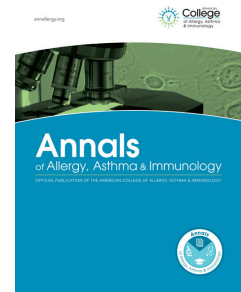


Journal Pre-proof

Post-hoc Analysis of Epicutaneous Immunotherapy for Peanut Allergy Phase 3 results: Relevance for Exposure Through Restaurant Meals

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PII: S1081-1206(20)31218-7

DOI: <https://doi.org/10.1016/j.anai.2020.11.015>

Reference: ANAI 3430

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 28 August 2020

Revised Date: 12 November 2020

Accepted Date: 23 November 2020

Please cite this article as: Remington BC, Campbell DE, Green TD, Fleischer DM, Koppelman SJ, Post-hoc Analysis of Epicutaneous Immunotherapy for Peanut Allergy Phase 3 results: Relevance for Exposure Through Restaurant Meals, *Annals of Allergy, Asthma and Immunology* (2020), doi: <https://doi.org/10.1016/j.anai.2020.11.015>.

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Title:

Post-hoc Analysis of Epicutaneous Immunotherapy for Peanut Allergy Phase 3 results:
Relevance for Exposure Through Restaurant Meals

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Dianne E. Campbell and Todd D. Green are employees of DBV Technologies. Benjamin C. Remington reports grants, travel support, and personal fees from DBV Technologies; and reports travel support from ILSI Europe. David M. Fleischer has served as a consultant for DBV Technologies, AllerGenis, Aquestive Therapeutics, Aravax, Genentech, Nasus, and Intromune Therapeutics, and receives royalties from UpToDate. Stef J. Koppelman reports consultancy fees from DBV Technologies and stock in DBV Technologies.

Funding: This study was in part funded by DBV Technologies.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT02636699

Key words: Peanut allergy; Immunotherapy; Restaurant; Risk assessment; Risk reduction modelling; Threshold

Wordcount: 1085

Figures: none; *Tables:* one

Peanut allergy is the most common persistent food allergy in children and is prevalent in the US¹ and other Western countries. Peanut-induced allergic reactions can be severe and sometimes (though rarely) fatal, as recently reviewed.² Management of peanut allergy relies upon avoiding consumption of peanut and being prepared to treat possible allergic reactions from accidental exposure with rescue medication.³ The difficulty of allergen avoidance is illustrated by the observation that half of all food-allergic patients report experiencing a severe allergic reaction that required emergency department attendance, and about 1 in 5 have had such a reaction in the past year.¹ Eating meals outside the home is an important cause of exposure to peanut, as shown by a retrospective study in Canada where 15 of 40 fatal reactions to peanut occurred at a restaurant or catering setting.⁴ This is further supported by a prospective study of 157 food-allergic patients in the Netherlands, which revealed that meals outside the home were responsible for 24% of allergic reactions.⁵

Immunotherapy for peanut allergy has been demonstrated to increase the reaction threshold (ie, the amount at which an individual experiences an allergic reaction), which is predicted to reduce the risk of reaction to accidental exposure regardless of the means of immunotherapy.³ In a recent phase 3 trial on treating peanut allergy, epicutaneous immunotherapy (EPIT) with a patch containing 250 µg of peanut protein (referred to as 250-µg patch) over a 12-month treatment period in children aged 4-11 years was shown to be superior to placebo in increasing the threshold at which peanut-allergic patients react, and treatment was generally well tolerated and associated with a low rate of serious adverse events (PEPITES trial).⁶ EPIT may thus provide a “buffer” against reactions to accidental peanut exposures, with a favorable safety profile. The study did not meet with lower bound of the confidence interval, which is one potential measure of clinical relevance. The clinical relevance of not meeting this lower bound with respect to the treatment of peanut-allergic children with epicutaneous immunotherapy remains to be determined. Another potential clinical relevance measure is

reduction of risk of experiencing an allergic reaction in a real-world situation such, for example, as eating in restaurant. To calculate the potential reduction in risk for such a situation following treatment with EPIT, we conducted a post-hoc analysis using the baseline and 12-month eliciting dose results (as determined with double-blind placebo-controlled food challenge) from the PEPITES phase 3 clinical trial participants (treatment, n=238; placebo, n=118) which modeled the potential reduction in risk of having a reaction to peanut in a restaurant setting. Three Asian dishes were prepared in a professional kitchen by a chef, and peanut residues on shared kitchen utensils (whisks, tongs, spatulas, soup ladles, spoons) and equipment (wok, sauce pan) were measured after preparation of sauces or single-serve meals as previously reported.⁷ Residue amounts were modeled within a Monte Carlo framework to estimate the 4 different study populations' probability of an allergic reaction (placebo baseline, placebo 12 months, 250- μ g patch baseline, 250- μ g patch 12 months). Risk assessment scenarios included no cleaning and quick cleaning with water rinse or brush (Remington, in press in this Journal, 2020).

When using shared uncleaned materials in the preparation of single-serve meals, baseline absolute risk (AR) of allergic reaction per eating occasion of a contaminated meal varied between 65% (equipment) and 74% (utensils) in active and placebo groups (**Table 1**). Treatment with the 250- μ g patch for 12 months lowered the AR of reaction to 35% to 44%, with no change in risk for placebo group. If shared utensils were quickly rinsed with warm water, baseline AR was 21% to 23%, and treatment with the 250- μ g patch for 12 months lowered the AR to 6%, again with no change in risk for placebo group. Using this approach for single-serve meals, relative risk reduction (RRR) associated with 12 months of the 250- μ g patch treatment was as follows: 40% for scenarios where no cleaning of the utensils occurred and 71% for scenarios involving a quick rinse of utensils in warm water (**Table 1**). For scenarios of contaminated woks or pans, an RRR of 47% was predicted when no cleaning

occurred, and an 86% RRR was predicted if a quick brushing with warm water occurred. The RRR after 12 months of placebo treatment was <4% for all scenarios in the single-serve meal approach.

In an approach where utensils were used to prepare larger volumes of sauce (1 and 5L) meant for multiple servings, RRR obtained by treatment with the 250- μ g patch were shown to be comparable or greater compared to the single meal scenario, with no relevant RRR for placebo (Table 1).

One question is how the RRR is for individuals that do not consume a full serving size. While not all children consume the same amount during a meal, the RRR predicted for one child consuming a given amount remains essentially the same, assuming that the amount consumed is the same at baseline and post-therapy.

Best-practice allergen management requires equipment in restaurants to be cleaned and sanitized before use. However, best-practice allergen protocols are not always followed, as documented by a number of peanut-related allergic reactions involving restaurants.⁸ Not unexpectedly, our study shows a clear risk of allergic reaction in the peanut-allergic population when uncleaned shared kitchen materials are used to prepare an “allergy-free” meal. Our study also predicts that treatment with the 250- μ g patch for 12 months provides a potential buffer against unexpected reactions caused by shared kitchen materials through the RRRs shown in a variety of washing scenarios. It is probable that similar or even greater reductions in risk may arise following successful desensitization to peanut using other modalities, such as oral immunotherapy or sublingual immunotherapy, however the overall benefit/risk of each therapy may vary.

Meals outside of the home, including from restaurants, may be perceived to be at greater risk of cross-contamination than packaged foods due to the number of severe, even fatal, allergic

reactions that have occurred in this setting.^{4,5,9} As expected, the ARs per eating occasion of a contaminated meal in the current study are higher than those previously observed for packaged foods; however, the RRRs predicted by treatment with the 250- μ g patch for 12 months in the current study are similar to those previously found for packaged foods.¹⁰

In a post-hoc analysis using PEPITES study data, we demonstrate substantial modeled risk reduction for allergic reactions from accidental peanut exposures in restaurants among peanut-allergic children after 12 months of EPIT, supporting the potential real-world clinical relevance of this investigational immunotherapy.

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Table 1. Predicted absolute risk for an unexpected allergic reaction and relative risk reductions for the peanut-allergic study population after 12 months of treatment with a 250- μ g patch or placebo patch.

Study Population	Utensils Uncleaned	Utensils Cleaned	Equipment Uncleaned	Equipment Cleaned	1L Sauce Utensils Uncleaned	1L Sauce Utensils Cleaned	5L Sauce Utensils Uncleaned	5L Sauce Utensils Cleaned
Absolute risk percentage *								
Placebo patch population								
Baseline risk	73.5%	23.0%	65.8%	1.2%	27.3%	3.0%	7.0%	0.33%
12-month time point	71.1%	22.6%	63.5%	1.3%	26.8%	3.2%	7.3%	0.40%
250- μ g patch population								
Baseline risk	73.6%	20.7%	65.4%	0.9%	24.9%	2.1%	5.4%	0.17%
12-month time point	44.3%	6.0%	34.8%	0.1%	7.5%	0.3%	0.9%	0.01%
Relative risk reduction percentage * at the 12-month time point								
Placebo patch population	3.2%	1.5%	3.5%	-4.9%	1.9%	-8.2%	-4.8%	-21.3%
250- μ g patch population	39.8%	70.9%	46.8%	86.2%	69.9%	86.0%	83.6%	92.8%

* Absolute risks and relative risk reductions are presented per eating occasion of a single-serve meal prepared with a contaminated kitchen utensil or contaminated equipment, or a kitchen utensil that has come in contact with a contaminated sauce.