

Clinical Communications

Peanut oral immunotherapy protects patients from accidental allergic reactions to peanut

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Clinical Implications

- We could demonstrate that peanut oral immunotherapy leads to a reduced number and severity of allergic reactions after accidental peanut exposure compared with placebo, indicating that oral immunotherapy has a protective impact on peanut-allergic children regarding accidental reactions in daily life.

Peanut is a frequent elicitor of anaphylaxis in childhood.¹ Peanut-allergic patients are advised to strictly avoid peanut,² but accidental reactions are still common due to the widespread use of peanut in the food industry, for example, snack products or non-prepacked foods, for example, restaurants or ice cream parlors. Peanut oral immunotherapy (OIT) aims to protect patients from allergic reactions after accidental peanut exposure.³ Currently, the balance of risks and benefits of OIT in peanut allergy is debated. A recent meta-analysis on safety and efficacy of peanut OIT revealed that despite a good efficacy profile, OIT leads to a significantly higher risk of allergic reactions and anaphylaxis compared with avoidance or placebo.⁴ Most trials on OIT evaluate efficacy by desensitization, measured by a certain tolerated dose or a certain increase in the threshold dose at final food challenge while on therapy.⁵ However, the supervised oral food challenge displays only “a snapshot” in time

and the individual threshold dose is not always stable over time. More than 70% of peanut-allergic children of the placebo group in our peanut-OIT trial showed an unstable threshold at repeated peanut challenge after 16 months.⁶ Hence, the actual occurrence of allergic reactions after accidental peanut exposure overtime might be a more real-life approach to measure the efficacy of OIT, as was also suggested by the authors of the recent meta-analysis.⁴

We aimed to have a closer look at the frequency, severity, and temporal occurrence of allergic reactions after accidental peanut exposure in our double-blind, placebo-controlled trial on peanut OIT.

The study protocol and population have previously been described in detail.⁶ Briefly, 62 children (median age, 6.8 years) with challenge-proven peanut allergy were included and received either a low-dose peanut OIT or placebo for approximately 16 months. For the current analysis, all randomized patients receiving the allocated intervention were included (peanut $n = 30$, placebo $n = 31$).⁶ Before start of OIT as well as during the trial, the study team recorded details on all allergic reactions potentially caused by peanut exposure. Additional information on the study design, assessment, and classification of accidental allergic reactions and statistical analysis is described in this article's Online Repository at www.jaci-inpractice.org.^{7,8}

At baseline, no difference was found regarding clinical characteristics⁶ including the frequency or severity of allergic reactions in the clinical history of patients between both groups (further details are presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org). All but 2 children (96.8%) experienced at least 1 allergic reaction possibly caused by peanut (median $n = 3$) before or after their diagnosis of peanut allergy. More than half of all children had at least 1 severe allergic reaction (severity grade IV-V). About 38.7% of children in the placebo-OIT group and 29% of children in the peanut-OIT group had a further systemic food allergy next to peanut.

During OIT, 14 of 31 children of the placebo-OIT group (45.2%) experienced a total of 24 accidental allergic reactions possibly or certainly caused by peanut. In contrast, only 5 of

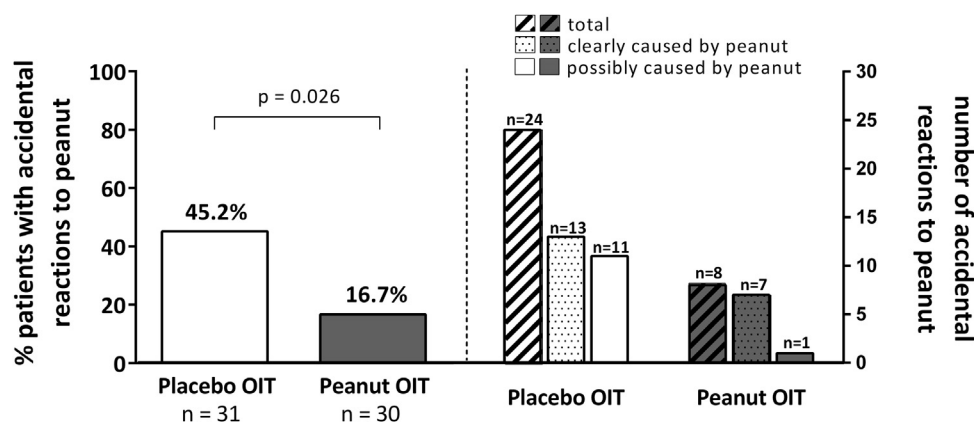


FIGURE 1. Patients with reported allergic reactions due to accidental exposure to peanut and number of allergic reactions categorized as possibly or certainly caused by accidental peanut exposure during OIT.

TABLE I. Details on reported allergic reactions due to accidental exposure to peanut (n = 32) during placebo and peanut OIT

Patient	OIT period	OIT dose (mg)*	Time of reaction after OIT dose	Elicitor/possible augmentation factor	Categorized as	Systemic FA other than PN	Symptoms	Severity	Treatment
Peanut OIT†									
#61	BU	1	23 h	Sushi meal in restaurant	Certainly PN	—	OAS, coughing, rhinoconjunctivitis	III	Antihistamine, corticosteroid, hospitalization
#23	BU	4.5	3.5 h	Peking duck with PN in restaurant/URI	Certainly PN	—	Coughing, somnolence	V	Antihistamine, corticosteroid, adrenaline, hospitalization
#4	BU	9	>2 h	Chocolate in advent calendar in kindergarten	Possibly PN	HE, CM (challenge proven)	OAS, rhinoconjunctivitis	III	Antihistamine
#23	BU	13	20 h	Unknown food in kindergarten	Certainly PN	—	Facial erythema, generalized hives	II	Antihistamine
#23	BU	13	19 h	Unknown food in kindergarten	Certainly PN	—	Angioedema	II	Antihistamine
#31	BU	13	18 h	Chocolate bar	Certainly PN	—	Vomiting	II	—
#31	BU	17.5	3.5 h	Cookie with chocolate	—	—	Angioedema, sneezing	II	Antihistamine
#21	BU	40	17 h	Unknown food in kindergarten/exercise	Certainly PN	—	Perioral hives	I	—
Placebo OIT‡									
#19	BU	0.5	16 h	Unknown food in kindergarten	Possibly PN	HE, sesame (challenge proven)	Angioedema, pruritus	II	Antihistamine
#51	BU	0.5	15 h	Whole PNs in school (indirect exposure)	Certainly PN	—	OAS, pruritus	II	Antihistamine
#41	BU	1	4 h	PN flips (indirect exposure)	Certainly PN	Soy (history)	Rhinoconjunctivitis	III	—
#51	BU	1	30 min	PN flips (indirect exposure)	Certainly PN	—	Conjunctivitis	II	Antihistamine
#41	BU	2.5	23 h	PN leftovers on bottle§	Certainly PN	Soy (history)	Coughing, shortness of breath	IV	Salbutamol
#41	BU	3.5	24 h	Mucosal contact with PN/exercise	Certainly PN	Soy (history)	Conjunctivitis, flush, hoarseness, coughing, shortness of breath	IV	No medication applied, hospitalization
#35	BU	4.5	1.5 h	Cookie from friend and bakery	Certainly PN	—	Abdominal pain, tiredness, vomiting, rhinoconjunctivitis, unconsciousness	V	Antihistamine, corticosteroid, emergency room for 2 h
#41	BU	4.3	19 h	Chocolate bar	Possibly PN	Soy (history)	Conjunctivitis, hoarseness, shortness of breath	IV	—
#47	BU	17.5	4 h	Dinner, chips	Certainly PN	—	Abdominal pain, coughing, wheezing	IV	—
#47	BU	20	22 h	Snack at school	Certainly PN	—	Abdominal pain, generalized hives, coughing, wheezing	IV	Antihistamine, corticosteroid, adrenaline, hospitalization
#51	BU	20	23 h	Friend's birthday party	Certainly PN	—	Conjunctivitis, shortness of breath	IV	Antihistamine

#12	BU	25	12 h	PN bar (indirect exposure)	certainly PN	HE, HN (challenge proven)	Coughing	III	—
#12	BU	35	4 h	Rice pudding	Possibly PN	HE, HN (challenge proven)	Generalized hives	II	Antihistamine
#6	BU	40	23 h	Whole meal cereal	Possibly PN	Soy (history)	Generalized hives	II	Antihistamine, corticosteroid
#6	BU	45	22 h	Sweet snack bar	Possibly PN	Soy (history)	Coughing, wheezing	IV	Salbutamol
#3	BU	45	3 h	Non-prepacked ice cream	Possibly PN	HN (history)	Nausea	—	—
#38	BU	4	5 h	Unknown food	possibly PN	Soy (history)	OAS, shortness of breath	IV	Antihistamine, salbutamol
#3	BU	50	> 2 h	Pretzel	Possibly PN	HN (history)	OAS	—	—
#34	BU	50	12 h	Unknown food at school	Certainly PN	—	Generalized hives	II	—
#3	BU	70	23 h	Prepacked ice cream	Possibly PN	HN (history)	One facial hive	I	—
#18	BU	150	24 h	PN sauce at barbecue	Certainly PN	—	OAS, angioedema, abdominal pain, coughing, generalized hives	III	Antihistamine, corticosteroid, salbutamol, hospitalization
#5	BU	175	12 h	Multigrain bread roll	Possibly PN	HE (challenge)	Angioedema, generalized hives, wheezing, shortness of breath	IV	Antihistamine, salbutamol
#28	M	250	1.5 h	Non-prepacked cookie from bakery	Certainly PN	—	Rhinoconjunctivitis	III	—
#62	M	250	>2 h	Non-prepacked ice cream	Possibly PN	HN, CM (challenge proven)	Perioral hives	I	—

BU, Build-up phase; CM, cow's milk; FA, food allergy; HE, hen's egg; HN, hazelnut; M, maintenance phase; OAS, oral allergy syndrome; PN, peanut; URI, upper respiratory tract infection.

*OIT dose in mg PN protein (PN-OIT group) or placebo (placebo-OIT group).

†None of the children of the PN-OIT group with an additional systemic food allergy reported on any accidental allergic reaction related to other food allergens other than PN.

‡Two patients of the placebo-OIT group with a systemic food allergy to sesame and lentil had 1 accidental allergic reaction clearly related to these allergens, respectively.

§From grandfather eating PN.

||No severity grading as only subjective symptoms occurred.

30 children of the peanut-OIT group (16.7%) experienced 8 accidental reactions ($P = .026$) (data already reported in Blumchen et al⁶ [Figure 1]). Frequent elicitors possibly or certainly containing peanut were chocolate, non-prepacked foods from ice cream parlors, bakeries, and restaurants, or foods consumed in kindergarten (Table 1). Reactions in the placebo group occurred at all different time points during placebo OIT (Table 1; see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). In contrast, in the peanut-OIT group, reactions occurred only within the build-up phase, when patients were on small daily peanut OIT doses ranging from 1 to 40 mg peanut protein.

In the placebo-OIT group, 7 patients (22.6%) experienced accidental allergic reactions rated as severe (severity grade IV or V) (Table 1; see Table E2 in this article's Online Repository at www.jaci-inpractice.org). In the peanut-OIT group, all but 1 reaction were rated as mild to moderate. The 1 patient (#23) experiencing a severe accidental reaction to peanut in a Chinese restaurant was in early-stage OIT-build-up phase receiving a daily dose of 4.5 mg peanut protein. In total, 1 of 8 accidental allergic reactions (12.5%) in the peanut-OIT group compared with 10 of 24 (42%) in the placebo-OIT group were rated as severe (grade IV-V).

On combining the occurrence of any objective allergic reactions during OIT possibly related to treatment or related to accidental peanut exposure, we found that 83.9% patients of the placebo-OIT group compared with 66.7% of the peanut-OIT group experienced any objective allergic reaction (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Regarding reactions of severity grade IV to V possibly related to treatment or related to accidental peanut exposure, about one-third of children of the placebo-OIT group and one-fourth of the peanut-OIT group experienced severe allergic reactions (Figure E2).

To our knowledge, this is the first detailed report on accidental allergic reactions in patients undergoing peanut OIT. Low-dose peanut OIT seems to protect patients from allergic reactions after unintended peanut exposure compared with placebo in daily life, especially after reaching the maintenance dose. Moreover, our results indicate a reduction in severe accidental allergic reactions in patients undergoing peanut OIT compared with placebo.

Our investigation has some limitations. First, we report on data of a small sample size. Second, our analysis is based on parent-reported accidental reactions only and the possible presence of peanut protein in the consumed foods was not investigated using laboratory analysis. However, all adverse events were further judged by a study physician as being related to an accidental peanut exposure. Furthermore, regarding only accidental allergic reactions categorized as "certainly caused by peanut," still almost twice as many accidental allergic reactions occurred in the placebo-OIT group compared with the peanut-OIT group. The rate of severe possibly treatment-related allergic reactions in our placebo group was quite high. Because this was a blinded trial, allergic reactions were judged by a study physician as being either related (within 2 hours after OIT ingestion) or unrelated to treatment (after 2 hours, ie, possibly related to an allergic comorbidity). All 4 patients of the placebo group experiencing shortness of breath judged as treatment-related had asthma, so

reactions might have been attributed to this comorbidity. However, that was also the case in 4 of 7 patients of the peanut OIT group, and overall allergic comorbidities were similar in both trial groups.⁶

Concerning our results with regard to recent findings on the risk of allergic reactions of peanut OIT,⁴ one may consider that peanut-allergic patients however benefit from OIT compared with allergen avoidance only. Even though an effective OIT is associated with expected treatment-related allergic reactions, especially in the first treatment year, a clinically meaningful benefit might be achieved if that means on the same time that OIT protects from severe unexpected allergic reactions on peanut exposure. However, results from long-term studies on peanut OIT with a larger sample size are warranted to confirm our finding.

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Conflicts of interest: K. Blumchen reports personal fees and nonfinancial support from Novartis; personal fees from HAL Allergy, ThermoFisher, and Bencard Allergie; and grants and personal fees from Aimmune Therapeutics and DBV technologies outside the submitted work. G. Hansen reports personal fees from Novartis, MedUpdate, and Sanofi GmbH. T. Holzhauser reports personal fees and nonfinancial support from Akademie Fresenius and nonfinancial support from the European Academy of Allergy and Clinical Immunology, Deutscher Allergie- und Asthmabund eV, and Deutsche Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie eV; German Research Foundation; German Federal Office of Consumer Protection and Food Safety; and EU-COST Action ImpARAS; all outside the submitted work. K. Beyer reports grants and personal fees from Aimmune Therapeutics; grants from DBV; and personal fees from Mabyon AG outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

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METHODS

Study overview

The study protocol and population have previously been described in detail.^{E1} Briefly, 62 children aged 3 to 17 years (median age, 6.8 years) with challenge-proven peanut allergy were included. Children were randomized 1:1 to receive either a low-dose peanut OIT (median maintenance dose, 125 mg peanut protein) or placebo for approximately 16 months including a slow, long-term up dosing period (median, 13 months). Consistency of OIT challenge meals, that is, absence of peanut protein in placebo and standardized, homogenous levels of peanut protein in active meals, was analytically monitored and confirmed throughout the study period. During OIT, all patients and caregivers were advised to strictly avoid peanut in the child's diet. The study protocol and consent forms were approved by ethic committees. All caregivers of the study participants gave written informed consent before the start of the study.

Assessment of accidental allergic reactions

Before start of OIT, the study team recorded details on all allergic reactions potentially caused by peanut exposure in the clinical history of all patients individually. All allergic reactions, those occurring before the diagnosis of peanut allergy as well as those occurring after diagnosis on accidental exposure to peanut, were assessed at baseline.

During OIT, all adverse events (AEs) including allergic reactions possibly caused by accidental peanut exposure were (1) recorded daily by the parents using a diary and (2) assessed every 1 to 2 weeks by the blinded study physician either during up dosing visits or during a telephonic interview. Furthermore, there was a 24-hour emergency phone number available for the parents. All AEs were rated as related or nonrelated to peanut OIT/placebo OIT if symptoms occurred within or after 2 hours following OIT ingestion, respectively. In addition, the study physician further categorized all AEs as being an allergic reaction after accidental allergen exposure. For this purpose, only clear allergic immediate-type reactions were included. Severity of symptoms was determined on a scale from I to V using a modified grading system for food-induced anaphylaxis.^{E2,E3} Except for throat tightness, only objective symptoms were included within this grading system. The most severe objective symptom determined the grade:

- *grade I*—skin symptoms: mild angioedema, perioral urticaria, mild flushing;

- *grade II*—skin symptoms: more severe angioedema, generalized urticaria, flushing, and/or gastrointestinal tract symptoms: single episode of vomiting and/or respiratory symptoms: mild nasal congestion, repeated sneezing;
- *grade III*—skin symptoms: any of above, and/or gastrointestinal tract symptoms: repeated vomiting or diarrhea, and/or respiratory symptoms: marked nasal congestion, rhinorrhea, conjunctivitis, throat tightness, dry cough, and/or cardiovascular symptoms: tachycardia (increase 15 beats/min);
- *grade IV*—skin symptoms and/or gastrointestinal tract symptoms: any of the above, respiratory symptoms: any of the above and/or hoarseness of voice, dysphagia, barking cough, wheezing, dyspnea, cyanosis, cardiovascular symptoms: any of the above and/or dysrhythmia, mild arterial hypotension;
- *grade V*—skin symptoms and/or gastrointestinal tract symptoms: any of the above, respiratory symptoms: any of the above and/or respiratory arrest, cardiovascular symptoms: any of the above and/or severe bradycardia or hypotension or cardiac arrest or loss of consciousness.

Furthermore, accidental allergic reactions during OIT were categorized as “possibly caused by peanut” if the reported elicitor was unclear and if the child had further systemic food allergies other than peanut, or “certainly caused by peanut” if peanut was the identified reported elicitor and/or if the child had no further systemic food allergy. A systemic food allergy other than peanut was defined as either a challenge-proven food allergy or a parent-reported systemic allergic reaction and proven sensitization to another food allergen. In case of available information, the route of accidental exposure was categorized as direct exposure (= reported oral ingestion) and/or indirect exposure (= reported cutaneous contact or inhalation [if patients or parents reported a reaction without ingestion or cutaneous contact but with the presence of peanut in the indoor environment]).

Statistical analysis

Values are expressed as median and ranges or counts and percentages as appropriate. For the current analysis of accidental allergic reactions during OIT, all randomized patients receiving the allocated intervention were included (peanut $n = 30$, placebo $n = 31$) as the safety population.^{E1} Group comparisons of categorical variables were compared between both randomization arms using the χ^2 test for contingency tables (Fisher exact test). All statistical tests were 2-tailed, and a 2-sided P value of .05 was considered for significance. The statistical analyses were performed using SPSS version 22.0 (SPSS, Inc, Chicago, Ill).

TABLE E1. Frequency and severity of reported allergic reactions due to possible exposure to peanut in patient's history before start of OIT

Allergic reactions in patient's history	Placebo OIT (n = 31)	Peanut OIT (n = 31)
Patients with history of allergic reactions,* n (%)	29 (93.5)	31 (100)
Patients with history of allergic reactions certainly caused by PN, n (%)	28 (90.3)	31 (100)
No. of allergic reactions per patient, median (range)	3 (0-15)	3 (1-6)
Patients with most severe allergic reaction of severity, n (%)†		
Grade I	2 (7.0)	1 (3.2)
Grade II	8 (27.6)	6 (19.4)
Grade III	3 (10.3)	6 (19.4)
Grade IV	15 (51.7)	18 (58.1)
Grade V	1 (3.5)	0 (0)
Age at first allergic reaction (y), median (range)‡	2.2 (0.5-6)	2 (0.5-7)
Patients with history of accidental allergic reactions,‡ n (%)	26 (83.9)	23 (74.2)
Patients with history of accidental allergic reactions certainly caused by PN, n (%)	22 (71.0)	22 (71.0)
Total number of allergic reactions, n	109	87
Total number of allergic reactions certainly caused by PN, n (%)§	83 (76.1)	72 (82.8)
Reported to be caused by oral ingestion, n (%)	60 (72.3)	55 (76.4)
Reported to be caused by indirect exposure (skin/inhalation), n (%)	23 (27.7)	17 (23.6)
Total number of accidental allergic reactions, n	74	48
Total number of allergic reactions certainly caused by PN, n (%)§	49 (66.2)	36 (75.0)

PN, Peanut.

*Include all reported allergic reactions before diagnosis of PN allergy and accidental allergic reactions after diagnosis.

†Only of patients with allergic reaction(s) in clinical history.

‡Include all reported accidental allergic reactions after diagnosis.

§% of total number of allergic reactions in clinical history.

||% of total number of allergic reactions certainly caused by PN in clinical history.

TABLE E2. Severity of reported allergic reactions due to accidental exposure to peanut during OIT

Severity of allergic reactions	Placebo OIT (n = 31)	Peanut OIT (n = 30)
Patients with most severe accidental allergic reaction of severity, n (%)		
Grade I	2 (6.5)	1 (3.3)
Grade II	2 (6.5)	1 (3.3)
Grade III	3 (9.7)	2 (6.6)
Grade IV	6 (19.4)	0 (0)
Grade V	1 (3.2)	1 (3.3)
Patients with accidental allergic reaction treated with medications, n (%)	10 (32.3)	4 (13.3)
Treated with adrenaline, n (%)	1 (3.2)	1 (3.3)
Total number of accidental allergic reactions, n	24	8
No. of accidental allergic reactions with severity grade, n (%)*		
Not applicable (subjective symptoms only)	2 (8.3)	0 (0.0)
Grade I	2 (8.3)	1 (12.5)
Grade II	6 (25.0)	4 (50.0)
Grade III	4 (16.7)	2 (25.0)
Grade IV	9 (37.5)	0 (0.0)
Grade V	1 (4.2)	1 (12.5)

*% of total number of accidental allergic reactions to peanut during OIT.

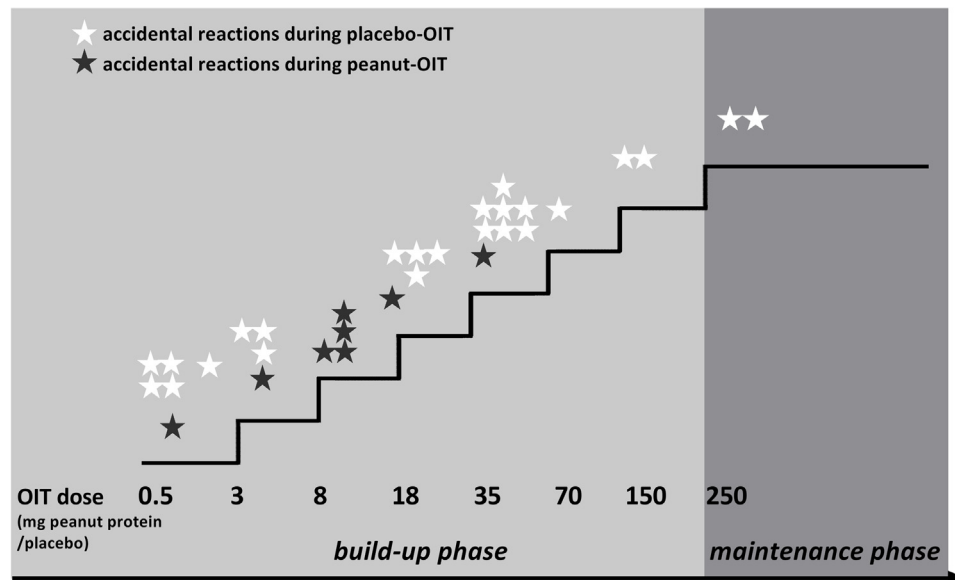


FIGURE E1. Occurrence of allergic reactions due to accidental exposure to peanut during the time course of peanut OIT or placebo OIT.

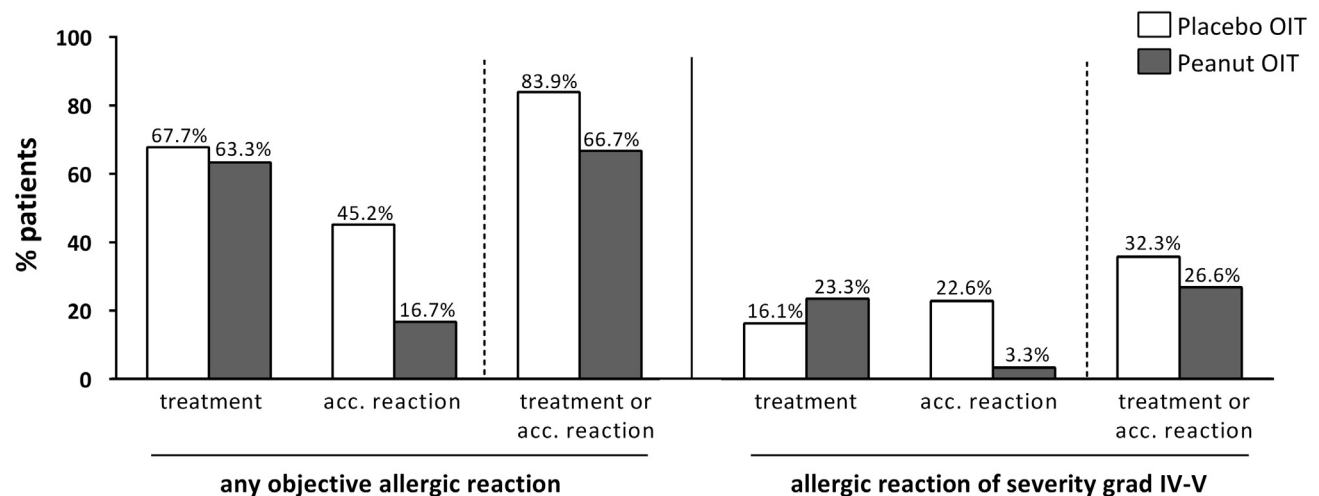


FIGURE E2. Patients with objective and severe* allergic symptoms during OIT related to treatment and/or related to accidental peanut exposure. *Five patients of the placebo group had a severe allergic reaction rated as related to treatment, including 4 patients with shortness of breath (severity grade IV) and 1 patient with unconsciousness (severity grade V). The reaction of the last patient was in parallel judged as related to accidental peanut exposure because the reaction occurred within 2 hours after treatment ingestion and within 1 hour after consumption of a certainly peanut-containing cookie. Seven patients of the peanut OIT group had a severe allergic reaction rated as related to treatment.

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