

Table 1

Description of Patient's Characteristics, Reactions, Suspected Drug, Intradermal Tests (IDT) Results, and Drug Provocation Tests (DPT)

Patient number	Sex, age	Reported reaction	Suspected PPI	IDT results	DPT
1	F, 40	Urticaria, dyspnea, hypotension (Grade 5 anaphylaxis)	Pantoprazole	Positive to: Pantoprazole 1:10 Omeprazole 1:100 Esomeprazole 1:10 Lansoprazole 1:10 Rabeprazole 1:10	Not performed Treatment with ranitidine
2	M, 69	Urticaria, dyspnea (Grade 3 anaphylaxis)	Omeprazole	Positive to: Omeprazole 1:100 Pantoprazole 1:100 Negative to esomeprazole	Esomeprazole - negative
3	F, 48	Laryngeal edema (Grade 4 anaphylaxis)	Omeprazole	Positive to: Omeprazole 1:100 Negative to pantoprazole and esomeprazole	Esomeprazole – negative
4	F, 49	Urticaria	Esomeprazole	Positive to: Esomeprazole 1:100 Pantoprazole 1:100 Negative to omeprazole	Omeprazole—negative

Abbreviations: F, female; M, male; PPI, proton pump inhibitor.

Bolded text indicates the IBP's that were negative in skin tests were used to perform the drug provocation test, with negative result.

was not observed in this particular patient. Therefore, CR between these drugs remains uncertain.

To our knowledge only 1 published case report has described a case of hypersensitivity to all PPIs (in a patient with anaphylaxis to pantoprazole⁹) and 1 case series of 5 patients with positive skin tests to all PPIs (SPT or IDT) has been reported.¹⁰ In these particular cases, performing skin tests to all PPIs available, and eventually proceeding to a desensitization are important for a better gastric disorder treatment.

Finally, contrarily to previous studies in which SPTs were very useful in diagnosing PPI hypersensitivity (Ozdemir et al⁵ describe positive SPTs in 95% of patients), they were not useful in our series. Our results may have a bias because of our small population. When SPTs are negative, IDT must be performed to identify the culprit PPI. A DPT must follow, considering IDT results.

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References

- Mota I, Gaspar A, Chambel M, Morais-Almeida M. Anaphylaxis induced by proton pump inhibitors. *J Allergy Clin Immunol Pract*. 2016;4(3):535–536.
- Bose S, Guyer A, Long A, Banerji A. Evaluation and management of hypersensitivity to proton pump inhibitors. *Ann Allergy Asthma Immunol*. 2013;111(6):452–457.
- Bonadonna P, Lombardo C, Bortolami O, et al. Hypersensitivity to proton pump inhibitors: diagnostic accuracy of skin tests compared to oral provocation test. *J Allergy Clin Immunol*. 2012;130(2):547–549.
- Otani IM, Banerji A. Immediate and delayed hypersensitivity reactions to proton pump inhibitors: evaluation and management. *Curr Allergy Asthma Rep*. 2016;16:17.
- Kepil Ozdemir S, Yilmaz I, Aydın O, et al. Immediate-type hypersensitivity reactions to proton pump inhibitors: usefulness of skin tests in the diagnosis and assessment of cross-reactivity. *Allergy*. 2013;68:1008–1014.
- Kepil Ozdemir S, Öner F, Ünal D, et al. Management of hypersensitivity reactions to proton pump inhibitors: a retrospective experience. *Int Arch Allergy Immunol*. 2016;171(1):54–60.
- Cernadas JR, Brockow K, Romano A, et al. European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity: general considerations on rapid desensitization for drug hypersensitivity—a consensus statement. *Allergy*. 2010;65:1357–1366.
- Cox L, Sanchez-Borges M, Lockey R. World Allergy Organization systemic allergic reaction grading system: is a modification needed? *J Allergy Clin Immunol Pract*. 2017;5(1):58–62.
- Turedi O, Sozener Z, Kendirlihan R, Baybek S. A case of pantoprazole anaphylaxis with cross reactivity to all proton pump inhibitors: finding a safe alternative. *Curr Drug Saf*. 2017;12(3):198–200.
- Sobrevia E, Garcés S, Ferrer C, Segura A, Monzón B, Colás S. Study of cross-reactivity between proton pump inhibitors. *J Invest Allergol Clin Immunol*. 2010;20(2):157–161.

The Glycerin Associated Pain (GAP) study



Fifty percent glycerin is often used in allergen immunotherapy (AIT) extracts to preserve extract potency.¹ However, glycerin is also an irritant, and it is recommended to dilute glycerin to reduce pain and inflammation associated with immunotherapy.^{2,3} The 2011 allergen immunotherapy practice parameter warns that “higher glycerin concentrations are associated with injection pain, which correlates with the total amount of glycerin injected.”⁴ To date, 2 studies evaluating the role of glycerin during allergen immunotherapy differed regarding their methods and conclusions.^{2,5} We conducted a “real-life” study in

patients receiving conventional AIT to address the limitations of these 2 studies.

This was a prospective, single-blind, controlled study conducted at 2 hospital-based allergy clinics. We recruited adults ages 18 years and older who were scheduled to start AIT with 1 aeroallergen injection with 1 or more allergens. Per protocol, subjects received a second glycerin-only shot in the opposite arm at 12 specific times (at 0.5 mL 1:1000 v/v; 0.5 mL 1:100 v/v; 0.3 mL, 0.4 mL, and 0.5 mL of 1:10 v/v; and 0.05 mL, 0.07 mL, 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL of 1:1 v/v) during their conventional AIT buildup. The participant was blinded to which injection was aeroallergen vs glycerin only. The glycerin shot was composed of 50% glycerin solution (Alk Abello, Round Rock, Texas) and HSA

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Table 1
Pain and Erythema Results

	Glycerin injection n = 133	AIT injection n = 133	P value
Immediate pain			
No pain ^a	61	37	<.001
Mild pain ^a	67	83	.06
Moderate pain ^a	3	8	.22
Severe pain ^a	2	5	.44
Overall pain results ^b			<.001
Pain at 30 minutes			
No pain ^a	117	93	<.001
Mild pain ^a	15	36	<.01
Moderate pain ^a	0	3	.25
Severe pain ^a	0	0	1.0
Overall pain results ^b			<.01
Erythema			
0 mm ^a	117	49	<.0001
1–10 mm ^a	12	25	.03
11–25 mm ^a	1	23	<.0001
26 mm+ ^a	1	36	<.0001

^aχ² analysis.

^bWilcoxon signed-rank analysis.

diluent (Jubilant Hollister Stier, Spokane, Washington) that matched the allergen extract glycerin concentration for each visit. After receiving their injections, participants were asked to rate injection site pain in each arm both immediately and at 30 minutes on a validated numerical rating score from 0 to 10.^{6,7} The scale identifies 0 as “no pain,” 1–3 as “mild pain,” 4–6 as “moderate pain,” 7–9 as “severe pain,” and 10 as “worst possible pain.” Injection site erythema was measured as the longest diameter observed at 30 minutes by an allergen technician blinded to the allergen injection site.

Sixteen participants enrolled in the study, and 12 participants completed the study per protocol. Median age was 37 years (range, 19–64); 75% were men; 72% took an oral antihistamine on the day of their allergen shot visit. Regarding allergen extracts, the median glycerin percentage of the 1:1 v/v vial was 17.5% (range, 5–45), the median mL of 50% glycerin solution in the 1:1 v/v 10 mL vial was 3.5 mL (range, 1–9 mL), and the median allergen content was 4.13 mL (range, 1.5–10 mL). Immediate pain scores were significantly higher from the allergen injection than the glycerin shot ($P < .001$) (Table 1). Glycerin shots were more often rated as 0 (“no pain”) compared with the allergen shot for immediate pain (46% vs 28%) ($P < .001$). Fifty percent of glycerin shots (67/133) were rated as mild pain vs 63% (83/133) in the allergen arm. Allergen injections were reported as moderate or severe pain more often compared with glycerin shots, although these data were not statistically significant (Table 1). Immediate pain scores were analyzed using a linear regression model, and the glycerin dose did not affect immediate pain scores when compared with the allergen dose. The model demonstrated a slope of 5.66 ($P = .003$).

When comparing immediate pain and glycerin content in the maintenance 1:1 v/v injections, 5 of 18 (28%) instances of pain reported occurred from vials with 1%–10% glycerin, 12 of 18 (67%) occurred in vials with 11%–20% glycerin, and 1 of 18 (6%) occurred in a vial with 41%–50% glycerin. No moderate or severe pain scores were reported from vials of 21%–30% or 31%–40% glycerin. At 30 minutes, 89% (117/132) of glycerin shots were rated with a pain score of 0 vs 70% (93/132) of allergen shots ($P < .001$). We also observed a significant difference in the local reaction size after injection between the glycerin and allergen shots. The mean

glycerin local reaction size was 0.8 mm (± 4.3 mm), and the mean allergen local reaction size was 16.6 mm $\pm$ 20.9 mm ($P < .0001$) (Nickel size = 21 mm). A total of 117 of 131 (89%) of glycerin-only shots left no detectable erythema after 30 minutes, and only 1 injection (1/131; 0.7%) resulted in erythema of 26 mm or more. Alternatively, 84 of 131 (64%) of allergen shots were associated with a local reaction; 36 of 84 (43%) were 26 mm or larger (quarter size = 24 mm). However, increased pain was not associated with larger local reactions ($P = .13$). Of the 36 local reactions 26 mm or larger, only 2 were associated with a moderate pain score; 34 were mild. For local reactions larger than 10 mm that occurred in both the glycerin and allergen arms, no increase was found in frequency or diameter with increasing glycerin concentration.

In our study, we observed that increasing glycerin did not correlate with increasing pain or local erythema. The allergen practice parameter states that glycerin concentrations up to 50% are not associated with significantly higher local reaction rates, but higher glycerin concentrations are associated with injection pain.^{2,4} We observed that larger reactions at 30 minutes were rarely associated with clinically significant pain. Eighty-nine percent of the glycerin shots left no measurable erythema, and of the ones that did, 12 of 14 local reactions were 10 mm or larger. Conversely, 63% of the allergen shots were associated with local reactions at 30 minutes; 43% of those reactions being 26 mm or larger. Pain was significantly greater after the allergen shot than the glycerin shot both immediately and at 30 minutes. Finally, our linear regression model, which took into account pain scores, glycerin content, and allergen content in each shot, found that glycerin did not contribute to pain when accounting for the allergen content in the shot. Our study limitations include small numbers of patients and the single blinded protocol. In conclusion, we observed that glycerin was not associated with increased local reactions, pain, or erythema. The allergen acts as an irritant and contributes most to producing injection-associated pain. Thus, allergists should feel comfortable ordering all of their extracts in 50% glycerin and using 50% glycerin as their diluent for their red (1:1 v/v) vial.

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References

- Nelson HS. Effect of preservatives and conditions of storage on the potency of allergy extracts. *J Allergy Clin Immunol*. 1981;67:64–69.
- Van Metre Jr TE, Rosenberg GL, Vaswani SK, Ziegler SR, Adkinson NF. Pain and dermal reaction caused by injected glycerin in immunotherapy solutions. *J Allergy Clin Immunol*. 1996;97:1033–1039.
- Hurst DS, Gordon BR, Krouse JH. The importance of glycerin-containing negative control tests in allergy research studies that use intradermal skin tests. *Otolaryngol Head Neck Surg*. 2002;127:177–181.
- Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127(1 Suppl):S1–S55.
- Calabria CW, Coop CA, Tankersley MS. The GILL study: glycerin-induced local reactions in immunotherapy. *J Allergy Clin Immunol*. 2008;121:222–226.

6. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs*. 2005;14:798–804.

7. Breivik EK, Bjornsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. *Clin J Pain*. 2000;16:22–28.

Implementation of the NIAID Peanut Allergy Guidelines Outcomes and experience



The publication of the Learning Early About Peanut Allergy study in 2015 represented a paradigm shift in the field of food allergy with the finding of an 81% reduction in the incidence of peanut allergy when early introduction of peanut was compared with strict avoidance in high-risk infants.¹ In 2017, the National Institute of Allergy and Infectious Disease (NIAID) provided official recommendations for early peanut introduction with the publication of the Addendum Guidelines to the 2010 Guidelines for Diagnosis and Management of Food Allergy in the United States. These guidelines provide risk stratification for at-home introduction, in-office challenge, or strict avoidance for infants at high risk of peanut allergy based on peanut serum immunoglobulin E and peanut skin prick wheal size.² The limitations of widespread implementation of early peanut introduction, including cost, availability of testing, and availability of allergy specialists, have all been topics of expert discussion.^{3–5} However, few reports have examined the practical outcomes of implementing the NIAID guidelines in the clinical setting.

We performed a retrospective chart review and identified infants seen by 1 of our 5 providers in the Vanderbilt Pediatric Allergy clinic between January 2017 and October 2017 who were given recommendations regarding peanut introduction reflective of the NIAID guidelines. Infants met the following inclusion criteria: 12 months of age or younger at the initial allergy clinic visit, a history of severe atopic dermatitis or a history of egg allergy, no prior history of peanut ingestion, and documentation of peanut skin prick test (SPT). All patients identified were referred by a primary care provider or self-referred for the evaluation of atopic dermatitis or suspected food allergy.

Among 26 infants identified, 54% were male, 58% were white, and median age at initial allergy clinic visit was 9 months. Of the 26 infants, 81% had a history of severe atopic dermatitis as defined by either failure of topical steroids or greater than 50% body surface area involvement, and 58% had a history of egg allergy. History of allergy to foods was reported if a clinical history of an index reaction was present and an SPT to the food showed a wheal size 3 mm greater than a negative control. Seventy-three percent of infants had a history of food allergy, with cow's milk the most common allergy after egg at 27% of infants (eTable 1).

Eight of the 26 infants had an initial peanut SPT wheal size of 0 to 2 mm. Five of these 8 infants underwent an oral food challenge (OFC). In all 5 of these cases, the parents elected in-office challenges after the provider presented the options of at-home introduction vs an in-office challenge. All 5 of these patients passed their OFC. The other 3 families elected to introduce peanut at home.

Fourteen of the 26 infants had an initial peanut SPT wheal size of 3 to 7 mm, and all of these children underwent an OFC. Six of these 14 patients failed their challenge, representing a 43% positive challenge rate. The reactions in 4 of these cases were urticarial only and responded to treatment with an age-appropriate dose of oral H1 antihistamines. Two reactions met criteria for

anaphylaxis and required treatment with intramuscular epinephrine. The remaining 8 patients had negative OFCs, and families were educated on how to regularly integrate peanut into the diet.

Finally, 4 of the 26 infants had a peanut SPT wheal of 8 mm or greater, and all were counseled to strictly avoid peanut (Table 1).

This is an observational study, and, based on search methods available, we were unable to determine how many infants did not have a screening skin prick test to peanut placed despite meeting criteria for early peanut introduction. Also, follow-up information on adherence was not available for all patients. However, despite the small cohort size, specific challenges to successful implementation of the NIAID guidelines can be identified.

First, the median age of the patients at their initial allergy clinic visit was 9 months. This highlights the challenge of identifying and referring the appropriate patients to the closest allergist in a timely manner when the goal age of peanut introduction in this group is 4 to 6 months.

Second, the importance of appropriate preparedness for performing oral challenges in this high-risk patient cohort, which has been previously reported,⁶ is further supported by the reaction rate noted during OFCs at our institution. Forty-three percent of our patients with a peanut SPT wheal between 3 and 7 mm developed immunoglobulin E–mediated type reactions, which is consistent with a reported 42% reaction rate among infants in this wheal size range in a recent study of the implementation of these guidelines in a larger cohort of infants.⁷ Of note, the severity of the reactions in our cohort is higher than previously reported, with 2 of 14 (14%) of those in the 3- to 7-mm peanut wheal size group developing anaphylaxis. The first patient that developed anaphylaxis was a 6-month-old with a peanut SPT of 5 mm, severe atopic dermatitis, and no history of food allergy. The patient developed diffuse urticaria, hoarse cry, and cough after the second step of the OFC. The second patient was 13 months old at the time of the OFC, had a peanut SPT of 3 mm, severe atopic dermatitis, and history of cow's milk protein allergic proctocolitis. The patient developed emesis, urticaria and coarse breath sounds also after the second step of the

Table 1
Outcome Based on Skin Prick Test Size (mm Wheal Diameter)

Peanut introduction	0–2	3–7	≥8
Total, n (%)	8 (30.8)	14 (53.8)	4 (15.4)
Recommendations, n (%)			
At-home introduction	3 (37.5)	0	0
In-office challenge	5 (62.5)	14 (100)	0
Strict avoidance	0	0	4 (100)
Reactions, n (%) ^a			
Total	0	6 ^b (42.9)	N/A
Facial hives	0	3 (21.4)	
Generalized hives	0	1 (7.1)	
Anaphylaxis	0	2 (14.3)	

^aPercentage reported according to number of children advised to introduce peanut.

^bTwo of these patients underwent subsequent successful oral challenges to peanut after peanut component testing had been obtained and was reassuring.

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