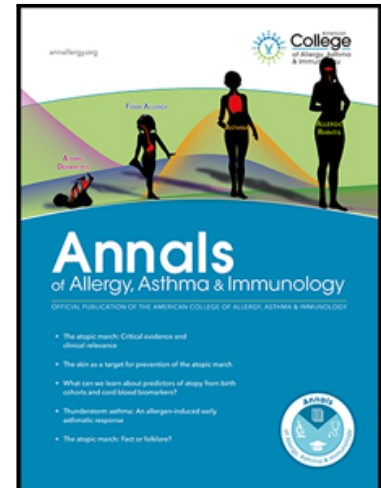


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Mitchell M Pitlick MD , Andrea N Sitek MD , Susan A Kinate PA-C ,
Avni Y Joshi MD , Miguel A Park MD

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**Polyethylene Glycol and Polysorbate Skin Testing in the Evaluation of COVID-19 Vaccine
Reactions: Early Report**

Mitchell M Pitlick, MD¹, Andrea N Sitek, MD¹, Susan A Kinate, PA-C², Avni Y Joshi, MD^{1*},
Miguel A Park, MD^{1*}

¹Division of Allergic Diseases, Mayo Clinic, Rochester, MN, USA

²Division of Allergic Diseases, Mayo Clinic, Scottsdale AZ, USA

Corresponding author

Miguel A Park, MD

Consultant, Mayo Clinic, Division of Allergic Diseases

200 First Street SW

Rochester, MN 55905

Phone: 507-284-3783

Fax: 507-284-0902

Email: park.miguel@mayo.edu

*Co-senior authors

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PEG: polyethylene glycol

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In December 2020, the U.S. Food and Drug Administration (FDA) issued Emergency Use Authorizations for coronavirus disease 2019 (COVID-19) vaccines from Pfizer-BioNTech and Moderna, and widespread vaccination is ongoing. Contraindications to vaccination include a history of immediate allergic reaction to a component or prior dose of an mRNA COVID-19 vaccine.¹ As of January 18, 2021, anaphylaxis to the Pfizer-BioNTech and Moderna vaccines have occurred at rates of 4.7 and 2.5 cases per million doses, respectively.² The mechanism of allergic reaction is unknown, although inactive vaccine components such as polyethylene glycol (PEG) have been proposed as possible culprit antigens.

PEG is a primary ingredient in osmotic laxatives and a widely used excipient in many medications. It has not been previously used in vaccines, and the molecular weight and structure of the PEG 2000 used in the mRNA COVID-19 vaccines is distinct as compared to laxative preparations.³ Allergy to PEG has been described, particularly with higher molecular weight concentrations.⁴⁻⁶ A review of FDA adverse event reports from 2005 to 2017 showed an average of 4 cases of anaphylaxis to PEG per year.⁵ Skin testing has been successfully used to confirm suspected allergy to PEG-containing laxatives and medications, and guidelines for skin testing with non-irritating concentrations of PEG 3350 and polysorbate are available.^{5, 7} Recent expert opinion has also provided an algorithm that includes skin testing as part of COVID vaccine reaction evaluation, but the predictive values of PEG and polysorbate skin testing in relation to risk of hypersensitivity reaction to COVID-19 vaccines are still unknown.⁸ We report the first 15 cases of PEG and polysorbate skin testing completed in patients who had allergic symptoms following their first dose of the mRNA COVID-19 vaccines or reported a PEG/polysorbate allergy prior to their first vaccine dose.

Skin testing was performed in patients referred to the allergy divisions of Mayo Clinic in Rochester, MN and Scottsdale, AZ. The clinical need for skin testing and test selection were provider-determined at the time of evaluation. PEG 3350 (MiraLAX) testing was performed using sequential skin pricks at 1.7 mg/mL, 17 mg/mL, and 170 mg/mL. Methylprednisolone acetate (PEG-containing), methylprednisolone sodium (control), and triamcinolone acetonide (polysorbate 80 containing) testing were performed starting with a skin prick at 40 mg/mL with subsequent 1:100 and 1:10 intradermals with an additional 1:1 intradermal for triamcinolone. Polysorbate 20 testing was performed as a 1:1 skin prick followed by 1:100 and 1:10 intradermals with a 0.5 mg/mL concentration with a sterile water diluent. This study was an IRB-approved retrospective chart review.

Between 1/15/21 and 2/1/21, 15 patients underwent skin testing. 8 had testing due to a reaction to the first dose of COVID-19 vaccine, and 7 had testing prior to vaccination due to reported PEG/polysorbate allergies, the characteristics and skin testing results of which are presented in table 1. All 8 patients with first vaccine dose reactions had negative PEG 3350 testing. 4 patients had methylprednisolone acetate testing, 3 had triamcinolone acetonide testing, and 2 had polysorbate 20 testing, all of which were negative. One patient had a positive polysorbate 20 1:10 intradermal, but a sterile water intradermal resulted in an identical wheal and flare, thus his test was interpreted as false-positive/negative due to irritation. 7 patients successfully received their second COVID-19 vaccine dose without pre-medication or split dosing with the final patient delaying the second dose until vaccine skin testing or split dosing capabilities are available. In the 7 patients with prior PEG/polysorbate allergy, 1 patient had positive testing to PEG 3350 and methylprednisolone acetate with negative testing to methylprednisolone sodium, triamcinolone acetonide, and polysorbate 20. The 6 other patients all tested negative for PEG. 3

patients with expanded skin testing also tested negative for polysorbate 20, methylprednisolone acetate, and triamcinolone acetonide. All 6 patients who tested negative received the first dose of vaccine without any reaction. The patient who tested positive is not yet eligible to receive the vaccine.

This is one of the earliest reports on the utility of skin testing to evaluate both possible COVID-19 vaccine reactions and prior PEG/polysorbate allergies prior to vaccination. In our cohort, only one patient had positive testing. No patients with reactions to their first vaccine dose had positive testing. It may be hypothesized in these cases that PEG is not the culprit antigen or that non-IgE mediated mechanisms such as complement activation related pseudoallergy are involved. Additionally, the short interval between reaction and skin testing may increase the risk of false negatives. A preliminary success has been seen with the safe administration of the second vaccine dose after negative skin testing following a possible first dose reaction. One area of uncertainty is the ability of skin testing to predict COVID-19 vaccine reactions in patients who report prior PEG/polysorbate allergies. Systemic reactions to PEG are dependent on a combination of the molecular weight and absolute amount of PEG in the culprit medication, which can differ significantly between injectable and oral forms of PEG.⁴ Additionally, the threshold needed to induce a systemic reaction likely differs among individuals.⁴ These facts make interpretation of skin tests difficult in patients who have yet to receive a COVID-19 vaccine. An additional area of interest has been the recognition of the innumerable medications and vaccines that contain PEG/polysorbate.⁸ One of our patients with a COVID-19 vaccine reaction also reported a possible reaction to a polysorbate 80 containing influenza vaccine. The magnitude of risk these prior reactions confer upon individuals yet to receive a COVID-19 vaccine, and the ability of skin testing to quantify that risk, remains unclear.

While our cohort size precludes any inferences regarding the predictive value of this skin testing, it is clear that the allergist will play an essential role in the COVID-19 vaccination effort. As vaccination numbers increase, the absolute number of adverse reactions will also increase, which will provide opportunities to both refine testing strategy (with no or limited testing potentially being the best strategy) and address vaccination hesitation, with the ultimate goal being accurate risk stratification and safe vaccine administration to the population as a whole.

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Table 1: Characteristics and Skin Test Results of Patients with Reaction to First COVID-19 Vaccine Dose and Prior PEG/Polysorbate Allergy[^]

Patient	Age/ Sex	Prior Allergic Disease	Culprit Agent(s)	Symptoms	Anaphylaxis [€]	Time to Onset	Treatment	ED	Time to Resolution	Skin Test Performed	Time From Reaction to Skin Test	Skin Test Result	Time Between Vaccine Doses	Vaccine Outcome [¥]
1	24F	None	Pfizer vaccine	Urticaria	No	3 hours	Antihistamines	No	4 days	PEG	12 days	Negative	23 days	No reaction
2	54F	Drug allergy	Pfizer vaccine	Tachycardia, rhinorrhea	No	10 minutes	None	No	10 minutes	PEG, MP acetate	7 days	Negative	18 days	No reaction
3	36F	None	Pfizer vaccine	Facial flushing	No	5 minutes	Antihistamines	No	1 hour	PEG, MP acetate , TC acetoni de PEG	20 days	Negative	21 days	No reaction
4	52M	Venom anaphylaxis	Pfizer vaccine	Oral pruritus, throat fullness	No	Immediate	None	No	5 minutes	PEG	10 days	Negative	21 days	No reaction
5	45F	Food allergy	Pfizer vaccine	Urticaria , throat tightness	No	8 hours	None	No	Unknown	PEG	20 days	Negative	29 days	No reaction
6	33F	Asthma , venom anaphylaxis	Pfizer vaccine	Urticaria , tachycardia	No	15 minutes	Antihistamines	No	12-24 hours	PEG	20 days	Negative	23 days	No reaction

7	20M	Vaccine allergy (Flu)	Moderna vaccine	Angioedema	No	3 hours	Steroids, antihistamines	Yes	24 hours	Expanded	20 days	Negative	N/A	Not given
8	22F	Allergic rhinitis	Moderna vaccine	Angioedema, wheezing, throat pruritus	Level 1	20 minutes	Antihistamines, steroids	Yes	6 hours	Expanded	21 days	Negative	51 days	Minor lip/tongue tingling
9	69M	Drug allergy	Moviprep (PEG)	Rash, flushing	No	During prep	Antihistamines	No	1 hour	PEG	2 years	Negative	N/A	No reaction (Pfizer)
10	73F	Asthma, Drug allergy	Moviprep (PEG)	Headache, nausea	No	Unknown	Unknown	No	Unknown	PEG	5 years	Negative	N/A	No reaction (Moderna)
11	46F	Vaccine allergy (Flu)	Methylprednisolone acetate (PEG)	Urticaria, dizzy, flushing	No	15 minutes	Epinephrine, steroids, antihistamines	No	12 hours	Expanded*	3 months	Positive (PEG and MP acetate) [†]	N/A	Not given
12	74M	Drug allergy	Triamcinolone acetonide (polysorbate 80)	Urticaria, wheezing	Level 1	1 hour	Steroids, antihistamines	Yes	Unknown	PEG, MP acetate, TC acetonide	3 years	Negative	N/A	No reaction (Pfizer)
13	55F	Anaphylaxis	Influenza vaccines [‡] (polysorbate 20/80)	Flushing, wheezing, cough,	Level 1	20 minutes	Epinephrine, steroids, antihistamines	Yes	Unknown	PEG, Polysorbate 20	7 years	Negative	N/A	No reaction (Pfizer)

				throat tightness			mines							
14	67F	Food allergy, anaphylaxis	Miralax (PEG)	Oral urticaria	No	2 hours	Unknown	No	Unknown	Expanded	Unknown	Negative	N/A	No reaction (Moderna)
15	60M	Vaccine allergy (Shingrix)	Shingrix (polysorbate 80)	Flushing, urticaria	No	2 hours	Antihistamines, steroids	Yes	2 days	Expanded	3 months	Negative	N/A	No reaction (Moderna)

[^]Patients 1-8: Reaction to 1st COVID vaccine dose; patients 9-15: No prior vaccine dose, reported prior PEG/polysorbate allergy

[€]Determined by using Brighton criteria⁹

[¥]Refers to 2nd vaccine dose in patients 1-8 or 1st vaccine dose in patients 9-15. All doses given with 30 minute observation period

^{*}Expanded skin testing included PEG, methylprednisolone acetate, methylprednisolone sodium, triamcinolone acetonide, and polysorbate 20

[£]PEG 1:1 skin prick: 5 × 5 wheal, 10 × 10 flare; Methylprednisolone acetate 0.1 mg/mL intradermal: 6 × 6 wheal, 8 × 8 flare

[‡]H1N1, FluBlok, Fluxrix

Abbreviations: PEG: polyethylene glycol; ED: Emergency Department; MP: methylprednisolone; TC: Triamcinolone