance period and the week 160 DBPCFC to peanut (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The baseline demographics and dosing metrics of the per-protocol group are summarized in Tables I and II. The baseline characteristics, including comorbidities, peanut allergy history, and peanut wheal size, were similar between the participants when grouped by outcomes (not desensitized, desensitized, and remission), with the exception of age at time of screening, and the cumulative tolerated dose of peanut at the screening DBPCFC. In particular, younger age and higher baseline cumulative tolerated dose were features of the group achieving remission. Lastly, the maximum maintenance dose and average daily maintenance dose were significantly different between the outcome groups, with higher maintenance doses noted among those achieving remission compared with those not reaching remission, although the dose ranges overlapped (Table II).

Biomarkers

Baseline serum biomarker comparisons among participants receiving pOIT revealed distinct differences between the treatment outcome groups (Table I). Participants who achieved remission had significantly lower baseline Ara h2–specific IgE, peanut-specific IgE, and peanut-specific IgE/total IgE ratio, and a significantly higher baseline peanut-specific IgG_4/IgE ratio compared with participants who did not achieve remission.

Baseline biomarkers were assessed for association with desensitization and remission using a simple logistic regression analysis. Of the biomarkers, baseline age (in months) ($P = .002$) and Ara h2–specific IgE ($P = .004$) negatively associated with remission significantly. After adjusting for age, a higher baseline peanut-specific IgE ($P = .02$) negatively associated with desensitization but not remission, while both the baseline peanut-specific IgE/total IgE and baseline peanut-specific IgG_4/IgE ratios negatively associated with remission ($P = .004$ and $P = .01$ respectively) but not desensitization ($P = .057$ and $P = .15$, respectively). Baseline Ara h2–specific IgE negatively associated with both desensitization ($P = .03$) and remission ($P = .02$) significantly. Neither baseline peanut-specific IgG_4 nor baseline peanut-specific IgG_4 Ara h2 associated with

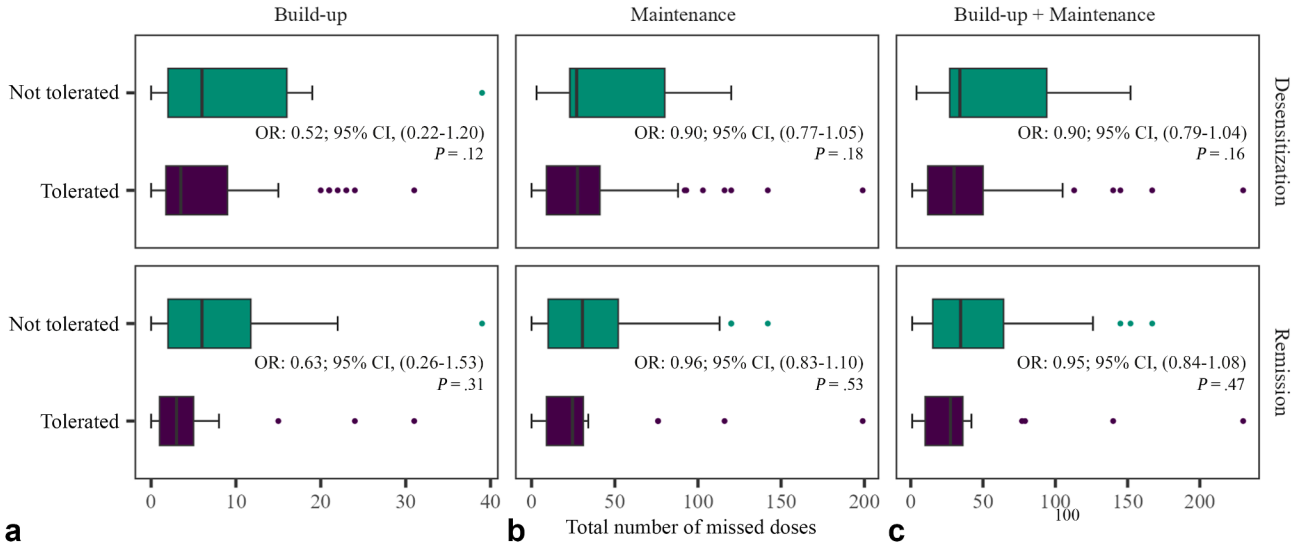

FIGURE 1. Total number of missed doses during each study phase. Multivariable logistic regression modeling clinical outcomes at week 134 (desensitization) and week 160 (remission) by the total number of missed doses during the (**A**) build-up, (**B**) maintenance, and (**C**) build-up and maintenance phases, corrected for baseline age and Ara h2–specific IgE. Purple represents participants who tolerated the DBPCFC; green represents participants who did not. ORs and CIs represent a 10-unit increase in the number of missed doses.

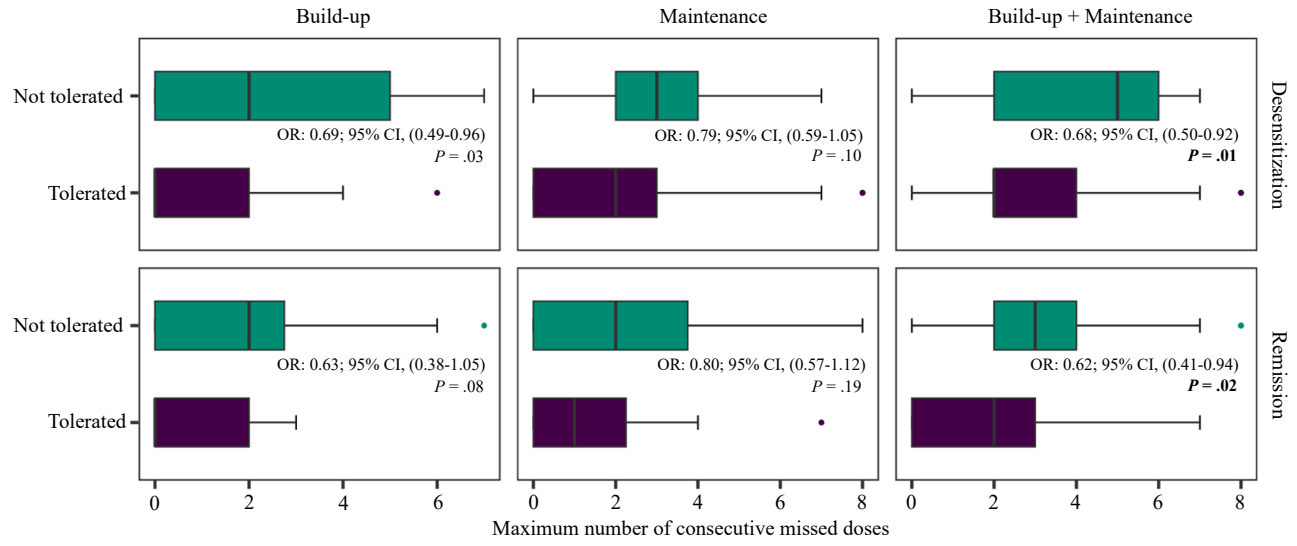

FIGURE 2. Maximum number of consecutive missed doses during each study phase. Multivariable logistic regression modeling clinical outcomes at week 134 (desensitization) and week 160 (remission) by the maximum number of consecutive missed doses during the (**A**) build-up, (**B**) maintenance, and (**C**) build-up and maintenance phases, corrected for baseline age and Ara h2–specific IgE. Purple represents participants who tolerated the DBPCFC; green represents participants who did not. The ORs and CIs represent a 1-unit increase in the maximum number of consecutive missed doses.

remission after adjusting for age. Furthermore, biomarker change from baseline over the course of the trial did not associate with clinical outcomes for any of the biomarkers. Based on these results, baseline age and baseline Ara h2–specific IgE were included in all subsequent models.

Missed doses

There was no significant association between the total number of missed doses and either outcomes of desensitization or remission during any phase of pOIT (Figure 1, *A-C*). The median (interquartile range [IQR]) number of missed doses for those who tolerated the desensitization challenge was 30.0 (IQR, 11.8-50.0) and for those who did not tolerate the desensitization challenge was 34.0 (IQR, 27.0-94.0). The median number of missed doses for those who tolerated the remission challenge was 27.5 (IQR, 10.0-36.0), and 34.5 (IQR, 15.3-64.3) for those who did not tolerate the remission challenge.

TABLE III. Reasons for consecutive missed doses

Reason for consecutive missed doses	Events (N = 415)	Participants (N = 64)
Concurrent illness	211	57 (89.1)
Participant/guardian forgot	110	25 (39.1)
Other	67	23 (35.9)
Reaction to OIT during home dosing	27	12 (18.8)

n (%) is displayed. Participants are counted only once for each reason. Percentages are based on the number of participants with at least 1 consecutive missed dose.

However, the maximum number of consecutive missed doses during build-up negatively associated with desensitization ($P = .03$; OR, 0.69; 95% CI, 0.49-0.96), whereas the maximum consecutive missed doses during the maintenance phase did not significantly associate with desensitization ($P = .10$; OR, 0.79; 95% CI, 0.59-1.05) (Figure 2, *A* and *B*). Combining the build-up and maintenance phases of the study, the maximum number of consecutive missed doses significantly and negatively associated with both desensitization ($P = .01$; OR, 0.68; 95% CI, 0.50-0.92) and remission ($P = .02$; OR, 0.62; 95% CI, 0.41-0.94) (Figure 2, *C*). The maximum number of consecutive doses missed ranged from 0 to 8. The median (IQR) consecutive missed doses for participants who achieved desensitization was 2.0 (IQR, 2.0-4.0) compared with 5.0 (IQR, 2.0-6.0) in nondesensitized participants; and 2.0 (IQR, 0-3.0) for participants who achieved remission and 3.0 (IQR, 2.0-4.0) for those who did not. In addition, of the 81 participants who were included in the desensitization analyses (at week 134), 50 had more than 1 occasion of 2 or more consecutive missed doses. Of the 70 participants who were included in the remission analyses (at week 160), 42 had more than 1 occasion of 2 or more consecutive missed doses. In either analysis population, multiple occasions of consecutive missed doses did not have a significant impact on the desensitization and remission outcomes. However, maximum number of consecutive missed doses did impact outcome.

After excluding 3 participants who did not reach a maintenance dose of 1600 mg of peanut protein, sensitivity analysis showed a negative association between the maximum number of consecutive missed doses during build-up and desensitization, though the results did not reach significance ($P = .07$; OR, 0.75; 95% CI, 0.55-1.02). However, for the combined build-up and maintenance phases of the study, the association between maximum number of consecutive missed doses and desensitization ($P = .03$; OR, 0.68; 95% CI, 0.49-0.96) and remission remained significant ($P = .02$; OR, 0.62; 95% CI, 0.41-0.94) (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

Reasons for consecutive missed doses

The most common reasons for missed doses were concurrent illness and participant/guardian forgetting to administer the dose (Table III). Approximately, only 6.5% of consecutive missed doses were attributed to therapy-related reactions during home dosing. The reasons for missed doses during pOIT are shown grouped by outcomes in Table E2 in this article's Online Repository at www.jaci-inpractice.org.

Dosing reactions

The total number of dosing reactions during build-up did not significantly associate with desensitization ($P = .57$; OR, 0.95; 95% CI, 0.79-1.14) or remission ($P = .50$; OR, 0.89; 95% CI, 0.63-1.26) (Figure 3, *A*). However, the total number of dosing reactions experienced during the maintenance phase was significantly and negatively associated with desensitization ($P = .01$; OR, 0.71; 95% CI, 0.54-0.93) (Figure 3, *B*) but not remission ($P = .52$; OR, 0.90; 95% CI, 0.65-1.25) (Figure 3, *C*). Categorizing the adverse reactions by Consortium of Food Allergy Research 3 grading system for allergic reaction (see Table E1), mild reactions (median, 17.0; IQR, 7.0-32.0) occurred more frequently than moderate reactions (median, 0.00; IQR, 0.0-2.0). Furthermore, the numbers of both mild and moderate dosing-related reactions were higher in the build-up phase compared with maintenance. Four severe dosing-related reactions occurred with at-home pOIT dosing in 2 participants during build-up and 2 participants during maintenance. Three of these 4 participants achieved desensitization and none achieved remission.

Mild dosing reactions during build-up did not significantly associate with clinical outcomes (Figure 4, *A*), but mild dosing reactions during maintenance negatively and significantly associated with desensitization ($P = .03$; OR, 0.73; 95% CI, 0.54-0.97) (Figure 4, *B*). Moderate reactions during build-up ($P = .02$; OR, 0.00; 95% CI, 0.00-0.23) and maintenance ($P = .01$; OR, 0.01; 95% CI, 0.00-0.36) phases both separately, and when both phases are combined together ($P = .005$; OR, 0.02; 95% CI, 0.00-0.29), negatively associated with desensitization only (Figure 4, *A-C*).

After exclusion of 3 participants who did not reach a maintenance dose of 1600 mg of peanut protein, sensitivity analysis showed a negative association between the total number of dosing reactions during maintenance and desensitization. This association remained significant and largely unchanged ($P = .01$; OR, 0.69; 95% CI, 0.52-0.91) when compared with the primary analysis. Sensitivity analysis of mild dosing reactions was also similar to the primary analysis. Mild dosing reactions during maintenance negatively associated with desensitization ($P = .02$; OR, 0.70; 95% CI, 0.52-0.95) and reached significance. However, unlike the primary analysis, moderate reactions negatively associated with desensitization only during the maintenance and combined build-up/maintenance phases. Significance was no longer observed at the desensitization end point during build-up.

A graphical representation, using a 3-dimensional bubble plot, captures the distribution of participants' baseline age, baseline Ara h2 IgE, and the maximum cumulative missed doses, grouped by desensitization and remission (Figure 5). Participants who achieved desensitization and remission are clustered around lower baseline age, baseline Ara h2 IgE, and cumulative missed doses. To determine whether there was an interaction between age, baseline Ara h2 IgE, and the maximum cumulative missed doses, a Pearson correlation coefficient was calculated. There was a weak positive correlation between baseline age and cumulative missed doses ($r = 0.14$; $P = .187$) and a weak negative correlation between baseline Ara h2 IgE and cumulative missed doses ($r = -0.02$; $P = .853$) that did not reach significance.

DISCUSSION

Here, we describe for the first time the potential impact of missed doses and dosing reactions on clinical outcomes in

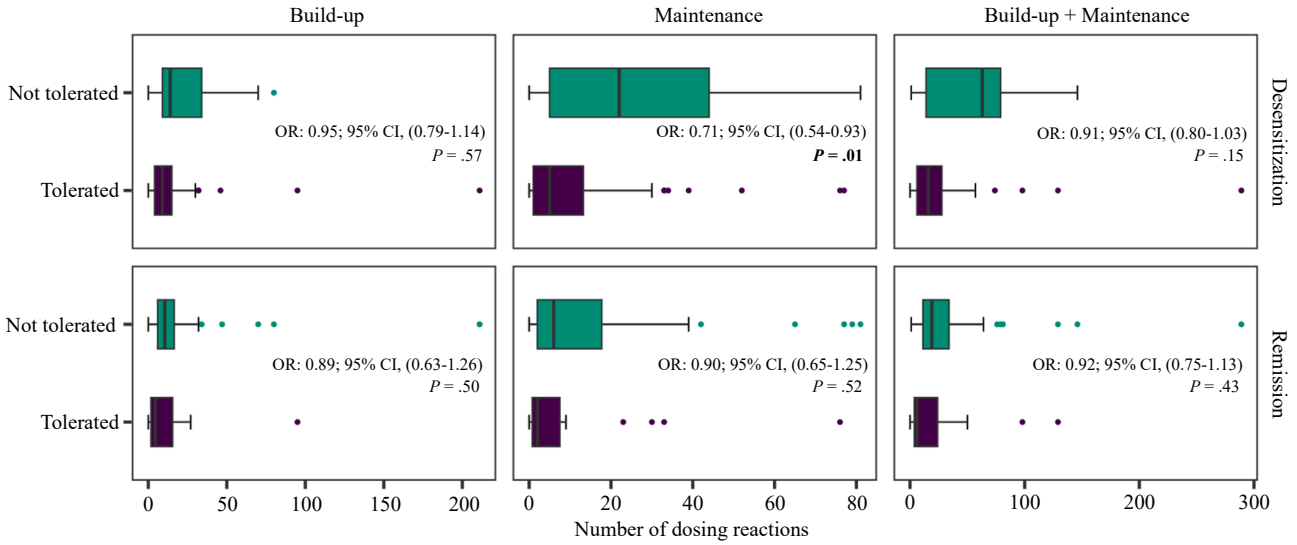

FIGURE 3. Total number of dosing-related reactions during each study phase. Multivariable logistic regression modeling clinical outcomes at week 134 (desensitization) and week 160 (remission) by the total number of dosing-related reactions during the (**A**) build-up, (**B**) maintenance, and (**C**) build-up and maintenance phases, corrected for baseline age and Ara h2–specific IgE. Purple represents participants who tolerated the DBPCFC; green represents participants who did not. The ORs and CIs represent a 10-unit increase in the number of dosing-related reactions.

peanut oral immunotherapy. Controlling for baseline age and baseline Ara h2–specific IgE, we found that the maximum number of consecutive missed doses during the build-up phase and the number of dosing reactions experienced during the maintenance phase were both associated with a lower likelihood of achieving positive clinical outcomes, desensitization, and remission. These data suggest that the extent of consecutive missed does and dosing reactions not only predict clinical outcomes but that their timing during the treatment phases of pOIT may also matter, acknowledging that the OR estimates are similar between the treatment phases. Adherence to the daily dosing regimen could be especially important during the build-up phase of the pOIT protocol. Interestingly, the most common reason for missed consecutives doses was concurrent illness, followed by parent/guardian forgetting to administer the dose.

These findings have practical real-world implications for pOIT protocols, clinicians, patients, and their families (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). For example, in addition to education for parents and caregivers on the importance of adherence to OIT protocols, build-up phases could be timed to support compliance by avoiding cold and flu season and busy sports schedules, thus minimizing the likelihood of consecutive missed doses. The effect of interruptions in dosing sequence on other clinical outcomes in food OIT protocols has also been investigated, and one study of milk oral immunotherapy (OIT) showed that adherent patients had lower incidence of allergic reactions, anaphylaxis, health care/emergency room visits, and epinephrine/antihistamine use compared with nonadherent patients.[25]

There was no significant correlation between the maximum total number of missed doses during the maintenance phase and clinical outcome, suggesting that missing 1 or 2 doses, even repeatedly, during maintenance may not significantly affect clinical outcomes. Daily dosing carries a significant burden to patients and caregivers, and other studies have shown that some parents/guardians of infants and toddlers with peanut allergy elect not to pursue pOIT because of the need for daily dosing.[26,27] An open-label extension study of pOIT in older children and adolescents found that daily dosing led to higher rates of desensitization than nondaily dosing.[28] There may possibly be differences in the need for daily dosing during maintenance depending on the age at which pOIT is initiated. Future studies are needed to confirm whether less frequent dosing during the maintenance phase yields similar desensitization and remission outcomes as does daily dosing in the infant/toddler age group.

Although dosing reactions were not a common reason for missed doses, dosing reactions that occurred during the maintenance phase negatively affected desensitization. Dosing reactions are common with pOIT, and most participants do experience some dosing-induced symptoms, particularly during the build-up phase.[19] The higher rate of dosing reactions experienced during build-up is likely due to the administration of escalating doses of peanut protein and potential for allergic reaction with each dose increase. In contrast, the risk of dosing reactions during maintenance is likely lower due to the stable dose exposure and the development of desensitization. Although previous evidence on the effects of dosing reactions on desensitization or remission is lacking, factors that influence the likelihood of dosing reactions and reaction severity during pOIT have been studied. Factors such as infection, exercise, nonadherence, menstruation, temperature changes, and uncontrolled asthma may increase the risk of dosing reactions.[19,29] The timing of daily dose ingestion may also be relevant, because evening ingestion has been described as a potential variable that increases the risk of reactions requiring epinephrine during pOIT in children.[30] In addition, Virkud et al[31] found that allergic rhinitis is a significant predictor of adverse events during

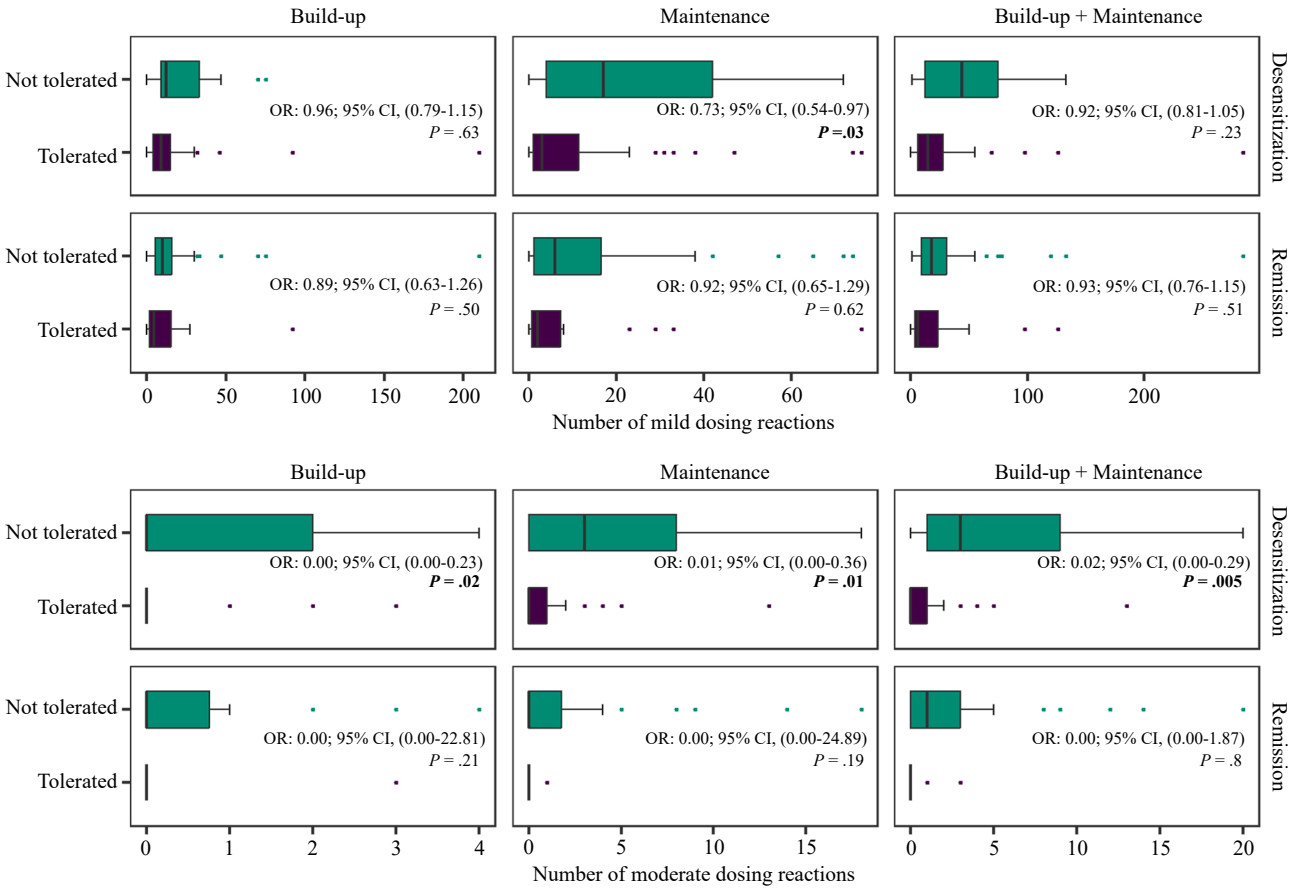

FIGURE 4. Total number of dosing-related reactions, by severity, during each study phase of pOIT. Multivariable logistic regression modeling clinical outcomes at week 134 (desensitization) and week 160 (remission) by the total number of mild dosing-related reactions during the (**A**) build-up, (**B**) maintenance, and (**C**) build-up and maintenance phases, corrected for baseline age and Ara h2–specific IgE. The total number of moderate dosing reactions during the (**D**) build-up, (**E**) maintenance, and (**F**) build-up and maintenance phases are also shown. Purple represents participants who tolerated the DBPCFC; green represents participants who did not. The ORs and CIs represent a 10-unit increase in the number of mild dosing reactions and a 1-unit increase in the number of moderate dosing reactions.

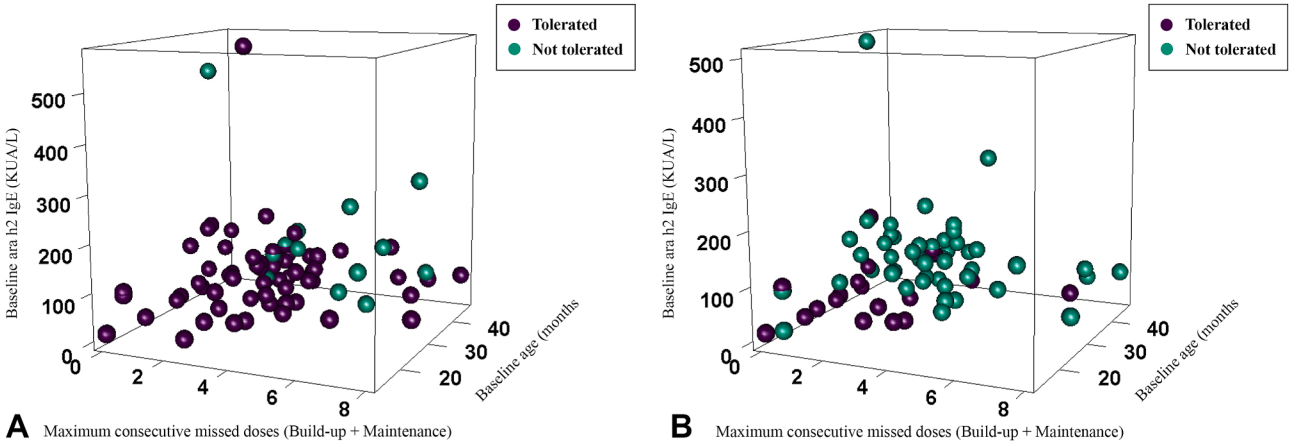

FIGURE 5. Distribution of clinical outcomes by consecutive missed doses, age, and baseline Ara h2–specific IgE. The number of consecutive missed doses, age, and baseline Ara h2–specific IgE of participants are plotted in participants who achieved (**A**) desensitization and (**B**) remission.

pOIT and patients with allergic rhinitis were more likely to experience these adverse events during peak pollen months. The findings from this study support continued clinician and patient/parent shared decision making in when to start pOIT and during treatment if the patient is having continued reactions during the maintenance phase. Treatment modifications, and perhaps discontinuation, should be considered for significant dosing reactions during the maintenance phase of pOIT.

A strength of this study is that the data come from a well-characterized participant population, allowing for control of biomarkers associated with pOIT outcomes, as well as carefully recorded data on daily dosing adherence and reactions. In addition, the outcomes were assessed with DBPCFCs. Similar to the previously reported studies that showed that age, baseline peanut-specific IgE, and baseline Ara h2−specific IgE were associated with positive clinical outcomes after pOIT,[11,12,15,19] here, both age and baseline Ara h2−specific IgE were each significantly associated with remission and when combined into a single model were both significantly associated with remission.

This study is not without limitations. IMPACT enrolled participants aged 1 to 4 years, and so the findings here may not be generalizable to older age groups. This is particularly important because outcome in food immunotherapy may be different in different age groups.[11-13,22,32] Another limitation is that only per-protocol participants who completed the DBPCFC at desensitization and/or remission were included in the analyses presented here. Because adherence was found to be an important predictor of outcome, including participants who did not meet per-protocol criteria would likely have overestimated the effect size of these results. Real-world adherence is typically lower than what is achieved in clinical trials, and so the findings here may be even more pronounced in clinical practice.

Given the inherent risks and burden of pOIT, especially in preschool children, it is crucial to identify which patients are more likely to have a clinical benefit and arm providers, patients, and their families with pOIT response-driven stratification data when deciding whether to pursue pOIT. The work presented here demonstrates for the first time that treatment-emergent variables occurring during OIT treatment—dosing interruptions in OIT during build-up phase and reactions during OIT maintenance—influence OIT's efficacy. By carefully preparing patients and caregivers for OIT, developing protocols that support consistent dosing, and monitoring treatment response, clinicians can maximize the benefits of OIT and minimize risks for patients.

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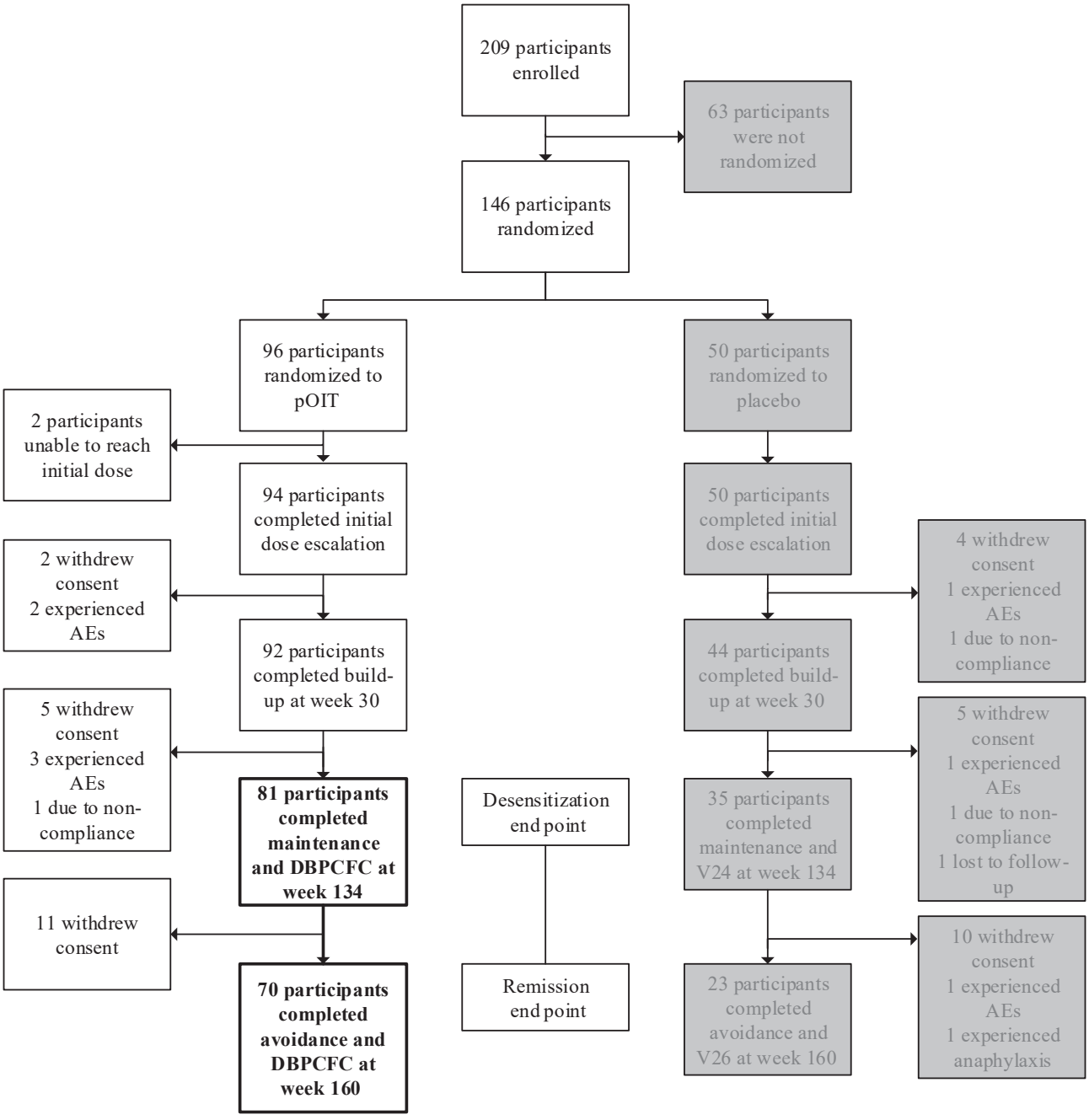

FIGURE E1. Consort diagram. The per-protocol population of 70 participants (in bolded boxes) who received pOIT and completed both week 134 DBPCFC to 5000-mg peanut protein (desensitization) and week 160 DBPCFC (remission) after peanut avoidance for 26 weeks were included in this study. *AE,* Adverse event.

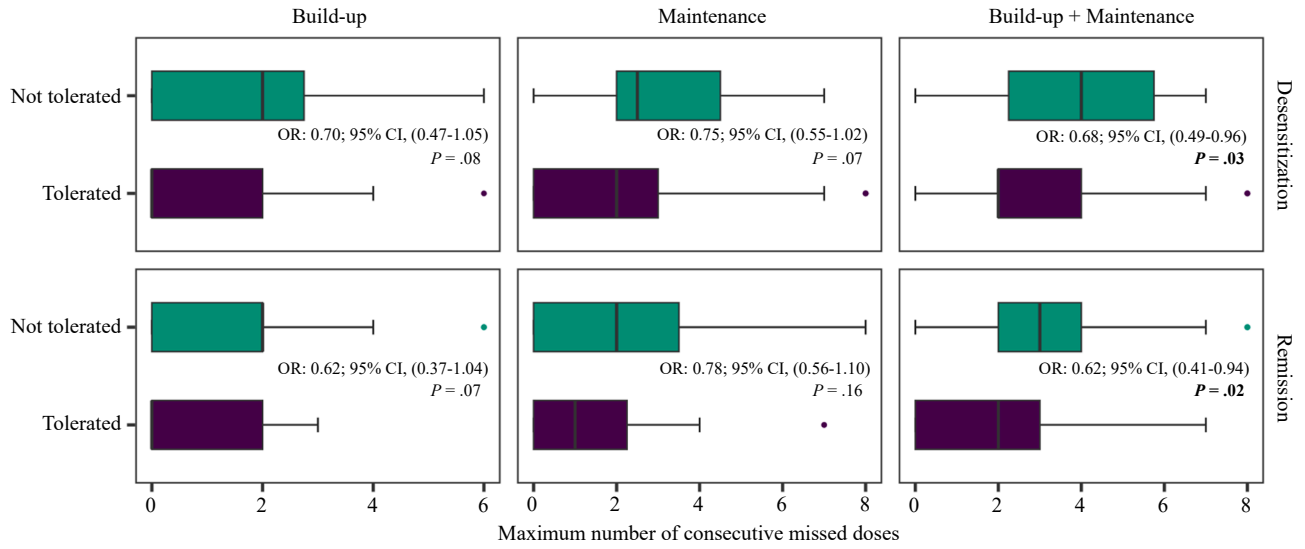

FIGURE E2. Maximum number of consecutive missed doses during each study phase, excluding participants who did not reach 1600 mg of peanut protein. Multivariable logistic regression modeling outcomes at week 134 (desensitization) and week 160 (remission) by the maximum number of consecutive missed doses during the (**A**) build-up, (**B**) maintenance, and (**C**) build-up and maintenance phases, corrected for baseline age and Ara h2–specific IgE. Purple represents participants who tolerated the DBPCFC; green represents participants who did not. The ORs and CIs represent a 1-unit increase in the maximum number of consecutive missed doses.

TABLE E1. Consortium for Food Allergy Research 3 grading system for allergic reactions

Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life-threatening	Grade 5: Death
Transient or mild discomforts (<48 h), no or minimal medical intervention/ therapy required. These symptoms may include pruritus, swelling or rash, abdominal discomfort, or other transient symptoms	Symptoms that produce mild to moderate limitation in activity, some assistance may be needed; no or minimal intervention/ therapy is required. Hospitalization is possible. These symptoms may include persistent hives, wheezing without dyspnea, abdominal discomfort/ increased vomiting, or other symptoms	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible. Symptoms may include bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, transient hypotension among others. Parenteral medication(s) are usually indicated	Extreme limitation in activity, significant assistance required; significant medical/therapy. Intervention is required; hospitalization is probable. Symptoms may include persistent hypotension and/ or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life-threatening symptoms	Death

TABLE E2. Reasons for consecutive missed doses, by clinical outcomes

	Not desensitized		Desensitized		Remission	
Reason for consecutive missed doses	Events (N = 96)	Participants (N = 11)*	Events (N = 198)	Participants (N = 42)*	Events (N = 121)	Participants (N = 11)*
Concurrent illness	46	9 (81.8)	117	39 (92.9)	48	9 (81.8)
Other	7	2 (18.2)	43	15 (35.7)	17	6 (54.5)
Participant/guardian forgot	26	6 (54.5)	28	14 (33.3)	56	5 (45.5)
Reaction to OIT during home dosing	17	6 (54.5)	10	6 (14.3)	0	0 (0)

*n (%) is displayed. Participants are counted only once for each reason. Percentages are based on the number of participants with at least 1 consecutive missed dose in the outcome category.

TABLE E3. Clinical pearls from the IMPACT trial: Baseline and treatment-emergent variables in young children undergoing pOIT*

Variables	IMPACT trial outcome	Possible clinical implication
Baseline variables		
Age	Younger age associated with both desensitization and remission	Starting pOIT at a younger age may lead to better outcomes
Ara h2−specific IgE	Lower Ara h2−specific IgE associated with desensitization and remission	Children with lower Ara h2−specific IgE may have better outcomes with pOIT
Treatment-emergent variables		
Missed doses		
Total individual missed doses	Did not associate significantly with outcome	Individual missed doses may not change outcome
Maximum consecutive missed doses during build-up	Associated with lower likelihood of desensitization and remission	Try not to miss multiple doses in a row during build-up
Maximum consecutive missed doses during maintenance	Did not associate significantly with outcome	There may be more leeway with consecutive missed doses during maintenance
Dosing reactions		
Dosing reactions during build-up	Did not associate significantly with outcome	Dosing reactions during build-up may be par for the course
Dosing reactions during maintenance	Associated with lower likelihood of desensitization	If dosing reactions occur during maintenance, proceed with caution

*All findings are from IMPACT, and future studies are needed to determine generalizability to other populations.