Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccination counseling with and without excipient skin testing in patients with suspected allergic reactions to mRNA COVID-19 vaccines and patients with atopy

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Background: Allergic reactions have been reported with mRNA vaccines for COVID-19 prevention. Patients perceived to be at higher risk for a reaction may be referred to an allergist, although evaluation strategies may differ between allergists.
Objective: Our aim was to determine outcomes of COVID-19 vaccinations in patients evaluated by an allergist using different approaches.
Methods: We conducted a retrospective case series evaluation of 98 patients seen at the University of Michigan Allergy Clinic for concerns regarding COVID-19 vaccination. Of these 98 patients, 34 underwent skin testing with polyethylene glycol (PEG) 2000 with or without PEG 3350/polysorbate 80 testing.
Results: Of the 34 patients on whom skin testing was performed, 16 underwent testing before vaccination and 18 underwent testing after a reported vaccine-related event. One patient had a positive skin testing result in response to PEG 3350 following a vaccination reaction and natural infection and was advised against a second dose. One patient with a significant history concerning of anaphylaxis in response to PEG had positive results of testing to identify allergy to PEG 2000, PEG 3350, and polysorbate 80 and was advised against vaccination. Of the 98 patients, 63 (64%) tolerated COVID-19 vaccination without complication after evaluation by an allergist.
Conclusion: No significant differences were found between vaccination counseling with and without skin testing to excipients. Patients who presented before the first dose of vaccination were more likely to proceed with COVID-19 vaccination and tolerate vaccination without complication. (J Allergy Clin Immunol Global 2022;1:209-16.)

Key words: *COVID-19 vaccine, vaccine allergy, polyethylene glycol, polysorbate 80*

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a pathogenic coronavirus that emerged in December of 2019.[1] Since then, SARS-CoV-2 has spread rapidly across the globe, resulting in the coronavirus disease 2019 (COVID-19) pandemic.[1] To combat this pandemic, several vaccines have been developed.[2] In the United States, the available vaccines include 2 mRNA-based COVID-19 vaccines, the Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) vaccines, as well as the adenovirus vector–based Janssen JNJ-78436735 vaccine.[3-5] Despite the high effectiveness of the COVID-19 vaccines, the fact that their rollout was followed by reports of immediate and delayed reactions, including anaphylaxis,[6] prompted recommendations from the US Centers for Disease Control and Prevention contraindicating COVID-19 vaccines in patients with a history of an immediate allergic reaction to the first dose of a vaccine or to vaccine excipients such as polyethylene glycol (PEG), which is found in mRNA vaccines, or polysorbate 80, which is found in the Janssen vaccine.[6] This has generated significant patient and provider concern about the safety of these vaccines, particularly in those with a history of atopy. Many individuals are now seeking recommendations regarding COVID-19 vaccination from allergists, but evaluation and recommendations may vary between physicians. Here we present our early experience counseling patients with atopy on mRNA COVID-19 vaccination and evaluating patients with adverse events attributed to mRNA COVID-19 vaccination.

METHODS

We conducted a retrospective case series evaluation of patients presenting to the University of Michigan allergy clinic for vaccine counseling from December 11, 2020, to April 30, 2021. Patient charts were identified for review in the electronic health record via the vaccine counseling diagnosis In all, 98 medical records with patients receiving vaccine counseling related to COVID-19 vaccines were identified (Fig 1). This encompassed patients referred for evaluation by other health care providers as well as self-referrals. Patients may have been evaluated after an adverse event related to vaccination or before any vaccination. Medical records were reviewed for demographic data (including age, ethnicity, biologic sex), serum tryptase level, atopic comorbidities, history of

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Supported in part by the National Center for Advancing Translational Sciences for the Michigan Institute for Clinical and Health Research (grant UL1TR002240 [to J.P.T.]).
Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication March 7, 2022; revised May 12, 2022; accepted for publication May 24, 2022.
Available online August 13, 2022.

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2772-8293

https://doi.org/10.1016/j.jacig.2022.05.012

Abbreviations used

COVID-19: Coronavirus disease 2019
DMG-PEG 2000: 1,2-Dimyrtistoyl-rac-glycero-3-methoxypolyethylene glycol-2000
NF: National Formulary
PEG: Polyethylene glycol

COVID-19 infection before vaccination, allergy testing outcome of allergy evaluation, and tolerance of further COVID-19 vaccination. The requirement for allergy testing was determined at the discretion of the patient's treating allergist and mutual decision making with consideration for patient preference. 1,2-Dimyrtistoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (DMG-PEG 2000) was obtained from Avanti Polar Lipids (Alabaster, Ala). We reconstituted 1 g of DMG-PEG 2000 in 10 mL of sterile diluent for allergenic extracts (normal saline 0.9%, phenol 0.4%, and human serum albumin 0.03%). This solution was filtered using a 0.22-μm sterile syringe filter (Millex-GP). Skin prick testing with 100 mg/mL of sterile filtered DMG-PEG 2000 was performed in 5 healthy controls to establish 100 mg/mL as a nonirritating concentration. Polysorbate 80 National Formulary (NF) (Letco Medical) was supplied by the University of Michigan central pharmacy. Skin prick testing was performed with undiluted polysorbate 80 NF in 5 healthy controls to establish undiluted polysorbate 80 NF as a nonirritating concentration. Skin testing to PEG 3350 (via MiraLAX) and methylprednisolone acetate (via Depo-Medrol) was modeled after the protocol published by Banerji et al.[7] Intradermal testing to identify allergy to PEG 3350 was performed using methylprednisolone acetate. Grading of the testing was based on previously accepted norms (a wheal size of 3 mm or more compared with the negative control, associated with a flare).

Adverse event history was characterized as immediate (defined per the US Centers for Disease Control and Prevention as occurring within 4 hours of vaccine administration) or delayed (defined has having an onset 4 hours or more after vaccination). To compare vaccination counseling strategies, patients were placed into 1 of 4 different groups (Fig 1). These groups were based on when the patient received vaccination counseling (before vaccination or after an adverse event attributed to COVID-19 vaccination) and whether the patient underwent skin testing by the evaluating allergist. The 4 groups were as follows: (1) patients who received vaccination counseling with skin testing before vaccination, (2) patients who received vaccination counseling with skin testing after reporting an adverse event related to vaccination, (3) patients who received vaccination counseling without skin testing before vaccination, and (4) patients who received vaccination counseling without skin testing after an adverse event related to vaccination.

Descriptive statistics were reported using means and SDs for continuous variables and frequencies and percentages for categoric variables. Comparisons were made using the Kruskal-Wallis test for continuous variables and the chi-square test (or Fischer exact test where appropriate) for categoric variables. Analyses were performed in SAS, version 9.4 (TS1M7).

The University of Michigan institutional review board reviewed and exempted the study.

RESULTS

Of the 98 patients reviewed, 51 presented after the first dose of one of the mRNA vaccines and 47 presented before any vaccination. Skin testing was performed in 34 patients: 18 of the 51 who presented after the first dose and 16 of the 47 who presented before the first dose. Most of the patients were female (Table I). Those patients who presented before vaccination were more likely to be older than 50 years; have a history of atopy (most commonly allergic rhinitis and drug allergy); and more likely to have a history of anaphylaxis or history of adverse symptoms related to injectable medications, vaccines, PEG exposure, or polysorbate exposure.

Vaccination counseling with skin testing before COVID-19 vaccination

Table I summarizes the demographic characteristics, allergy evaluation results, and outcomes for 16 patients who presented to our clinic before receiving the Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) vaccines and underwent allergy skin testing. Four of the 16 patients (25%) reported a history of adverse effects attributed to an injectable medication or vaccine, and all 16 reported a history of adverse symptoms thought to be related to PEG or polysorbate exposure. Six patients had a history of anaphylaxis due to either a vaccine or a drug containing polysorbate or PEG, 3 patients had onset of symptoms immediately (within 4 hours) after drug exposure, 3 patients had delayed onset of symptoms after drug exposure (more than 4 hours), and 4 patients did not have specific data regarding the timing of symptoms after drug or vaccine exposure. All 16 patients underwent skin testing with PEG 2000. One patient had a positive skin test result. Of the 16 patients, 10 (63%) underwent skin testing to PEG 3350 via MiraLAX and 1 patient had a positive result. Eight of 16 (50%) of patients underwent skin testing to polysorbate 80, and 1 had a positive result. Two patients underwent skin testing to methylprednisolone acetate; 1 had a positive result. Vaccination was recommended for 15 of the 16 patients (94%) after allergy evaluation. One of the 16 was counseled against vaccination because of a history of anaphylaxis related to PEG in conjunction with a positive result of skin testing to all forms of PEG and polysorbate. In all, 15 patients were counseled to receive vaccination under monitored conditions. Of these 15 patients, 10 (67%) underwent vaccination with an mRNA vaccine without any report of an immediate allergic reaction. Of the 15 patients, 1 received the Janssen vaccine, 4 received the Pfizer vaccine, and 6 patients received the Moderna vaccine. Four patients had no record of receiving further COVID-19 vaccination.

Vaccination counseling with skin testing after an adverse event attributed to COVID-19 vaccination

Table I summarizes the demographic characteristics, allergy evaluation, and outcomes for 18 patients who presented to our clinic after an adverse event attributed to either the Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) vaccine and underwent allergy skin testing. Of the 18 patients, 17 (94%) received the Pfizer vaccine and 1 received the Moderna vaccine. One patient presented following a reaction to the second dose after having tolerated the first dose of the Pfizer vaccine. Of the 18 patients, 13 (72%) had immediate onset of symptoms after vaccination (8 patients had onset of symptoms within 5 minutes of vaccination, 4 patients within 1 hour of vaccination, 1 patient within 2 hours of vaccination, and 5 patients 4 or more hours after vaccination). The symptom reported by patients most frequently was throat swelling. Many patients also reported symptoms involving the face, lips, and mouth (including swelling, tingling, and itching). After throat swelling, vertigo, rash, and urticaria were the next most frequently described symptoms. Gastrointestinal symptoms were less common. All 18 patients underwent skin testing to PEG 2000; none had a positive result. Of the 18 patients, 12 (67%) underwent skin testing to PEG 3350 via Miralax; 1 had a positive result. Twelve of the 18 patients (67%) underwent skin testing to polysorbate 80; none had a positive result. Six of 18

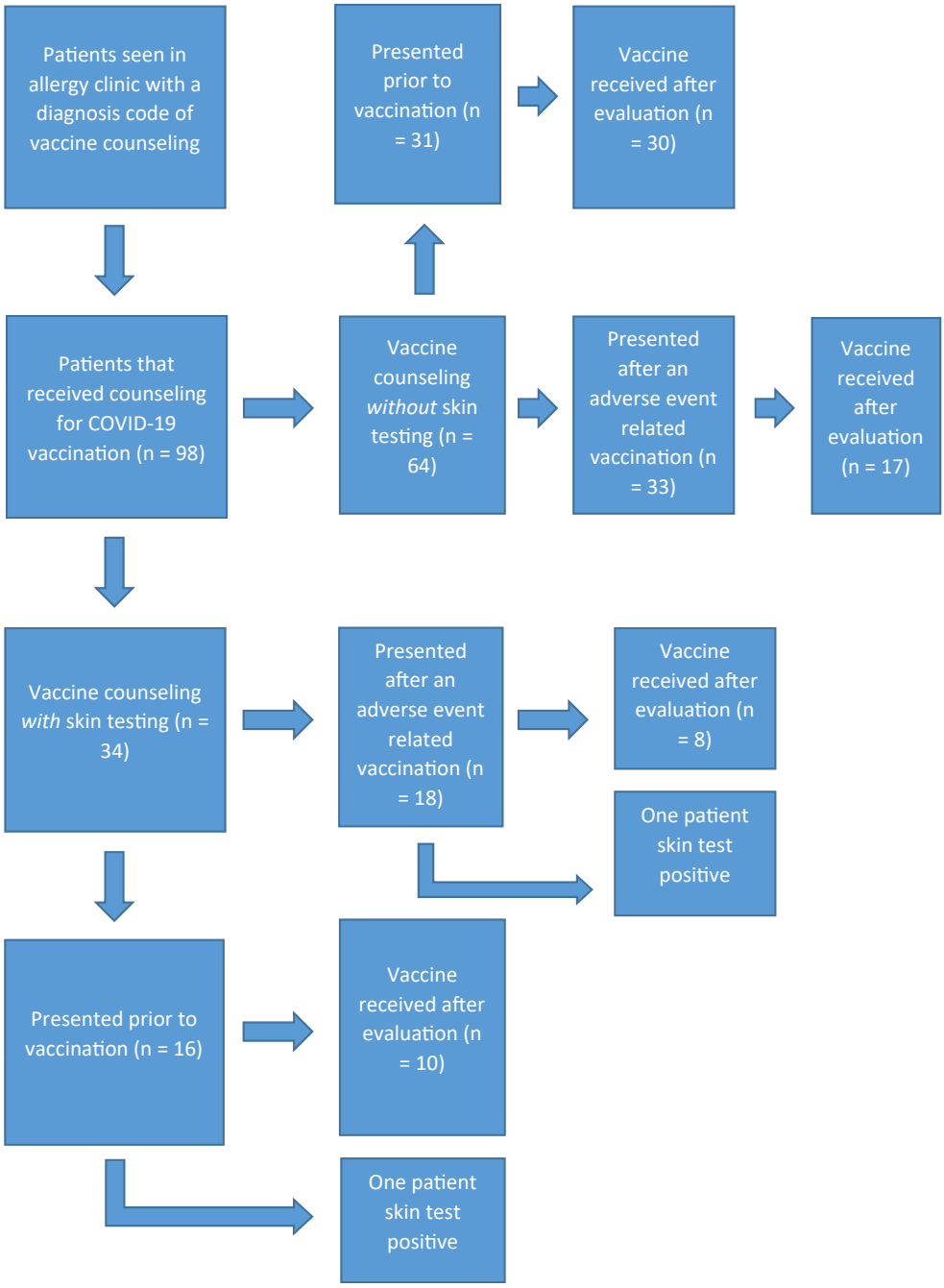

FIG 1. Flowchart of the study.

patients (33%) underwent skin testing to methylprednisolone acetate; none had a positive result.

The treating allergist of 13 of the 18 patients recommended proceeding with further vaccination.

Of the 5 patients given a recommendation against further vaccination, 1 had a positive result of skin testing to PEG 3350, 1 had persistent symptoms following vaccination after a skin biopsy suggestive of a hypersensitivity reaction, and 3 had histories highly concerning for anaphylaxis (acute onset of respiratory and cutaneous symptoms after vaccination, with improvement in their symptoms after administration of epinephrine, corticosteroids, and antihistamines). Of the 13 patients given a recommendation to proceed with vaccination, 7 (54%) underwent vaccination without any adverse effects reported, 5 had no record of proceeding with mRNA COVID-19 vaccination, and 1 had a negative result of skin prick testing to PEG 2000 but developed symptoms of an immediate allergic reaction after the second dose of the Pfizer vaccine. This patient had an event-related tryptase level that did not show any elevation from baseline (5.7 ng/mL). This patient did not have a severe adverse event, and the symptoms were the same as the previous symptoms but more rapid in onset.

TABLE I. Vaccination counseling with skin testing

Patient characteristic	Tested before vaccination (n = 16)	Tested after adverse event (n = 18)	*P* value
Age (y), mean ± SD	69.6 (16.9)	45.3 (18.3)	.02
Female sex, no. (%)	12 (75)	16 (89)	.39
Race, no. (%)			.73
African American	0 (0)	1 (6)	
Asian	1 (6)	0 (0)	
White	15 (94)	17 (94)	
Atopic history, no. (%)			
Food allergy	4 (25)	5 (28)	.99
Drug allergy	11 (69)	7 (39)	.10
Allergic rhinitis	10 (63)	5 (28)	.08
Urticaria	0 (0)	1 (6)	.99
Asthma	3 (19)	2 (11)	.64
Contact dermatitis	0 (0)	3 (17)	.23
Angioedema	0 (0)	1 (6)	.99
Baseline tryptase level (ng/mL), mean ± SD	4.5 ± 0.2 (n = 2)	4.3 ± 2.2 (n = 10)	.52
Adverse symptoms with prior vaccines or injectable medications, no. (%)	4 (25)	2 (11)	.39
Adverse symptoms related to polyethylene glycol or polysorbate in the past, no. (%)	16 (100)	2 (11)	<.001
History of prior known COVID-19 infection, no. (%)	0 (0)	1 (6)	.99
Vaccine received, no. (%)			
J&J	1 (6)	0 (0)	
Moderna	6 (38)	2 (11)	
Pfizer	4 (25)	16 (89)	
None	5 (31)	0 (0)	
Description of adverse event, n (%)			
Throat swelling	—	8 (44)	—
Vertigo	—	6 (33)	—
Rash	—	4 (22)	—
Urticaria	—	4 (22)	—
Throat itching	—	3 (17)	—
Lip tingling	—	3 (17)	—
Lip swelling	—	2 (11)	—
Headache	—	2 (11)	—
Dyspnea	—	2 (11)	—
Throat discomfort	—	2 (11)	—
Tongue swelling	—	2 (11)	—
Eye swelling	—	1 (6)	—
Diarrhea	—	1 (6)	—
Fever	—	1 (6)	—
Nausea	—	1 (6)	—
Vomiting	—	1 (6)	—
Vasovagal	—	1 (6)	—
Burning and pain of skin	—	1 (6)	—
Flushing	—	1 (6)	—
Face tingling	—	1 (6)	—
Hand itching	—	1 (6)	—
Mouth tingling	—	1 (6)	—
Face itching	—	1 (6)	—
Eye itching	—	1 (6)	—
Chest pain	—	1 (6)	—
Cough	—	1 (6)	—
Dose of mRNA vaccine recommended, no. (%)	15 (94)	13 (72)	.18
Received vaccine after allergy evaluation, no. (%)	10 (67)	8 (44)	—
Skin testing, no. of patients with negative test results*			
PEG 2000 1:1000 SPT	8 of 9	0 of 0	—
PEG 2000 1:100 SPT	9 of 9	0 of 0	—
PEG 2000 1:10 SPT	10 of 10	12 of 12	.99
PEG 2000 1:1 SPT	14 of 15	16 of 16	.48
PEG 3350 1:100 SPT	8 of 9	0 of 0	—
PEG 3350 1:10 SPT	9 of 9	4 of 5	.36
PEG 3350 1:1 SPT	10 of 10	11 of 11	.99

(Continued)

TABLE I. *(Continued)*

Patient characteristic	Tested before vaccination (n = 16)	Tested after adverse event (n = 18)	*P* value
Polysorbate 80 SPT 1:1	10 of 11	12 of 12	.48
Methylprednisolone acetate SPT 1:1	1 of 2	8 of 8	.20
Methylprednisolone acetate ID 1:10	1 of 1	4 of 4	.99

ID, Intradermal testing; *PEG,* polyethylene glycol; *SPT*, skin prick testing.
*One patient tested positive for PEG 3350 after vaccination, and 1 patient tested positive for PEG 2000, PEG 3350, methylprednisolone acetate, and polysorbate 80 before vaccination.

Vaccination counseling without skin testing, before vaccination or after an adverse event

Table II summarizes the demographic characteristics and outcomes for the patients who presented to our clinic for counseling regarding COVID-19 vaccination but did not undergo any allergy skin testing. In all, 31 patients presented for counseling before undergoing vaccination and 33 presented for counseling after receiving the first dose of an mRNA COVID-19 vaccine.

Of the 31 patients who presented before undergoing vaccination, approximately two-thirds were evaluated because of a history of atopy. Some patients were new referrals owing to a history of atopy and others were existing patients who had concerns about atopy and COVID-19 vaccination. The remainder presented because of a history of an adverse event related to either vaccines or PEG exposure. Three patients had a history of immediate onset of symptoms (within 4 hours) after PEG exposure. Vaccination was recommended for 97% of the patients. All 30 patients underwent COVID-19 vaccination without any reported complications.

In all, 33 patients presented for vaccine counseling after having adverse symptoms attributed to mRNA COVID-19 vaccination and not undergoing allergy skin testing and 23 patients reported adverse symptoms not consistent with an immediate hypersensitivity reaction. Five patients reported a history of adverse symptoms consistent with an immediate hypersensitivity reaction, and 5 patients reported recurrent urticaria and angioedema that occurred more than 4 hours after COVID-19 vaccination. It was recommended that 25 of the patients proceed with the second dose of vaccine. The 8 patients for whom COVID-19 vaccination was not recommended either had a history suggestive of an IgE-mediated reaction or had developed recurrent urticaria after COVID-19 vaccination. Of the 25 patients, 17 underwent subsequent vaccination: 16 patients reported no adverse symptoms with subsequent vaccination and 1 patient reported recurrent symptoms with the second dose of vaccine without significant sequelae.

Comparisons between patient groups

The group of patients who underwent skin testing and the group of those who did not were similar from the standpoints of sex (the majority were female), history of atopy, and age. Statistically significant differences were present between the groups when we compared those patients who presented before vaccination with those who presented after an event. Among the patients who underwent skin testing, those who were being evaluated were more likely to present for vaccine counseling before vaccination if they were older, had a history of atopy, or had a history of adverse symptoms attributed to PEG or polysorbate exposure (Table I). Those patients who were counseled without skin testing were more likely to present before vaccination if they were older, had a history of atopy, had a history of anaphylaxis, or a history of reaction to an injectable medication or vaccine (Table II). Patients who presented for counseling before vaccination were more likely to have the treating allergist recommend further vaccination (Tables I and II). Compared with those patients who presented before vaccination, those patients who presented after an event attributed to vaccination tended to be younger and did not have a significant history of atopy (Tables I and II). Regardless of whether skin testing was performed, those patients who presented after a vaccine-related event were less likely to proceed with vaccination after allergy evaluation (Tables I and II).

Table III summarizes the results of statistical analysis of vaccination complication rates between patient groups among the patients who underwent COVID-19 vaccination after allergy evaluation. There was no statistically significant difference between patients presenting before vaccination or after experiencing symptoms, regardless of whether they underwent skin testing. Hence, history and allergist review were as useful to safely proceeding to vaccination as was an excipient test in most subjects, except for possibly 1 subject who had a concerning history and positive result of testing to all PEG/polysorbate products and was counseled to not receive the mRNA vaccine. There were no complicated vaccinations among those patients who were counseled before vaccination. All but 2 patients tolerated COVID-19 vaccination after allergy evaluation: neither of these patients had a serious event. The baseline characteristics of these 2 patients were no different from those of the others.

DISCUSSION

The adverse reactions to vaccines practice parameter 2012 update states, "Patients who experience apparent anaphylactic reactions after immunization should undergo immediate type allergy skin testing to help confirm that the reaction was IgE-mediated and determine the responsible component of the vaccine."[8] This has been the recommended approach for vaccine hypersensitivity for years, and thus, it was not unreasonable that the initial approach taken for evaluation of suspected allergic reactions to mRNA COVID-19 vaccines was focused on vaccine components such as PEG,[7] especially in the absence of available vaccine under emergency use authorization for testing (as was the case at our institution, where limited supply and emergency use authorization prevented direct skin testing to COVID-19 vaccines).

Macrogols (such as PEG) are synthetic compounds used in foods, cosmetics, and medications. These hydrophilic polymers can vary significantly in molecular weight; higher-molecular-weight macrogols are more frequently identified as a cause of anaphylaxis.[9,10] Prior case reports of PEG anaphylaxis have

TABLE II. Vaccination counseling without skin testing

Patient characteristic	Before vaccination (n = 31)	After vaccination (n = 33)	*P* value
Female sex, no (%)	26 (83.9)	31 (93.9)	.2
Age (y), mean ± SD	65.7 ± 11.7	48 ± 13.5	<.001
History of atopy, no. (%)	30 (96.8)	15 (45.5)	<.001
History of anaphylaxis	14 (45.2)	4 (12.1)	.003
History of reaction to injectable medication or vaccination	10 (32.3)	1 (3.1)	.002
Reason for counseling, no. (%)			
Atopic history	21 (67.7)	N/A	
Adverse symptoms with prior vaccines	7 (22.6)	N/A	
History of PEG immediate hypersensitivity reaction	3 (9.7)	N/A	
Symptoms not consistent with immediate hypersensitivity reaction	N/A	23 (69.7)	
Symptoms consistent with immediate hypersensitivity reaction	N/A	5 (15.2)	
Recurrent urticaria/angioedema after vaccination	N/A	5 (15.2)	
Vaccination recommended, no. (%)	30 of 31 (96.8)	25 of 33 (75.8)	.02
Received vaccination, no. (%)	30 of 31 (96.8)	17 of 33 (51.5)	<.001
Uncomplicated vaccination, no. (%)	30 of 30 (100)	16 of 17 (94)	.18

N/A, Not applicable.

TABLE III. Vaccine complication rates after allergy evaluation between patient groups

Groups compared	*P* value
Counseling before vaccination (n = 0 of 30 [0%]) vs counseling after vaccination adverse event (n = 1 of 17 [5%])	.36
Counseling before vaccination (n = 0 of 30 [0%] vs testing before vaccination (n = 0 of 11 [0%])	N/A
Counseling after vaccination adverse event (n = 1 of 17 [5%]) vs testing after vaccination adverse event (n = 1 of 8 [12.5%])	.99

N/A, Not available.

suggested that patients have different thresholds of reactivity to PEG depending on the amount and the molecular weight of the PEG to which the patient was exposed.[10] Skin testing to medications containing PEG with different molecular weights has been proposed as a means of assessing for immediate hypersensitivity to PEG.[7,10] Because PEG 3350 is commonly used as both a medication and an excipient and is therefore a possible mode of sensitization for patients, we chose to test this weight of PEG along with that found in the mRNA vaccines (PEG 2000).

One patient in the group that underwent skin testing before vaccination had positive results of multiple skin tests (ie, skin tests to PEG 2000, PEG 3350, methylprednisolone acetate, and polysorbate 80). This patient had a history of anaphylaxis (hypotension, tachycardia, rash, and shortness of breath) with Miralax ingestion. The patient also reported itching with use of topical products containing PEG. The patient's treating allergist recommended against vaccination with available COVID-19 vaccines in the clinical realm, and the patient was referred for the National Institutes of Health clinical trial on allergic reactions to COVID-19 vaccines (ClinicalTrials.gov identifier NCT04977479). One patient in the group that underwent skin testing after an adverse event attributed to COVID-19 vaccination had a positive result of skin testing to PEG 3350. This patient had a history of COVID-19 infection before vaccination and received 1 dose of the Pfizer-BioNTech (BNT162b2) vaccine. The morning after vaccination the patient developed an erythematous patch on the back of the neck followed by diffuse hives. This was an acute episode that self-resolved, but the patient chose not to proceed with further COVID-19 vaccination until evaluation by an allergist had been completed. After a positive result of skin testing to PEG 3350 was noted, oral challenge to Miralax (1.06 g in 15 mL of water) was performed in the clinic. Within 30 minutes of ingestion, the patient developed a headache and a sore throat. The symptoms resolved over 30 minutes without intervention. The patient opted to not pursue further COVID-19 vaccination.

Skin testing to PEG in patients suspected of having allergic reactions to mRNA COVID-19 vaccines has proved to be of limited utility.[11,12] Our experience is consistent with the findings of others in that only 2 patients in our series had a positive result of skin testing to excipients and a negative result of skin testing to excipients did not preclude development of symptoms with subsequent vaccination in some patients. Consistent with findings of other authors, we also found no overarching evidence of polysorbate sensitivity in this patient population.[12] This may be due to a variety of factors, including the mechanism of these suspected allergic reactions, which may be due to IgG or IgM to PEG as opposed to IgE[11] versus no relationship to these excipients). Despite the limitations with excipient skin testing, it is important to note that more than 50% of patients who underwent skin testing in our series chose to proceed with further vaccination. There was a larger proportion of patients who chose to proceed with vaccination in the skin testing group before vaccination than in the group that underwent skin testing after an event (67% vs 44%). Therefore, there may be a role for skin testing in select patients to encourage proceeding with a potentially lifesaving vaccination, although counseling before vaccination may be a more successful strategy because of similar outcomes. It is vital for the patient and clinician to make a shared decision in this setting, weighing the limitations of testing and the benefits of vaccination.

In our cohort, patients attributed a variety of symptoms to mRNA COVID-19 vaccination, including some that could be consistent with anaphylaxis (Table I). Most patients reported some form of pruritus, angioedema, or rash (including urticaria). A minority of patients experienced gastrointestinal symptoms.

These findings are consistent with the findings of Blumenthal et al,[13] according to whom most patients with suspected allergic reactions to mRNA COVID-19 vaccination had cutaneous and/or respiratory symptoms, with a minority having gastrointestinal involvement. Recent work by Haas et al has demonstrated that approximately 30% of patients in the placebo arm of COVID-19 vaccine trials experience adverse events.[14] Haas et al estimate that up to 76% of adverse events occurring after the first COVID-19 vaccine dose and 52% occurring after the second dose may be due to the nocebo effect.[14] These reported events were not necessarily in the hypersensitivity realm; nonetheless, they do point to other confounders potentially at play. Our findings could be consistent with this; it should also be noted that most of the patients in our cohort presented with subjective symptoms. Regardless, many of the reported symptoms in our clinics do raise concern for allergic reaction and warrant evaluation by an allergist.

A history of atopy (especially any form of anaphylaxis) is perceived by many referring providers and patients as indicating that the patient is at high risk of allergic reaction to COVID-19 vaccination. Most of our cohort was female and had a diverse array of atopic conditions (including prior anaphylaxis). This is consistent with reports of suspected allergic reactions to mRNA COVID-19 vaccination in which many patients had histories of atopy, including anaphylaxis.[13] In our series, patients who presented for vaccine counseling before vaccination were more likely to have a history of atopy, history of anaphylaxis, and history of reaction to injectable medication or vaccine than were patients who presented after an adverse event related to vaccination (Table II). This is likely due to perceived higher risk of allergic reaction to COVID-19 vaccines with a history of atopy. Many approaches to assessing the risk of allergic reaction to COVID-19 vaccination rely on atopic history.[15] These patients may not be at an increased risk, but the perception of increased risk can create a real barrier to vaccination. In our series, most patients with a history of atopy chose to proceed with COVID-19 vaccination after evaluation by an allergist and tolerated vaccination without complication.

When comparing skin testing to evaluation without skin testing, we found no statistically significant differences in vaccine tolerance in patients who chose to proceed with vaccination after skin testing (Table III). This suggests that skin testing to excipients adds limited value in patients with suspected allergic reactions to mRNA COVID-19 vaccines. Although no evaluation strategy was found to be clearly superior in our series, there was a trend toward patients presenting before any COVID-19 vaccination being more likely to proceed with COVID-19 vaccination and tolerating vaccination without complication. This may be related to a significant portion of events being secondary to the nocebo effect (with counseling before vaccination alleviating many concerns and setting appropriate patient expectations). Overall, evaluation by an allergist allowed many patients to successfully proceed with vaccination.

Our study had several limitations. As is inherent to a retrospective chart review, we were unable to obtain outcome data on all patients who were evaluated. The clinical setting of a tertiary care academic institution limits the generalizability of our findings to patient populations in nonacademic settings. We relied on the diagnosis code of vaccine counseling to identify patients to include in our series; as a result, some patients may have been missed. Most patients had subjective symptoms that were in the realm of hypersensitivity, and this is likely reflective of the types of patients who will present to the allergist's clinic for evaluation.[13,15]

In our series, 63 of 98 patients (64%) received subsequent doses of vaccine without an allergic reaction and 2 of 98 (2%) received subsequent doses of vaccine with mild reactions (that were treatable). There was a large proportion of patients who proceeded with guidance and reassurance from the allergist, patients who may not have decided to undergo vaccination otherwise. Of the 31 patients who received counseling before vaccination, 30 underwent vaccination and did so successfully. It is likely that some of these patients may not have done so without our guidance. And even among those patients who had experienced previous reactions, many of those counseled to undergo vaccination (16 of 25) did so with no complications. Those who were counseled against vaccination may have decided not to proceed versus proceeding with caution, and since our study, we have more tools to perhaps help those patients. Approval of the vaccine by the US Food and Drug Administration and vaccine availability now allow direct testing and direct graded dosing. Therefore, our findings suggest that evaluation by an allergist can help many patients undergo successful COVID-19 vaccination, and perhaps even more so now than at the start of the administration of the vaccinations. Clinical history taking and overall allergist expertise in the understanding of hypersensitivity have played and will continue to play an important role in the prevention of COVID-19 and mitigation of the ongoing health crisis that this pandemic has caused.

Clinical implications: Most atopic patients safely receive the COVID-19 vaccine after evaluation by an allergist with or without skin testing to excipients.

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