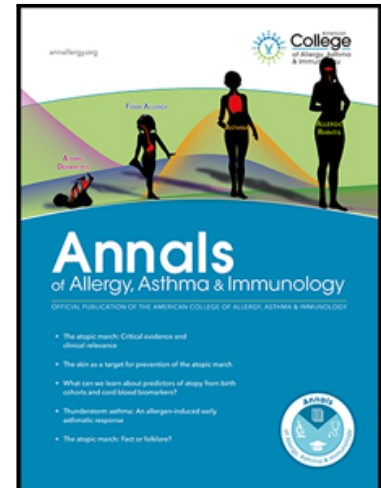


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Title: Polyethylene glycol and polysorbate testing in twelve patients prior to or after COVID-19 vaccine administration

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Abbreviations: FDA: Food and Drug Administration; COVID-19: coronavirus disease 2019; PEG: polyethylene glycol; LNP: lipid nanoparticle; IgE: Immunoglobulin E; mRNA: messenger ribonucleic acid

Immediate allergic reactions compatible with anaphylaxis have been reported severalfold higher with the coronavirus 19 disease (COVID-19) vaccine than other vaccines. It is hypothesized that immunoglobulin E (IgE) mediated reactions to polyethylene glycol (PEG) 2000, an excipient in the mRNA vaccines (such as Pfizer and Moderna) used to stabilize the lipid nanoparticle, are responsible for reported COVID-19 vaccine reactions.¹ COVID-19 vaccine-induced anaphylaxis has only been linked to PEG allergy in few patients to date^{2,3}, with many more patients having allergic reactions, making other mechanisms more likely. Activation of the contact system by the nucleic acid, complement recognition of vaccine-activating allergic effector cells, or direct mast cell activation may lead to similar clinical presentations.⁴

The adenovirus vaccine by Johnson & Johnson does not contain PEG, but contains polysorbate (PS), which is structurally similar and has clinical cross-reactivity.⁵ PEG has not been previously used in a vaccine, but PS is common in vaccines and can cause allergic vaccine reactions.⁶

In addition to being the active ingredient in a commonly used osmotic laxative, PEG is an ingredient in countless products as thickener, solvent, softener, and moisture carrier. While PEG was long considered safe and biologically inert, a growing number of PEG-associated anaphylaxis case reports suggest otherwise.⁵ Most reported adverse events occur on first exposure to a parenteral PEG-containing product, indicating previous sensitization, likely cutaneously.⁷

This study was a retrospective chart review approved by our institution's Institutional Review Board. We describe the clinical histories and skin testing results of twelve cases (Table 1) utilizing previously published recommendations for skin testing indications and procedure.¹ Two patients who developed systemic allergic reactions following first COVID-19 vaccine dose were referred to Allergy and Immunology Clinic for evaluation and underwent PEG and PS skin testing. Many other patients were referred for isolated cutaneous reactions or reactions not believed to be IgE-mediated and did not undergo testing. We also evaluated ten patients with clinical histories concerning for reaction to PEG or PS pre-COVID-19 vaccination. Specific details regarding patients (P) 1-4 will be described herein.

P1 developed symptoms 35 minutes after first COVID-19 Pfizer vaccination. She had pruritic urticaria throughout her chest/neck with dizziness, palpitations, diaphoresis, sense of impending doom, near syncope, hypertension, and tachycardia. She received anti-histamines and corticosteroids in the Emergency Department with symptom resolution within one hour. Epinephrine was not administered. Nine hours post-vaccination, she developed abdominal cramping and diarrhea. Skin testing to PEG and PS was negative (Table 1). Due to severity of her reaction to a PEG-containing vaccine, we recommended she complete her series with a PS-containing vaccine, which she did without complications.

P2 developed symptoms 40 minutes after first COVID-19 Pfizer vaccination. She had pruritic urticaria on her cheeks, mild lip angioedema, dizziness, and globus sensation in her throat. She took anti-histamines without seeking medical care and symptoms mostly resolved within one hour. Skin testing to PEG and PS was negative (Table 1). Of note, the patient has a history of

similar globus sensation previously. Due to her mild symptoms, we recommended that she receive her second Pfizer COVID-19 vaccine, which she did without complications.

P3 was evaluated pre-COVID-19 vaccination due to history of anaphylaxis to high-dose PEG-containing oral combined contraceptives for dysfunctional uterine bleeding. After taking the medication for 4 days, within a few minutes of taking the pill, she developed conjunctival injection, diffuse pruritic urticaria, wheezing, and laryngeal edema with difficulty swallowing. The Emergency Department administered anti-histamines, corticosteroids, and epinephrine, and her symptoms resolved. She tolerated an in-office challenge to an oral contraceptive with similar hormones without PEG. PEG skin testing was positive and PS was negative (Table 1). Due to her confirmed PEG allergy, we advised she receive a PS-containing COVID-19 vaccine, which the family elected not to receive. We suspect that her delayed reaction after 4 days was due to PEG's previously described dose-dependent allergic potential.⁵

P4 was evaluated pre-COVID-19 vaccination due to history of diffuse pruritic urticaria, wheezing, and throat pruritis one hour after taking oral PEG 3350 for the first time for constipation. The Emergency Department administered anti-histamines and corticosteroids. Symptoms resolved quickly. Years later, she had a PEG-containing cough syrup with similar symptoms, including a biphasic reaction. Skin testing to PEG and PS was positive, but patient tolerated PS-containing vaccines previously. She received a PS-containing COVID-19 vaccine without complications.

In our cohort, two patients with systemic allergic reactions to oral PEG had positive skin testing, confirming the correlation between positive skin testing and IgE-mediated reaction to PEG. However, two patients with systemic reactions to a PEG-containing vaccine had negative skin testing, suggesting their reactions were not IgE-mediated reactions to PEG. The remaining eight patients evaluated due to clinical histories compatible with a PEG or PS allergy, though less likely than P3 and P4, all had negative skin testing to PEG and PS, confirming a low false positive rate with PEG skin testing due to irritant reaction. Thus, in our experience, screening pre-vaccination did not yield any positive skin testing results and vaccination was generally well-tolerated. All vaccines administered as a single dose. P4 had positive PS skin testing but tolerated PS, likely due to cross reactivity not reflecting true allergy. Our results suggest that skin testing for PEG and PS following a suspected allergic reaction to a COVID-19 vaccine has limited utility and there are likely other explanations for some reactions that are not PEG IgE-mediated reactions. There has likely been an over-diagnosis and misdiagnosis of systemic allergic reactions to messenger ribonucleic acid (mRNA) COVID-19 vaccines.⁸ P2 demonstrates that some patients with mild anaphylaxis can safely receive the second vaccine, which confirms recent multisite US study,⁹

A major limitation of this study is limited sample size and inability to perform skin testing with the vaccine itself. It would also have been useful to have had tryptase values for P1 and P2 after vaccination (baseline tryptases were normal). However, our results reaffirm similar studies^{1,10} and can guide Allergists & Immunologists in their evaluation of patients pre and post COVID-19 vaccine administration.

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Patient Number	Age Sex	Allergic History	COVID-19 Vaccine History	Allergy Skin Testing
#1	63 Female	Anaphylaxis (Grade 3) to oral penicillin as a teenager. Tolerated PS-containing vaccines and	Evaluated post-vaccination. Anaphylaxis (Grade 3) to the Pfizer COVID-19 vaccine first dose. Second	Negative PEG Negative PS

		oral PEG 3350.	Pfizer dose not administered. Received J&J vaccine without complications.	
#2	60 Female	Tolerated PS-containing vaccines.	Evaluated post-vaccination. Anaphylaxis (Grade 1) to the Pfizer COVID-19 vaccine first dose. Received second Pfizer dose without complications.	Negative PEG Negative PS
#3	18 Female	Anaphylaxis (Grade 4) to high dose combined oral contraceptives containing PEG 8000. History of dermatitis to cosmetics. Tolerated PS-containing vaccines.	Evaluated pre-vaccination. Recommended patient receive PS-containing vaccine. Family chose not to administer the vaccine.	Positive PEG 3350 skin prick (1 mg/ml 10/10 mm, 10 mg/ml 10/15 mm, 100 mg/ml 12/17 mm). Negative PS
#4	27 Female	Anaphylaxis to oral PEG 3350 (Grade 4) and cough syrup containing PEG (Grade 4). Tolerated PS-containing vaccines.	Evaluated pre-vaccination. Patient received J&J vaccine without complications.	Positive PEG 3350 skin prick (1.7 mg/ml 5/10 mm, 17 mg/ml 14/20 mm, 40 mg/ml 11/19 mm, 170 mg/ml 12/20 mm). Negative PS 80 skin prick (40 mg/ml) and positive intradermal (4 mg/ml).
#5	54 Female	History of recurrent idiopathic anaphylaxis. Tolerated PS-containing vaccines.	Evaluated pre-vaccination. Received Moderna vaccine both doses with only side effect being vertigo for 48 hours after 2 nd dose.	Negative PEG Negative PS
#6	52 Female	Urticaria and/or angioedema to multiple oral/injectable medications and contrast. Tolerated PS-containing vaccines and oral PEG 3350.	Evaluated pre-vaccination. Received Pfizer vaccine both doses without complications.	Negative PEG
#7	35	Urticaria to multiple oral	Evaluated pre-vaccination.	Negative PEG

	Female	medications and urticaria after influenza vaccination (unknown if PS containing).	Received Pfizer vaccine both doses without complications.	
#8	60 Female	History of anaphylaxis or urticaria/angioedema to multiple oral and injectable medications. Tolerated PS-containing vaccines.	Evaluated pre-vaccination. Received Pfizer vaccine both doses without complications.	Negative PEG Negative PS
#9	77 Male	History of urticaria to pegylated interferon alfa, tolerates non-pegylated interferon alfa. Tolerated PS-containing vaccines and oral PEG 3350.	Evaluated pre-vaccination. Received Pfizer vaccine both doses without complications.	Negative PEG Negative PS
#10	68 Female	History of anaphylaxis (unknown grade) to taxotere, which contains PS. Tolerated PS-containing vaccines.	Evaluated pre-vaccination. Received Pfizer vaccine both doses without complications.	Negative PEG Negative PS
#11	65 Male	History of allergic reactions to multiple oral and injectable medications.	Evaluated pre-vaccination. Received Moderna vaccine both doses without complications.	Negative PEG Negative PS
#12	65 Female	History of angioedema of mouth to chlorhexidine mouthwash, which contains PEG, anaphylaxis (unknown grade) to swine flu vaccine in 1976 (ingredients unclear).	Evaluated pre-vaccination. Received Pfizer vaccine 1 st dose without complications, scheduled to receive the 2 nd dose.	Negative PEG Negative PS

Table 1. Clinical details for patients. Non-sterile MiraLAX used for PEG prick testing. Sterile methylprednisolone used for PEG intradermal testing and some PS testing. Sterile Refresh eye drops used for most PS testing. PEG 3350 skin prick testing performed with 1 mg/ml, 10 mg/ml, 40 mg/ml, 100 mg/ml concentrations. Intradermal skin testing performed with 0.4 mg/ml and 4 mg/ml concentrations. PS 80 skin prick testing performed with 40 mg/ml concentration and intradermal skin testing performed with 4 mg/ml concentration. Anaphylaxis severity gradings as per “Severity grading system for acute allergic reactions” by Dribin et al. (2021).

Abbreviations: Johnson & Johnson (J&J), polyethylene glycol (PEG), polysorbate (PS).