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Food reactions during avoidance: focus on peanut

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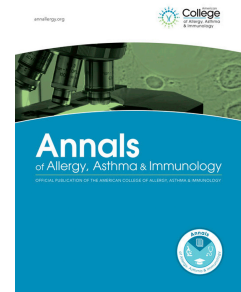
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Title: Food reactions during avoidance: focus on peanut

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Abbreviations/Acronyms: AE, accidental exposure, ED, eliciting dose, FA, food allergy, PN, peanut; TN, tree nut, OIT, oral immunotherapy, OFC, oral food challenge

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Objective : Peanut allergy has historically been difficult to manage, with most cases persisting into adulthood. Novel therapies for peanut allergy treatment are on the horizon, yet allergists must maintain a robust understanding of the risks and benefits of the current standard of therapy, avoidance diet.

Data Sources : A comprehensive literature search using PubMed of reviews and clinical articles was performed.

Study Selections : Articles discussing peanut or other food-related allergic reactions, accidental exposures or anaphylaxis pertinent to avoidance diet or comparative to oral immunotherapy trials were selected.

Results : Peanut remains a leading allergen associated with accidental ingestions responsible for food-related reactions, both mild and severe. Fatal reactions, however, are rare and measures such as anaphylaxis plans can significantly decrease the risk of accidental anaphylaxis. Patients may over estimate situations thought to increase risk for reactions to peanut, such as inhalation or contact through skin. In oral immunotherapy trials, the rate of anaphylaxis secondary to treatment was significantly higher than avoidance practices.

Conclusion : Clinicians should continue to discuss avoidance as a viable option for long-term peanut allergy management and empower patients to differentiate relevant situations in which accidental reactions might occur.

1 Introduction

2 IgE-mediated food allergy (FA) is a growing health concern, impacting up to 8% of
3 children and 2-3% of adults¹⁻³. Peanut allergy can be particularly difficult to manage, with
4 roughly 1-4.5% of the population affected, and with most cases persisting into adulthood⁴⁻⁶. The
5 standard of care has historically centered around strict avoidance and rescue medication use for
6 reactions secondary to accidental exposures (AE)^{2,7}. However, peanut-related allergic reactions
7 can be severe, with peanut often implicated in food-related fatalities⁸⁻¹⁰. This burden, naturally,
8 is associated with significant patient and parent anxiety and impairment in quality of life¹¹.

9 Nevertheless, at present, allergists, patients, and their families face emerging prospects
10 for prevention and treatment of peanut allergy. With the landmark 2015 Learning Early about
11 Peanut Allergy (LEAP) trial and subsequent studies, we learned that prevention of peanut allergy
12 is possible through early introduction^{12,13}. On the horizon is the probable implementation of
13 commercial peanut immunotherapy into clinical practice - the first treatment option for peanut-
14 allergic individuals. While the use of this therapy may understandably be attractive to both
15 clinicians and patients, a thorough understanding of the risks and benefits and comparison with
16 the current standard of allergen avoidance is paramount in deciding the appropriate strategy in
17 individual patients. Here we present an overview of the known data related to FA reactions
18 during avoidance, with a particular focus on peanut.

20 Peanut reactions during avoidance: incidence, risk and treatment

22 Allergic patients maintaining food avoidance diets must be aware of the possibility of
23 inadvertent food allergen exposures leading to allergic reactions that can range from mild to

severe, and in rare cases, result in fatality^{14,15}. Over the last two decades, reported annual incidence rates of accidental peanut reactions have varied considerably between studies, from 3%-55% with an average of 10% (Table 1)¹⁶⁻²⁴. Much of this variability may relate to differences in study inclusion criteria, for instance, differentiating individuals with previous clinical food reaction vs evidence of sensitization on allergy testing alone. Additionally, some studies included reactions to peanut exposure by routes other than ingestion. Neuman-Sunshine et al, for instance, distinguished the effect these factors had on AE rates, showing rates to be lower when only evaluating ingestion as the route of exposure and higher when only assessing those with a history of clinical reaction²⁰.

Some of the lowest rates of AE have been noted in a study by Clark et al, whose peanut and tree nut (TN) allergic participants received a comprehensive FA management plan upon diagnosis¹⁹. In addition to the typical avoidance counseling and emergency treatment plan, their study utilized additional safety measures, including notification of school/nurse regarding the allergy diagnosis as well as follow-up educational visits from trained pediatric community nurses. This study validated initial work by the same group, who had previously described an 8-fold reduction in AE frequency (decreased from annual rate of 55% to 7%) after implementation of a similar management plan¹⁷.

Several studies also examined risk factors that may be associated with an AE. Specific factors associated with reduction in the likelihood of experiencing an accidental reaction include longer disease duration, recruitment from FA advocacy associations, and having other FAs^{20,21,23}. In contrast, age ≥ 12 years, previous severe reaction to peanut and residing in a single-parent household have been associated with increased risk of an AE^{20,21,23}. Discussion of risk must also include location of exposure and reactions. Interestingly, the majority of studies show that the

largest proportion of reactions occur at a patient's home, a relative's home, or a friend's home and that most reactions occur secondary to food provided by the parent or patient themselves, as opposed to potentially unknowing individuals^{18,19,21,23,25}. Further, Eigenmann et al found that half of AE occurred either in the home, daycare, school, work, or even within the hospital, locations whereby proper anticipatory guidance could support adequate food avoidance measures²⁵.

The underuse of epinephrine during reactions to peanut has been well-established and presents a critical problem. Overall, the rate of epinephrine use during AEs has been estimated to be 1.1% per year²⁰. Large national registry studies of individuals with peanut allergy have shown consistent inability for patients to accurately recognize anaphylaxis symptomatically, which likely contributes to missed or under use of epinephrine²⁶. Perhaps of most concern, Sheikh et al demonstrated that even in patients who recognized reactions as anaphylaxis, epinephrine administration at time of reaction remained poor²⁷. In Fleischer et al discussed above, epinephrine administration was again found to be low (29.9%) even for reactions deemed to involve severe symptoms²², which has been replicated throughout the literature^{20,21,23,24}. Of course, the onus is not only on our patients. Neuman-Sunshine et al demonstrated that even when patients were treated by medical personnel in the ED, not all individuals presenting with severe symptoms and/or respiratory or cardiovascular symptoms received epinephrine²⁰. The reasons underlying these findings are without a doubt many, but fully emphasize the need for improved patient, caregiver, and healthcare professional education regarding appropriate indications for epinephrine use.

Severe and life-threatening peanut reactions

For both physicians and families of individuals affected with peanut allergy, the prospect of a life-threatening reaction may be quite palpable. Of course, not all food reactions are severe. In fact, the rate of reactions requiring ED level care, for all foods, including peanut, appears to be low¹⁴. Capucilli et al. demonstrated this in a large pediatric cohort, where the incidence rate of ED visits secondary to an accidental food reaction was only 0.5% per year²⁸. Peanut, in addition to TNs and milk, however, do repeatedly account for the majority of cases of anaphylaxes either directly leading to a fatal outcome, or other measures of severity including hospitalization, ED visits or ICU admission²⁸⁻³². In Bock et al, for instance, peanut or TN reactions accounted for more than 90% of fatalities³¹, and in a follow-up report to this study, peanut again stood out as a significant allergen associated with fatal anaphylaxis²⁹. Despite increases in FA prevalence, food-related fatalities have remained relatively stable³³. Robust estimates of FA mortality suggest an estimated yearly incidence of 1.81 per million person-years in food allergic individuals, notably lower than the risk of death due to any cause or accident-related death^{15,34}. Thus, relatively speaking, FA-related fatalities are rare, including those related to peanut allergy^{15,33,34}.

The coexisting diagnosis of asthma is a known risk factor in predisposition to a near-fatal or fatal anaphylactic reaction, with poor asthma control reported consistently in cases of food reactions leading to death^{9,33,35}. Diagnosis of asthma, independent of asthma control, however, should be of equal concern to clinicians. In Sampson et al, 12 of 13 children and adolescents with near fatal or fatal anaphylaxis held a diagnosis of asthma that was noted to be well-controlled⁹. Of the 6 children who died, symptom onset was within 3 to 30 minutes after ingestion, though only two received epinephrine within the first hour, reiterating the essential need for early symptoms recognition and prompt administration of epinephrine.

Data regarding FA in the critical care setting had been somewhat limited until recently. In 2018, Pouessel et al reported an initial retrospective analysis of anaphylaxis in the pediatric intensive care unit (ICU) in France based on ICD-10 codes and case validation by physicians³⁰. Similar to previous reports, milk, peanut and TNs accounted for 30%, 27% and 16% of respective anaphylactic reactions involving foods. Additionally, 3 deaths secondary to FA were reported, 2 suspected secondary to peanut. The epidemiology of pediatric anaphylaxis requiring ICU level care was also recently described in North America and Canada by Ramsey et al³². Of the nearly 2,000 patients admitted for anaphylaxis, 39% were secondary to a peanut reaction, accounting for the most common trigger overall. There were 19 fatal outcomes described, 2 of which were secondary to peanut. Intubation within the first hour of presentation (which occurred in 17 of 19 patients) was noted as a potential negative prognostic factor, though further studies are likely needed to validate this factor and to better define management of reactions in this population.

Comparing peanut reactions during oral immunotherapy vs avoidance

Particularly robust data regarding reactions to peanut during avoidance come from recent randomized trials on peanut-specific OIT, comparing efficacy outcomes and adverse events in those enrolled in active arms (receiving peanut OIT) and those in peanut placebo or avoidance groups. The commonly cited rate of anaphylaxis secondary to OIT therapy is 25%, with 5% developing eosinophilic esophagitis (EoE) as a side effect and 10-20% experiencing gastrointestinal symptoms leading to discontinuation of OIT³⁶. To date, 12 prospective trials comparing OIT vs no OIT have been implemented, the safety and efficacy of which have been

recently compiled in a meta-analysis by Chu et al.³⁷. These studies account for a total of nearly 1,000 participants (median age 8.7 years) across eight placebo-controlled trials, three avoidance trials, and one sublingual trial (Figure 1)³⁸⁻⁴⁸. Compared to the non-OIT groups, those undergoing active peanut OIT had significantly higher anaphylaxis risk (risk ratio 3.12), anaphylaxis frequency (incidence risk ratio 2.72), and epinephrine use (risk ratio 2.21). Of the studies reporting anaphylaxis and epinephrine rates, half (n=6) reported no evidence of either anaphylaxis or epinephrine use in the non-OIT groups during the course of the study. Looking specifically at the two trials of peanut OIT vs strict peanut avoidance (as opposed to peanut placebo), zero episodes of anaphylaxis or administration of epinephrine were recorded in the non-OIT group, which lends external validity to the current standard of practice^{47,48}. These data compare to nearly all trials reporting at least one or more cases of anaphylaxis and/or epinephrine use in those undergoing active OIT therapy.

Practical avoidance considerations

Reaction threshold

Practical avoidance of peanut involves an accurate understanding of the amount and means by which exposure can elicit a reaction (Figure 2). To examine this risk, understanding the threshold dose above which an allergic reaction following exposure will likely occur (eliciting dose) is necessary. Eliciting doses (ED) are determined via oral food challenges (OFCs), modeled by threshold dose distributions, and reported as ED1, ED5, ED10, ED50 (doses predicting an allergic reaction in 1%, 5%, 10%, 50% of the allergic population). Several studies

described a higher ED in patients having objective reaction symptoms, compared to those with reactions involving subjective findings^{49,50}. These studies were limited by use of graded protocols, making it difficult to differentiate whether a reaction was the result of a discrete threshold dose or the cumulative dose consumed during the challenge. In 2017, Hourihane et al sought to verify a predicted ED of 1.5 mg peanut protein while also addressing the question of discrete versus cumulative dose in a pediatric population. This single dose OFC resulted in objective reactions in only 8 participants (2% of participants) a rate of reactions that was lower than initially predicted⁵¹. Furthermore, no children experienced more than a mild reaction. Therefore, when considering objective symptoms of a reaction, a 1.5 mg peanut exposure will likely be tolerated in >95% of the peanut allergic population.

Route of exposure

The means by which exposure to peanut can lead to an allergic reaction should be well understood and included in anticipatory education for patients and families with peanut allergy. While reaction secondary to aerosolized food protein is of concern, reactions to peanut by inhalation have been mostly self-reported with the logistical probability of this route being more uncertain^{52,53}. Several studies have since evaluated the prospect of this, including a double-blind, placebo-controlled, randomized challenge by Simonte et al⁵⁴. In this study, 29 patients with peanut allergy were recruited, 37% of whom had reported a previous inhalation reaction. Peanut butter or soy butter placebo (masked for smell) was then held 12 inches from patients' noses for 10 minutes, designed to mimic unintentional casual exposures to peanut odor. Findings were notable for no objective or subjective reactions during inhalation challenge in peanut allergic individuals, and no significant changes in FEV1 for those who underwent spirometry. Perry et al

examined this further by collecting air samples in proximity to participants consuming peanuts, in a series of simulations designed to mimic real life situations. These included proximal peanut butter sandwich consumption, shelling of roasted peanuts, walking on discarded peanut shells, and opening and consuming a large number of peanut bags in close range⁵⁵. Under all simulations, airborne Ara h 1 was undetectable from distances up to 5 to 10 feet away. Similarly, Brough et al collected air samples in proximity to various potential peanut sources, including above a peanut jar, over a simmering pan of peanut sauce, near an individual consuming peanut, and over peanuts being deshelled. In this study, peanut protein above the lower limit of quantification (2.5ug) was only detected 1cm and 1m above peanuts being deshelled at levels of 331 mg/m³ and 4.8 mg/m³ that immediately became undetectable at both heights after deshelling⁵⁶.

Localized allergic reactions to contact on the skin underlies the basis of skin prick testing. However, the correlation between skin contact reactions and subsequent systemic reactions is not well defined, although systemic reactions to foods secondary to cutaneous exposure have been described⁵². More recent data, however, have been contradictory. In the Simonte et al study described above, participants were also assessed for risk of reaction from unintended skin exposure to peanut by applying 0.2 mL of peanut butter or soy butter placebo to the skin for 1 minute, meant to mimic contact to peanut from a poorly cleaned surface⁵⁴. Findings included no patients who experienced systemic reactions, though 2 participants experienced urticaria, 5 experienced pruritus, and 3 experienced erythema only. Similarly, Wainstein et al found that skin application of 1 gram of peanut butter vs placebo in 281 peanut sensitized children lead to no systemic reactions, though 41% of patients did develop local urticarial wheals⁵⁷. Notably, no systemic reactions were sustained in any of the OFC-confirmed peanut allergic participants,

including 4 who had previously experienced peanut-related anaphylaxis. Clark et al demonstrated similar findings in an observational study¹⁹. Of 785 children followed for peanut and TN allergy, all 40 episodes of accidental skin contact reactions were mild. Despite these reassuring data, caregivers should be particularly mindful in children of potential hand-mouth activity, which could precipitate a systemic reaction with proximal exposure. Taken together, the above data demonstrates that contact reactions with peanut tend not to precipitate severe systemic reactions, and that peanut inhalation poses only a theoretical risk that has not been substantiated other than in the transient situation of immediate peanut shelling and does not result in severe systemic reaction.

Allergen food labeling and limitations

The risk of peanut exposure in food products and limitations of food labeling can be a nuanced topic, and anticipatory guidance for patients and caregivers should include relevant discussion as it pertains to avoidance practices. Food labeling legislation has been implemented across most areas of the world, though differences exist regionally⁵⁸. Peanut, however, appears to be universally included in labeling regulations. It is important to note though, in the United States, for example, this labeling is mandated only on packaged foods, and excludes prepared foods or foods from restaurants⁵⁹. As such, food establishments outside of the home pose a particular high risk of reaction for allergic individuals. In the United States peanut and TN Allergy Registry (PAR), 13.7% of registrants reported a sustained reaction in a restaurant or other food establishment. Of the 156 episodes, 67% were secondary to peanut exposure, and occurred across various settings including, Asian restaurants (19%), ice cream shops (14%) and

bakeries (13%). Desserts (43%) were associated with the highest number of AEs, followed by entrées (35%) and appetizers (13%). Especially concerning is the reported 55% of reactions in which restaurant personnel were not alerted of the allergy. Additionally, in 78% of reactions, although FA status was established, visual identification of the allergen was limited in food presentation, preventing identification and potential avoidance⁶⁰. Other identified issues include limited training in FA awareness for food service personnel and few restaurants with separate equipment or food preparation areas designated for allergen-free food⁶¹.

Labeling laws also fail to extend to foods with unforeseen of trace amounts of food allergen, those that may be contaminated by close contact, shared food preparation facilities, or other mechanisms. As such, many food production companies use precautionary allergen labeling (PAL) with phrases such as “may contain,” “may contain trace amounts,” “produced in a factory with,” “manufactured on shared equipment”, “packaged in a shared facility” or “peanut-free,” to warn of the potential presence of unintended food allergens in an otherwise safe product. The potential risk of reaction from individual foods with PAL, however, is difficult to assess, and widespread labeling can be confusing to patients and families^{62,63}. Further, the lack of standardized guidelines for the use of PAL, and the voluntary nature of PAL labeling contributes to difficulties in assessing the safety of these products and establishing consistent recommendations to families^{62,64,65}. Efforts have been taken to better assess peanut content in PAL-labeled products. In 2010, Ford et al found that allergenic food residues could be detected in 5.3% of foods with PAL, compared to 1.9% of similar products without labeling⁶⁵. This difference occurred more often with peanut, compared to egg and milk. Imported products present a potentially greater risk. In one study, for example, 30-60% of imported European chocolate bars contained detectable levels of peanut protein, despite absence of PAL⁶⁶. Further,

food company size appears to play a role with 5.1% of contaminated products originating from smaller companies, compared to 0.75% from large companies⁶⁵.

The implication of these data on family peanut-avoidance practices is important to consider. As discussed in Greenhawt (2018), a survey conducted by a food allergy advocacy group found that 82-90% of over 30,000 respondents indicated that they would never purchase food products with PAL including “may contain” or “shared equipment” statements^{67,68}. Additionally, almost half (47%) of participants in another study attributed AE to a known allergen to inappropriate product labeling or manufacturing labeling error⁶⁹. On the other hand, given the burden of PAL labeling and significant dietary limitations associated, many consumers have been known to ignore PAL statements, sometimes leading to unanticipated reactions⁷⁰. As such, more robust food labeling regulations and improved standardization of safety profiles is likely necessary.

Conclusion

Peanut remains a leading food associated with AEs and unintended food reactions. Notably, peanut (along with TN and milk) often account for the most severe and sometimes fatal FA reactions, though these reactions are rare overall, and factors such as delay in epinephrine administration or comorbid asthma are often contributory. Since peanut allergy tends to persist over time, patients must have a robust understanding of avoidance practices, both in regard to the risk of accidental reactions, but also a sound means to differentiate peanut exposures that can and those that cannot lead to a meaningful allergic reaction. Measures such as providing up to date prescription of injectable epinephrine and thorough review of anaphylaxis management plans are imperative and can reduce the rate of reactions by over 8-fold to 7%¹⁷. In studies of natural

254 history, the rate of reaction is approximately 10% indicating the rate of reactions occur but not as
255 high rate expressed by many families believe. In addition, clinicians need to empower peanut-
256 allergic individuals to differentiate relevant situations in which accidental reactions are more
257 likely to occur vs other situations where individuals can feel safe, so as to minimize the burden
258 on patient and family quality of life. As novel therapies for peanut allergy become commercially
259 availability, clinicians should continue to discuss avoidance as a viable option for long-term FA
260 management. This is particularly important given the significantly higher rates of allergic
261 reaction to therapies such as peanut OIT vs avoidance demonstrated in nearly all clinical trials.

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- 205

Figure 1. Reported anaphylaxis, epinephrine, and adverse event rates during clinical trial period outside of oral food challenge (modified from Chu³⁷). Studies excluded per parameter if no data reported. Abbreviations: OIT, oral immunotherapy

Figure 2. Practical considerations for peanut route of exposure and reactions. *Mean (range) rate of accidental peanut exposure leading to allergic reaction or anaphylaxis¹⁶⁻²⁴. †Mean (range) rate of anaphylaxis secondary to oral immunotherapy³⁶⁻⁴⁸. ‡ Percent of contaminated food products despite precautionary allergy labeling⁶⁵. Contamination rates in precautionary allergy-labeled foods may be higher in imported products (not shown)⁶⁶. Abbreviations: none

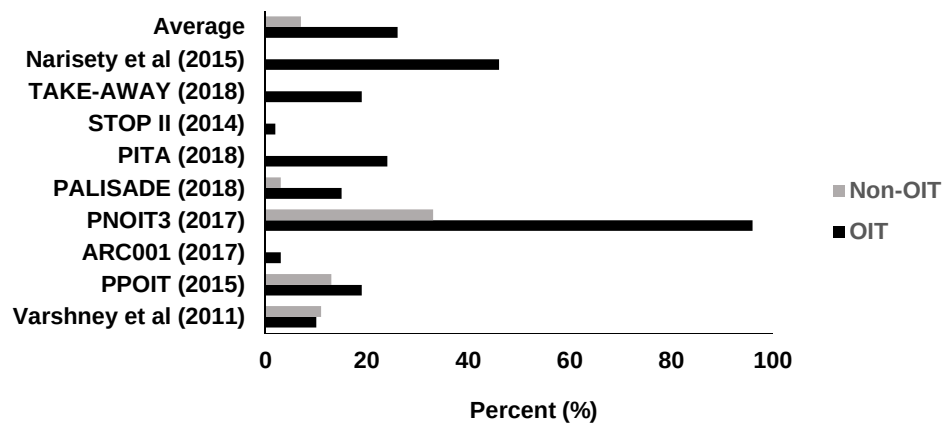
IMAGES WITH ILLUSTRATOR

Table 1: Studies of peanut reactions on avoidance diet in pediatric patients

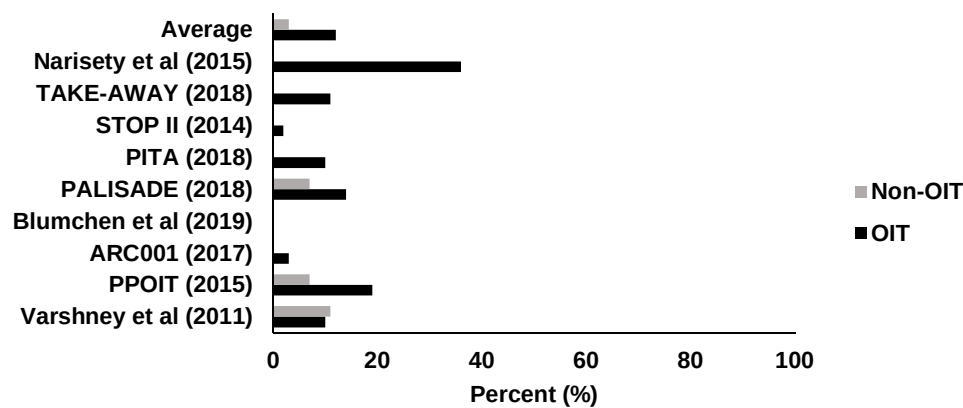
Study	Country	Patients	Inclusion criteria	Annual rate (%)	Routes of exposure	Location	Epinephrine use	Notes
Vander Leek et al (2000) ¹⁶	United States	83	-Clinical reaction or positive DBPCFC and SPT ≥ 3 (100%)	33	N/A	N/A	N/A	
Ewan et al (2005) ¹⁷	United Kingdom	747	-Clinical reaction and SPT ≥ 3 (100%)	55 (pre-management plan); 7 (post-management plan)	N/A	N/A	7% in moderate-severe reactions	Comprehensive management plan and included tree nuts.
Yu et al (2006) ¹⁸	Canada	252	-Positive OFC -Clinical reaction and SPT ≥ 3 mm or IgE ≥ 0.35 kU/L (87 %) -Unclear history or no exposure and SPT ≥ 3 mm AND IgE ≥ 15 kU/L (13%)	14.3	74% ingestion, 20% contact, 3% mucosal	40% home, 34% relative/friend's home, 17% restaurant, 3% daycare/school	50% in severe reactions; 20% in moderate-severe reactions	
Clark et al (2008) ¹⁹	United Kingdom	785	-Clinical reaction and SPT ≥ 3 (100%)	3.1	65% ingestion, 35% contact	53% home, 5% school	9% in moderate-severe reactions	Comprehensive management plan and included tree nuts.
Neuman-Sunshine et al (2012) ²⁰	United States	782	-Positive OFC or clinical reaction and SPT >3 mm or IgE > 14 kU/L (62%) -No history of exposure and IgE >14 kU/L (38%)	7.3	64% ingestion, 19% contact, 9% inhalation	N/A	34% in severe reactions	
Nguyen-Luu et al (2012) ²¹	Canada	1411	-Positive OFC (3.8%) -Clinical reaction and SPT ≥ 3 mm or IgE ≥ 0.35 kU/L (79.8%) -Unclear history or no exposure and SPT ≥ 3 mm AND IgE ≥ 15 kU/L (16.4%)	11.9	65% ingestion, 24% contact, 5% inhalation	40% home, 17% relative/friend's home, 11% restaurant, 10% daycare/school	37% in severe reactions; 21% in moderate-severe reactions	Expanded cohort from Yu et al (2006)
Fleischer et al (2012) ²²	United States	512	-Clinical reaction and positive SPT (60%) -Moderate-Severe atopic dermatitis and positive SPT (milk/egg only) (40%)	6.0	80% ingestion alone, 13% contact alone, 4.5% ingestion and contact, 0.7% inhalation alone, other 0.7%	N/A	7.5% for PN reactions (all severity) 30% for severe reactions to milk, egg or PN	Route of exposure not differentiated for PN; included all foods
Cherkaoui et al (2015) ²³	Canada	1941	-Positive OFC (3.6%) -Clinical reaction and SPT ≥ 3 mm or IgE ≥ 0.35 kU/L (87.5%) -Unclear history or no exposure and SPT ≥ 3 mm AND IgE ≥ 15 kU/L (9%)	12.4	N/A	37% home, 14% relative/friend's home, 9% restaurants, 8% daycare/school	50% in severe reactions; 11% in moderate-severe reactions	Expanded cohort from Nguyen-Luu et al (2012)
Kansen et al (2019) ²⁴	Netherlands	41	-Failed DBPCFC (100%)	49.6	N/A	N/A	0% in severe reactions	
Total/Average		6554		10%*post-FAMP				

Abbreviations: DBPCFC, double-blinded, placebo-controlled food-challenge; FAMP-Food Allergy Management Plan; OFC, oral food challenge; PN, peanut; SPT, skin prick test.

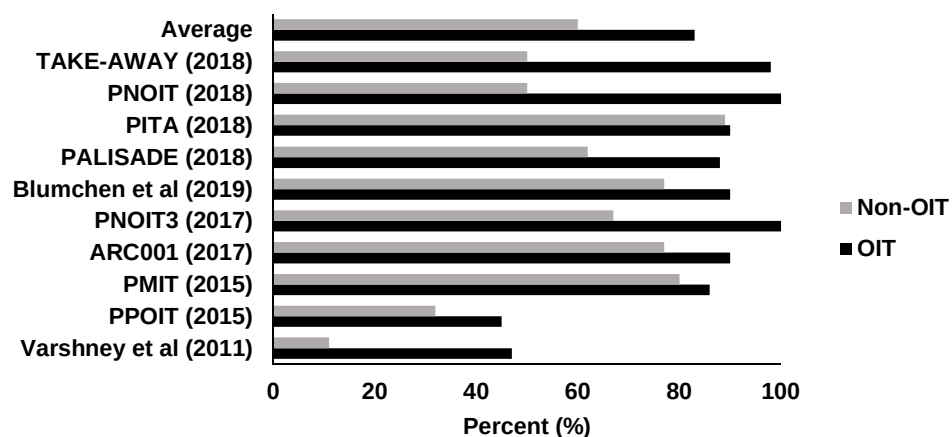
A. Anaphylaxis (%) OIT vs Non-OIT ^{37-43,45-48}



B. Epinephrine (%) OIT vs Non-OIT ³⁸⁻⁴⁸



C. Adverse/Allergic Events (%) OIT vs Non-OIT ^{37-39,41-46,48}



December 20, 2019

Gailen D. Marshall, Jr., MD, PhD
Editor-in-Chief
Annals of Allergy, Asthma & Immunology

Dear Dr. Marshall,

Thank you for reviewing our original manuscript, **“Food reactions during avoidance: focus on peanut.”** We appreciate the chance to resubmit the revised version for further consideration of publication. We sincerely thank the reviewers for their thoughtful comments and believe that their input has allowed us to craft a tighter, more impactful piece. Based on the reviewer comments, we have made significant changes to the manuscript and present the enclosed version with the specific changes as detailed below.

Thank you again for your consideration.

Best regards,

Peter Capucilli on behalf of the authors

A handwritten signature in black ink, reading "Peter Capucilli". The signature is written in a cursive, flowing style.

Peter Capucilli, MD
Division of Allergy and Immunology
Children's Hospital of Philadelphia

Comments from the Reviewers:

Reviewer 1: This is an interesting review with excellent references. However, the article lacks a clear thesis and direction. I think the key message that the authors should focus on and develop further is management of peanut allergy with avoidance versus OIT and the risks of reactions during both of these. The discussions of reactions with casual contact and discussions of allergen labeling are interesting, but are long and shift the focus away from the key points of the article. Additionally, the writing in places is unclear or imprecise, so I recommend addressing this in the revision.

RESPONSE: Thank you for this review and suggestion. We agree that a focus on peanut allergy avoidance vs OIT is a worthwhile comparison for a targeted review. That said, in this particular review, our primary aim is to provide a comprehensive overview of food avoidance in patients at risk for peanut reactions with thorough practical and clinical considerations for both the provider and patient. We feel this discussion warrants inclusion of some of the nuances of reactions associated with casual contact and allergy labeling in addition to OIT. We have made additional changes as ahead to ameliorate some of the writing concerns.

Specific comments:

1. I am not sure the abbreviation "PN" for "peanut" is needed, since it does not save on words.

RESPONSE: All "PN" abbreviations have been changed to "peanut"

2. Line 39: I think there is a typo in "annual rate of 55%-7%"

RESPONSE: Thank you. This sentence has been changed for clarification of a decrease in rate. Line 48 (marked manuscript version).

3. Lines 48-51: I suggest revising these sentences for clarity. I recommend further elaboration or discussion of who deems these areas "safe." It isn't clear to me if this is a perception by the patients or the authors. I do not think "as such" follows with the previous sentence" and the comma following this phrase should be removed.

RESPONSE: Thank you. We have clarified this paragraph within lines 62-65.

4. Line 144-146: I suggest rewording this sentence for clarity. I am not sure what "protects" means in this situation.

RESPONSE: We agree and have reworded this sentence for clarity. Lines 185-186.

5. Lines 147-166: I think a better transition is needed into this segment. While these are important studies, I feel like discussion of casual contact reactions seems out of place with the rest of the article, which is a discussion of accidental exposures and allergic reactions during avoidance versus OIT.

RESPONSE: Thank you for this suggestion. We refer to the above comment regarding the focus of this review. We have improved the transition for this discussion and have included a sub-title heading for the section. Lines 190-191.

6. Line 170: This line should be modified for clarity.

RESPONSE: We agree and have clarified this paragraph, lines 228-230.

7. Line 194: "including" should be "included."

RESPONSE: Thank you, change made.

8. Lines 208-215: These sentences are confusing and somewhat misleading. I recommend revising and rewording.

RESPONSE: Thank you. We have revised this paragraph, lines 332-339.

9. There is a legend for Figure 2 but there is no Figure 2.

RESPONSE: Figure 2 is currently in production with the journal illustrator.

Reviewer 2: This is a well-written, timely, important review as we move into an era where more allergy practices (some with perhaps inadequate resources) are feeling the pressure to implement oral immunotherapy to peanut and other foods because of the increasingly prevalent public opinion that this form of therapy will provide a cure or at least decrease the likelihood and frequency of fatal peanut anaphylaxis. Thus, a review of the available evidence comparing the two approaches and emphasizing the need to continue monitoring reactions and outcomes is necessary, as is the need to reassure those patients who prefer to continue with avoidance only. In addition, this review will likely generate more vigorous debate regarding this topic. My other comment is that a comparison of the cost of the two approaches would be an interesting addition.

RESPONSE: Thank you for these supportive comments. We agree that a discussion of cost comparison between avoidance vs OIT would be worthwhile. We are not aware of any established original data on this topic at the present time and so are unable to include this in the current review, but hope this can be addressed in a future publication.

1 KEY MESSAGES

- 2 • Accidental peanut exposure remains a risk factor associated with avoidance diets in
3 peanut allergic individuals, however, fatal reactions tend to be rare.
- 4 • Proper safety measures such as prescription of up to date injectable epinephrine and
5 anaphylaxis management plans can significantly reduce rates and severity of reactions.
- 6 • Despite patient/caregiver concern, cutaneous contact and peanut inhalation tend not to be
7 associated with severe systemic reactions, though casual exposures in food products,
8 including some of those with precautionary labeling should be anticipated.
- 9 • Rates of anaphylaxis or related adverse outcomes have repeatedly been shown to be
10 higher in individuals pursuing peanut therapy options such as oral immunotherapy
11 compared to avoidance diets.