Polyethylene glycol and polysorbate testing in 12 patients before or after coronavirus disease 2019 vaccine administration

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 messenger RNA 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] Polyethylene glycol has not been previ-

Table 1
Clinical Details of Patients

Patient number	Age (y)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 oral PEG 3350.	Evaluated postvaccination. Anaphylaxis (grade 3) to the Pfizer COVID-19 vaccine first dosage. Second Pfizer dosage not administered. Received J & J vaccine without complications.	Negative PEG Negative PS
#2	60 Female	Tolerated PS-containing vaccines.	Evaluated postvaccination. Anaphylaxis (grade 1) to the Pfizer COVID-19 vaccine first dosage. Received second Pfizer dosage without complications.	Negative PEG Negative PS
#3	18 Female	Anaphylaxis (grade 4) to high-dosage combined oral contraceptives containing PEG 8000. History of dermatitis to cosmetics. Tolerated PS-containing vaccines.	Evaluated prevaccination. Recommended patient receive PS-containing vaccine. The 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 prevaccination. The patient received the 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 prevaccination. Received Moderna vaccine in both doses with the only adverse effect being vertigo for 48 h after the second dosage.	Negative PEG Negative PS
#6	52 Female	Urticaria or angioedema to multiple oral or injectable medications and contrast. Tolerated PS-containing vaccines and oral PEG 3350.	Evaluated prevaccination. Received Pfizer vaccine in both doses without complications.	Negative PEG
#7	35 Female	Urticaria to multiple oral medications and urticaria after influenza vaccination (unknown if PS-containing).	Evaluated prevaccination. Received Pfizer vaccine in both doses without complications.	Negative PEG
#8	60 Female	History of anaphylaxis or urticaria/angioedema to multiple oral and injectable medications. Tolerated PS-containing vaccines.	Evaluated prevaccination. Received Pfizer vaccine in both doses without complications.	Negative PEG Negative PS
#9	77 Male	History of urticaria to pegylated interferon alfa tolerates nonpegylated interferon alfa. Tolerated PS-containing vaccines and oral PEG 3350.	Evaluated prevaccination. Received Pfizer vaccine in 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 prevaccination. Received Pfizer vaccine in both doses without complications.	Negative PEG Negative PS
#11	65 Male	History of allergic reactions to multiple oral and injectable medications.	Evaluated prevaccination. Received Moderna vaccine in 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 the swine flu vaccine in 1976 (ingredients unclear).	Evaluated prevaccination. Received Pfizer vaccine first dosage without complications, scheduled to receive the second dosage.	Negative PEG Negative PS

Abbreviations: COVID 19, coronavirus disease 2019; J & J, Johnson & Johnson; PEG, polyethylene glycol; PS, polysorbate.
NOTE. Nonsterile MiraLAX used for PEG prick testing. Sterile methylprednisolone was used for PEG intradermal testing and some PS testing. Sterile Refresh eye drops are 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. Skin prick testing for PS 80 was performed with 40 mg/mL concentration and intradermal skin testing was performed with 4 mg/mL concentration.

Disclosures: The authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.

ously 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 typically used osmotic laxative, PEG is an ingredient in countless products as thickener, solvent, softener, and moisture carrier. Although 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 cutaneous.[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 12 cases (Table 1) using previously published recommendations for skin testing indications and procedures.[1] Two patients who developed systemic allergic reactions after the first COVID-19 vaccine dosage were referred to the 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 10 patients with clinical histories concerning reaction to PEG or PS before COVID-19 vaccination. Specific details regarding patients 1 to 4 will be described herein.

Patient 1 developed symptoms 35 minutes after the first Pfizer COVID-19 vaccination. She had pruritic urticaria throughout her chest and neck with dizziness, palpitations, diaphoresis, sense of impending doom, near-syncope, hypertension, and tachycardia. She received antihistamines and corticosteroids in the emergency department with symptom resolution within an hour. Epinephrine was not administered. Nine hours postvaccination, she developed abdominal cramping and diarrhea. Skin testing to PEG and PS was negative (Table 1). Because of the 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.

Patient 2 developed symptoms 40 minutes after the first Pfizer COVID-19 vaccination. She had pruritic urticaria on her cheeks, mild lip angioedema, dizziness, and a globus sensation in her throat. She took antihistamines without seeking medical care and symptoms mostly resolved within an hour. Skin testing to PEG and PS was negative (Table 1). Of note, the patient has a history of similar globus sensation previously. Because of her mild symptoms, we recommended that she receive her second Pfizer COVID-19 vaccine, which she did without complications.

Patient 3 was evaluated before COVID-19 vaccination because of a history of anaphylaxis to high-dosage 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 antihistamines, corticosteroids, and epinephrine, and her symptoms resolved. She tolerated an in-office challenge to an oral contraceptive with similar hormones without PEG. Skin testing to PEG was positive and PS was negative (Table 1). Owing to her confirmed PEG allergy, we advised her to receive a PS-containing COVID-19 vaccine, which the family elected not to receive. We suspect that her delayed reaction after 4 days was because of PEG's previously described dose-dependent allergic potential.[5]

Patient 4 was evaluated before COVID-19 vaccination because of a history of diffuse pruritic urticaria, wheezing, and throat pruritis 1 hour after taking oral PEG 3350 for the first time for constipation. The emergency department administered antihistamines 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 the patient tolerated PS-containing vaccines previously. She received a PS-containing COVID-19 vaccine without complications.

In our cohort, 2 patients with systemic allergic reactions to oral PEG had positive skin testing results, confirming the correlation between positive skin testing and IgE-mediated reaction to PEG. However, 2 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 8 patients evaluated because of clinical histories compatible with a PEG or PS allergy, though less likely than patients 3 and 4, all had negative skin testing to PEG and PS, confirming a low false-positive rate with PEG skin testing because of irritant reaction. Thus, in our experience, screening prevaccination did not yield any positive skin testing results, and vaccination was generally well tolerated. All vaccines are administered in a single dosage. Patient 4 had a positive PS skin test result but tolerated PS, likely because of cross-reactivity not reflecting true allergy. Our results suggest that skin testing for PEG and PS after a suspected allergic reaction to a COVID-19 vaccine has limited use and there are likely other explanations for some reactions that are not PEG IgE-mediated reactions. There has likely been more than a diagnosis and misdiagnosis of systemic allergic reactions to messenger RNA COVID-19 vaccines.[8] Patient 2 has exhibited that some patients with mild anaphylaxis can safely receive the second vaccine, which confirms a recent multisite study in the United States.[9]

A major limitation of this study is the 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 patients 1 and 2 after vaccination (baseline tryptases were normal). However, our results reaffirm similar studies[1,10] and can guide allergists and immunologists in their evaluation of patients before and after COVID-19 vaccine administration.

Taya Carpenter, DO[*]
Justin Konig, MD[†]
Jillian Hochfelder, MD[*,‡,§]
Subhadra Siegel, MD[*,‡,§]
Melissa Gans, MD[‖]
[*] *Department of Pediatrics*
Maria Fareri Children's Hospital at Westchester Medical Center
Valhalla, New York
[†] *Department of Internal Medicine*
Westchester Medical Center
Valhalla, New York
[‡] *Division of Pediatric Pulmonology, Allergy and Immunology, and Sleep Medicine*
Boston Children's Health Physicians
Valhalla, New York
[§] *New York Medical College*
Valhalla, New York
[‖] *Department of Pediatrics, Division of Allergy and Immunology*
University of Miami, Miller School of Medicine
Miami, Florida
CarpenterT@wcmc.com

References

1. Banerji A, Wolfson AR, Wickner PG, et al. COVID-19 vaccination in patients with reported allergic reactions: updated evidence and suggested approach. *J Allergy Clin Immunol Pract*. 2021;9(6):2135–2138.
2. Kuehn BM. Rare PEG allergy triggered postvaccination anaphylaxis. *JAMA*. 2021;325(19):1931.
3. Sellaturay P, Nasser S, Islam S, Gurugama P, Ewan PW. Polyethylene glycol (PEG) is a cause of anaphylaxis to the Pfizer/BioNTech mRNA COVID-19 vaccine. *Clin Exp Allergy*. 2021;51(6):861–863.
4. Risma KA, Edwards KM, Hummell DS, et al. Potential mechanisms of anaphylaxis to COVID-19 mRNA vaccines. *J Allergy Clin Immunol*. 2021;147(6):2075–2082.e2.

5. Stone CA, Liu Y, Relling MV, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. *J Allergy Clin Immunol Pract*. 2019;7(5):1533–1540.e8.
6. Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. *BMJ Case Rep*. 2012;2012. bcr0220125797.
7. Zhou ZH, Stone Jr CA, Jakubovic B, et al. Anti-PEG IgE in anaphylaxis associated with polyethylene glycol. *J Allergy Clin Immunol Pract*. 2021;9(4):1731–1733.e3.
8. Kelso JM. Misdiagnosis of systemic allergic reactions to mRNA COVID-19 vaccines. *Ann Allergy Asthma Immunol*. 2021;127(1):133–134.
9. Krantz MS, Kwah JH, Stone CA Jr, et al. Safety evaluation of the second dose of messenger RNA COVID-19 vaccines in patients with immediate reactions to the first dose [e-pub ahead of print]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2021.3779, accessed September 15, 2021.
10. Pitlick MM, Sitek AN, Kinate SA, Joshi AY, Park MA. Polyethylene glycol and polysorbate skin testing in the evaluation of coronavirus disease 2019 vaccine reactions: early report. *Ann Allergy Asthma Immunol*. 2021;126(6):735–738.

Evaluation of anaphylaxis risk by skin testing with coronavirus disease 2019 messenger RNA vaccines on patients with anaphylaxis

Vaccination has been found to be effective in reducing the risks of infection of severe acute respiratory syndrome coronavirus 2 and severe coronavirus disease 2019 (COVID-19) outcomes. In the United States, Pfizer-BioNTech and Moderna COVID-19 vaccines (aka the messenger RNA [mRNA] vaccines) have been used safely for these purposes.[1,2] First postmarket reports on the use of these vaccines describe 4.7 cases of anaphylaxis per million doses of Pfizer vaccine and 2.5 cases per million Moderna doses given.[3] These early reports also describe 43.8 cases of nonanaphylactic allergic reactions per million Pfizer doses given.[4] Among individuals who experienced anaphylaxis to the Pfizer vaccine, 81% had a documented history of allergies triggered by drugs, vaccines, medical products, foods or insect stings, and 33% of these individuals experienced anaphylaxis in the past. Similarly, 90% of individuals with a history of anaphylaxis to the Moderna vaccine had a documented history of allergic reactions, and 50% of these individuals experienced anaphylaxis in the past.

The presumed causes of allergic reactions are the different polyethylene glycols (PEGs) in the mRNA vaccines. Although PEG allergy is rare, PEG has been found to cause anaphylaxis.[5] Moreover, skin testing of PEGs of differing molecular weights has been found to be effective in confirming anaphylaxis to PEGs in patients with a documented history of anaphylaxis to PEG.[6] Nevertheless, in a cohort of 8 individuals with allergic reactions to the first dosage of an mRNA vaccine, PEG skin testing result was found to be negative.[7]

The 2012 vaccine practice parameters published by the American Academy of Allergy, Asthma, and Immunology (AAAAI), recommend that individuals with suspected anaphylaxis to a particular vaccine receive skin testing with that vaccine to evaluate their risk of anaphylaxis.[8] Because the mRNA vaccines contain components other than PEG that may cause allergic reactions, the AAAAI recommendations for evaluating risk of anaphylaxis to vaccines are appropriate for the mRNA vaccines as well. In fact, Greenhawt et al[9] recently suggested using the 2012 parameters for patients with a previously documented allergy to one of the mRNA vaccines.[9]

Many of our patients who have experienced anaphylaxis express hesitancy toward receiving vaccines, owing to fears of anaphylaxis, and continue to delay their COVID-19 vaccination. To meet this demand, we offered skin testing with mRNA vaccines for our patients who requested evaluation of their risk of anaphylaxis.

In this communication, we will describe our first 30 patients (female, n = 27; male, n = 3) who had skin testing with the mRNA vaccines. The patients were either self-referred or referred to us by other physicians. All patients had a self-reported history of anaphylaxis to a variety of substances, including foods, venoms, drugs, environmental, flu vaccine, unknown sources or the first dosage of a COVID-19 mRNA vaccine. The risks and benefits of skin testing were discussed with the patients, and consent forms were accordingly signed. The patients were probed for self-reported reactions to PEG-containing products (ie, toothpaste and colonoscopy preparation). Ages of the patients ranged from 27 to 80 years. Of the patients, 2 had a history of COVID-19 confirmed by polymerase chain reaction testing.

Skin testing occurred from January 22, 2021, to March 25, 2021. Remnants of the mRNA vaccines were collected on the morning of testing from the Johnson City Medical Center in coordination with the Tennessee Department of Health and used for skin testing within 6 hours from opening of the vials. The patients were advised to refrain from using antihistamines and oral glucocorticoids starting 3 days before the testing. Skin testing was performed on the ventral forearms of the patients using the protocol recommended by the AAAI with modifications to increase safety. Testing began with standard histamine and normal saline applied by prick technique and by intradermal injection of 0.05 mL of each as positive and negative controls, respectively. Next, a 1:10 dilution with normal saline of the Pfizer or Moderna vaccine was applied by prick technique. After 20 minutes, wheal sizes were measured and recorded. Whenever the result was negative, every 20 minutes a dosage of 0.05 mL of diluted vaccine was applied intradermally, starting with a 1:1000 dilution, then a 1:100 dilution, and finally a 1:10 dilution. After recording the final wheal size, pictures of the skin tests were taken, the patients were observed for an additional 30 minutes, and they were requested to submit pictures of their skin test at 4 to 6 hours after testing to evaluate late-phase reactions and at 24 hours after testing to evaluate delayed reactions. Afterward, the patients were evaluated by direct interviews for their reaction to subsequent vaccination.

The results are presented in Table 1. There were 5 patients who had positive immediate skin reactions at doses ranging from 1:100 to 1:10 dilution of an mRNA vaccine. Of these patients, 1 had an anaphylactic reaction during skin testing of 1:100 dilution of the Moderna vaccine. These 5 patients also had positive late-phase reactions. There were 6 patients who had late-phase reactions without immediate reactions. Unfortunately, most patients did not comply with our request to submit pictures from delayed reaction. Patients with positive immediate reactions were recommended to receive the Janssen COVID-19 vaccine. Patients with negative immediate reactions (n = 25) were recommended to receive their choice of COVID-19 vaccine. None of the patients with negative skin test result to an mRNA

Disclosures: The authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.