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.

Ann Allergy Asthma Immunol 128 (2022) 153–160

Contents lists available at ScienceDirect

Utility and futility of skin testing to address concerns surrounding messenger RNA coronavirus disease 2019 vaccine reactions

Mitchell M. Pitlick, MD*; Andrea N. Sitek, MD*; Michael E. D'Netto, MD*; Kelley N. Dages, MD†; Sergio E. Chiarella, MD*; Alexei Gonzalez-Estrada, MD‡; Avni Y. Joshi, MD*; Miguel A. Park, MD*

* Division of Allergic Diseases, Mayo Clinic, Rochester, Minnesota
† Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota
‡ Division of Pulmonary, Allergy, and Sleep Medicine, Mayo Clinic, Jacksonville, Florida

ARTICLE INFO

Article history:
Received for publication September 7, 2021.
Received in revised form October 27, 2021.
Accepted for publication November 10, 2021.

ABSTRACT

Background: The mechanism of coronavirus disease 2019 (COVID-19) vaccine hypersensitivity reactions is unknown. COVID-19 vaccine excipient skin testing has been used in evaluation of these reactions, but its utility in predicting subsequent COVID-19 vaccine tolerance is also unknown.
Objective: To evaluate the utility of COVID-19 vaccine and vaccine excipient skin testing in both patients with an allergic reaction to their first messenger RNA COVID-19 vaccine dose and patients with a history of polyethylene glycol allergy who have not yet received a COVID-19 vaccine dose.
Methods: In this multicenter, retrospective review, COVID-19 vaccine and vaccine excipient skin testing was performed in patients referred to 1 of 3 large tertiary academic institutions. Patient medical records were reviewed after skin testing to determine subsequent COVID-19 vaccine tolerance.
Results: A total of 129 patients underwent skin testing, in whom 12 patients (9.3%) had positive results. There were 101 patients who received a COVID-19 vaccine after the skin testing, which was tolerated in 90 patients (89.1%) with no allergic symptoms, including 5 of 6 patients with positive skin testing results who received a COVID-19 vaccine after the skin testing. The remaining 11 patients experienced minor allergic symptoms after COVID-19 vaccination, none of whom required treatment beyond antihistamines.
Conclusion: The low positivity rate of COVID-19 vaccine excipient skin testing and high rate of subsequent COVID-19 vaccine tolerance suggest a low utility of this method in evaluation of COVID-19 vaccine hypersensitivity reactions. Focus should shift to the use of existing vaccine allergy practice parameters, with consideration of graded dosing when necessary. On the basis of these results, strict avoidance of subsequent COVID-19 vaccination should be discouraged.

Introduction

Ever since the US Food and Drug Administration issued emergency use authorizations for Pfizer-BioNTech and Moderna messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccines, there has been abundant investigation in the diagnosis and evaluation of allergic reactions to these vaccines. The estimate of mRNA vaccine-induced anaphylaxis has fluctuated over this time, with initial reports revealing a rate of 11.1 cases per million doses of the Pfizer-BioNTech COVID-19 vaccine but subsequent reports revealing a lower rate of 4.7 and 2.5 cases per million doses of the Pfizer-BioNTech and Moderna COVID-19 vaccines, respectively.[1,2] Another recent systematic review revealed an anaphylaxis case rate of 7.91 cases per million doses of all available COVID-19 vaccines.[3] All these numbers are higher than the historically quoted rate of vaccine-induced anaphylaxis (1.3 cases per million doses), which has partially contributed to vaccine hesitation.[4,5] Aside from anaphylaxis, less severe immediate and delayed reactions to the mRNA vaccines have been reported.[6-8] The mechanisms and culprits of all these reactions remain unclear. Vaccine excipients including polyethylene glycol (PEG, found in the mRNA COVID-19 vaccines) and polysorbate (found in the adenovirus vector COVID-19 vaccine) have been proposed as possible culprits, although the evidence supporting this is currently lacking.[9-13]

Guidelines for skin testing with nonirritating concentrations of PEG and polysorbate are available, and expert opinion suggested an algorithm using them in the evaluation of mRNA COVID-19 vaccine reactions.[9,14,15] Nonirritating concentrations of the Pfizer-BioNTech COVID-19 vaccine have also been published.[16] Multiple professional organizations and expert opinions have stressed the need for a systematic approach to COVID-19 vaccine reactions, investigation into

Reprints: Mitchell M. Pitlick, MD, Division of Allergic Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 E-mail: Pitlick.mitchell@mayo.edu.
Disclosures: The authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.

https://doi.org/10.1016/j.anai.2021.11.006
1081-1206/

the mechanisms of reaction, limiting the overdiagnosis of vaccine anaphylaxis, and safely vaccinating the maximum number of individuals in a rapid fashion.[17-22] There have been multiple reports describing excipient skin testing in the evaluation of mRNA COVID-19 vaccine reactions, which have largely revealed a low rate of skin test positivity and high rate of subsequent vaccine tolerance.[23-25] These results have raised concerns regarding the utility of excipient skin testing in the evaluation of COVID-19 vaccine reactions. Areas that have not been as rigorously studied include the utility of COVID-19 vaccine skin testing and COVID-19 vaccine-component skin testing in patients with a previous PEG or polysorbate allergy who have yet to receive a vaccine.

In this study, we describe a large cohort of more than 100 patients who underwent excipient or vaccine skin testing in the evaluation of an mRNA COVID-19 vaccine reaction or for evaluation of PEG or polysorbate allergy before receiving a COVID-19 vaccine.

Methods

Study Design, Participants, and Data Source

In this multicenter, retrospective review, skin testing was performed in adult patients referred to the Mayo Clinics based in Rochester, Minnesota, Scottsdale, Arizona, and Jacksonville, Florida, from January 14, 2021 to July 14, 2021. The patients were separated into the following 2 cohorts: those who had a possible allergic reaction to 1 of the mRNA COVID-19 vaccines and those who reported a previous PEG or polysorbate allergy and had not yet received a COVID-19 vaccine dose.

Variables

The clinical need for skin testing and test selection was determined by the provider at the time of evaluation. Skin testing to PEG 3350 (MiraLAX), methylprednisolone acetate (containing PEG), methylprednisolone sodium (control), triamcinolone acetonide (containing polysorbate 80), Prevnar (containing polysorbate 80), Havrix (containing polysorbate 20), Flublok (containing polysorbate 20), fresh polysorbate 20 compound, Pfizer-BioNTech COVID-19 vaccine, Moderna COVID-19 vaccine, and Janssen COVID-19 vaccine was performed with methods partially adapted from previously published guidelines and reports (Table 1).[9,23] After skin testing to the COVID-19 vaccines or their components, patient charts were reviewed to evaluate whether they had received and tolerated a COVID-19 vaccine. Demographic characteristics, including atopic and nonatopic comorbidities, were collected along with details of the index reaction. Reaction symptoms were defined both by time of onset (<4 hours: immediate, ≥4 hours: delayed) and by body system involved (cutaneous, upper airway, lower airway, cardiovascular, gastrointestinal, other). Anaphylaxis was defined using Brighton criteria.[26,27] Each case was reviewed independently by 2 of the authors (M.M.P. and M.E.D.). When there was discordance in the assigned Brighton classification, the case was adjudicated by a third author (A.N.S.). The primary outcome was tolerance of any COVID-19 vaccine after skin testing, which was defined as the absence of patient-reported allergic symptoms after vaccination.

Data were analyzed using BlueSky Statistics Software version 7.2 (BlueSky Statistics LLC, Chicago, Illinois). Statistical comparisons were made between the following 2 groups: those who tolerated a subsequent vaccine dose and those who had allergic symptoms with a subsequent vaccine dose. Continuous variables between groups were compared using either analysis of variance or independent group *t* tests. Proportions of categorical variables between groups were compared using Fisher's exact test. Results were deemed significant when a 2-sided *P* value was less than .05.

Results

A total of 129 patients underwent skin testing. There were 55 who had a history of a reaction to a dose of an mRNA COVID-19 vaccine, and 74 had a previous history of PEG or polysorbate allergy without having received a COVID-19 vaccine. In each of these groups, patients were separated based on outcome of post-skin testing vaccination (tolerated, experienced symptoms, or deferred). A flow diagram of patient testing and outcomes is found in Figure 1.

Coronavirus Disease 2019 Vaccine Reaction Cohort

Demographic Characteristics

Demographic characteristics are found in Table 2. Most of the patients were of female sex (80%) and white (83.6%). The most common allergic comorbidities were patient-reported drug allergy (60%) and anaphylaxis (29%) followed by asthma and food allergy (25.5% each). There was a significantly higher proportion of patients with previous COVID-19 infection in those who had symptoms with their second COVID-19 vaccine dose compared with those who did not (57.1% vs 8.3%, *P* =.008). Otherwise, there were no substantial differences between the groups.

Reaction Details

Details regarding the index reaction are found in Table 2. There were 72.7% (40 of 55) of the patients who had experienced symptoms after their first dose of the Pfizer-BioNTech COVID-19 vaccine with the other 27.3% (15 of 55) being evaluated for symptoms after their first dose of the Moderna vaccine. In addition, 74.5% (41 of 55) of the reactions were immediate with 65.5% (36 of 55) occurring within 1 hour of vaccination. Cutaneous symptoms were most common, occurring in 78.2% of the patients, with no substantial differences in

Table 1
Skin Testing Protocol

Steps	PEG 3350		Control	Polysorbate 20			Polysorbate 80		COVID-19 vaccine[a]		
	Miralax (170 mg/mL)	Methylprednisolone acetate (40 mg/mL)	Methylprednisolone sodium (40 mg/mL)	Polysorbate 20 (0.5 mg/mL)[b]	Flublok[c]	Havrix[d]	Triamcinolone acetonide (40 mg/mL)	Prevnar-13	Pfizer-BioNTech	Moderna	Janssen
Step 1	1:100 SP	1:1 SP	1:1 SP	1:1 SP	1:1 SP	1:1 SP	1:1 SP	1:10 SP	1:1 SP	1:1 SP	1:1 SP
Step 2	1:10 SP	1:100 ID	1:100 ID		1:100 ID	1:100 ID	1:100 ID	1:100 ID	1:100 ID		1:10 ID
Step 3	1:1 SP	1:10 ID	1:10 ID		1:10 ID	1:10 ID	1:10 ID		1:10 ID		
Step 4							1:1 SP		1:1 ID		

Abbreviations: COVID-19, coronavirus disease 2019; ID, intradermal; PEG, polyethylene glycol; SP, skin prick.
[a]Intradermal testing to the Pfizer-BioNTech and Janssen vaccines was performed in 2 patients in our cohort.
[b]Polysorbate 20 compound made by using polysorbate 20 at a 0.5 mg/mL concentration with a 0.45% saline diluent.
[c]Influenza vaccine from Sanofi Pasteur (Lyons, France).
[d]Hepatitis A vaccine from GlaxoSmithKline (Brentford, United Kingdom).

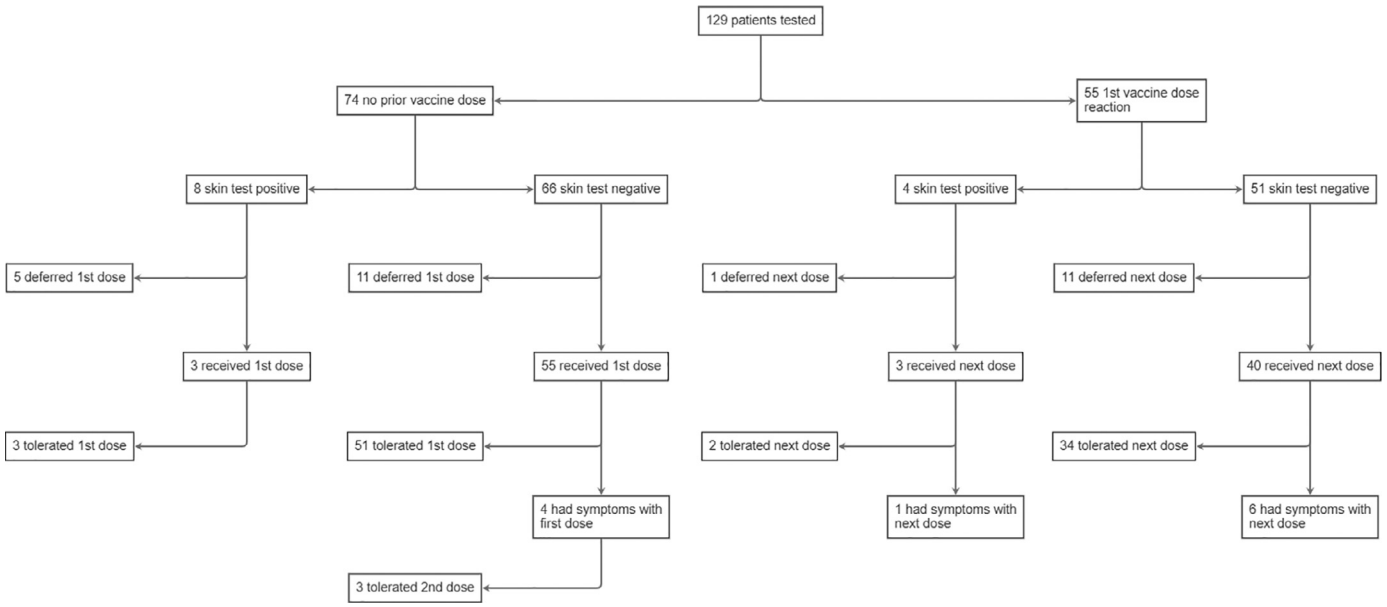

Figure 1. Flow diagram of patient evaluation, testing, and outcome.

symptomatology between the groups. Furthermore, 4 patients (7.3%) experienced Brighton class 1 reactions, but there was no difference in reaction severity (based on Brighton classification) between the groups. There was also no major difference in the treatment received for the index reaction between the groups.

Skin Test Results

There were 4 patients who had positive skin test results, all of which were to polysorbate-containing products (Table 3). Nevertheless, there was no difference in skin test positivity between the groups. In addition, 11 patients had mRNA COVID-19 vaccine skin prick testing with 1 also undergoing intradermal testing, all of which were negative.

Subsequent Vaccine Tolerance

Of the patients tested, 78.2% (43 of 55) chose to receive their second dose, all of whom except 1 received the same vaccine as their index reaction (Table 2). There were 83.7% of the patients (36 of 43) who tolerated their second dose with no allergic symptoms. Of the 7 patients who experienced allergic symptoms with the second dose, only 1 had a positive skin test result (triamcinolone acetonide), and none received any treatment beyond antihistamines. Of the 36 patients who tolerated their second dose, 6 (16.7%) received pretreatment with antihistamines compared with 2 of the 7 who had symptoms with their second dose (28.6%). There was no difference in subsequent vaccine tolerance or days between vaccine doses between those who received the Pfizer-BioNTech COVID-19 vaccine and those who received the Moderna COVID-19 vaccine.

Polyethylene Glycol and Polysorbate Allergy Cohort

Demographic Characteristics

Demographic characteristics are found in Table 4. Most of the patients were of female sex (87.8%) and white (91.9%). The most common allergic comorbidities were patient-reported drug allergy (100%) and non–COVID-19 vaccine allergy (35.1%) followed by allergic rhinitis (31.1%) and asthma (29.7%). There were 37 patients (50%) who reported a history of reaction to a PEG-containing medication and 17 patients (23.0%) who reported a previous reaction to a polysorbate-containing medication. The remainder of the patients were referred owing to either a history of multiple drug allergies or previous reactions to unknown vaccines. Additionally, 46% of the patients had documented evidence of previous tolerance of polysorbate-containing vaccines. There were no differences between the groups.

Reaction Details

Details regarding the index reaction are found in Table 4. Of the reactions, 59.5% (44 of 74) were immediate (with 33 occurring within 1 hour of exposure), 9.5% were delayed, and timing was unknown in the remaining 31.0%. Cutaneous symptoms were most common, occurring in 68.9% of the patients, with no differences in symptomatology between the groups. There were no substantial differences in severity of reaction among the groups, with most of the patients experiencing Brighton class 5 reactions (75.7%) and 5 patients (6.8%) experiencing Brighton class 1 reactions. Furthermore, 7 patients reported receiving epinephrine for their index reaction (9.5%), but many patients did not recall what treatment they received (45.9%). There were no major differences in type of treatment or rates of emergency department visits or hospitalization between the groups.

Skin Test Results

Skin test results are found in Table 5. There were 8 patients (10.8%) who had PEG only skin testing, with the other 66 (89.2%) having some other additional polysorbate or vaccine testing performed. In total, 8 patients had positive skin test results (3 PEG, 4 polysorbate, 1 vaccine), 5 of whom deferred subsequent vaccine doses. There was no difference in skin test positivity between those who tolerated a subsequent vaccine dose compared with those who had symptoms with a subsequent dose. A total of 13 patients had COVID-19 vaccine skin prick testing (1 also had intradermal testing) with 1 patient having a positive test to the Pfizer-BioNTech COVID-19 vaccine (skin prick test; undiluted).

Subsequent Vaccine Tolerance

Of the patients tested, 78.4% (58 of 74) chose to receive their first COVID-19 vaccine dose. In all, 35 received the Pfizer-BioNTech COVID-19 vaccine, 12 received the Moderna COVID-19 vaccine, and

Table 2
Demographic Characteristics and Reaction Details of Patients With First-Dose Messenger RNA Coronavirus Disease 2019 Vaccine Reactions

Demographics and reaction details	Tolerated[a] second vaccine dose, n = 36	Symptoms[a] with second vaccine dose, n = 7	Deferred second vaccine dose, n = 12	*P* value[b]
Age, mean (SD)	50.9 (16.3)	40.3 (15.2)	44.8 (12.1)	.30
Sex (female, %)	31 (86.1)	5 (71.4)	8 (66.7)	.32
Race (%)				.46
White	31 (86.1)	6 (85.7)	9 (75.0)	
African American	3 (8.3)	0 (0)	1 (8.3)	
Asian	1 (2.8)	1 (14.3)	0 (0)	
Other	1 (2.8)	0 (0)	2 (16.7)	
Nonatopic comorbidities (%)				
Obesity	8 (22.2)	0 (0)	5 (41.7)	.31
Hypertension	6 (16.7)	1 (14.3)	3 (25.0)	.99
Diabetes	1 (2.8)	0 (0)	0 (0)	.99
Chronic obstructive pulmonary disease	1 (2.8)	0 (0)	0 (0)	.99
Previous COVID-19 disease	3 (8.3)	4 (57.1)	1 (8.3)	.008
Allergic and atopic comorbidities (%)				
Allergic rhinitis	7 (19.4)	1 (14.3)	1 (8.3)	.75
Asthma	9 (25.0)	2 (28.6)	3 (25.0)	.99
Mast cell disease[c]	0 (0)	0 (0)	0 (0)	.99
Non–COVID-19 vaccine allergy	0 (0)	0 (0)	2 (16.7)	.07
Chronic spontaneous urticaria	0 (0)	0 (0)	1 (8.3)	.36
Food allergy	6 (16.7)	3 (42.9)	5 (41.7)	.15
Anaphylaxis	10 (27.8)	1 (14.3)	5 (41.7)	.67
Drug allergy	20 (55.6)	4 (57.1)	9 (75.0)	.94
History of PEG or polysorbate allergy	0 (0)	0 (0)	0 (0)	.99
Venom allergy	5 (13.9)	0 (0)	2 (16.7)	.57
Previous tolerance of polysorbate containing vaccines (%)	18 (50.0)	4 (57.1)	4 (33.3)	.79
Culprit vaccine (%)				
Pfizer-BioNTech	27 (75.0)	5 (71.4)	8 (66.7)	.91
Moderna	9 (25.0)	2 (28.6)	4 (33.3)	.91
Reaction symptoms (%)				
Cutaneous[d]	27 (75.0)	7 (100)	9 (75.0)	.31
Upper airway[e]	13 (36.1)	2 (28.6)	4 (33.3)	.70
Lower airway[f]	6 (16.7)	1 (14.3)	3 (25.0)	.88
Cardiovascular[g]	4 (11.1)	0 (0)	2 (16.7)	.35
Gastrointestinal[h]	1 (2.3)	0 (0)	1 (8.3)	.66
Other[i]	14 (38.9)	3 (42.9)	6 (50.0)	.84
Brighton classification[j] (%)				
1	3 (8.3)	0 (0)	1 (8.3)	.43
2	0 (0)	1 (14.3)	2 (16.7)	.16
3	0 (0)	0 (0)	0 (0)	.99
4	0 (0)	0 (0)	1 (8.3)	.99
5	33 (91.7)	6 (85.7)	8 (66.7)	.52
Reaction timing[k] (%)				
Immediate	25 (69.4)	5 (71.4)	11 (91.7)	.92
Delayed	11 (30.6)	2 (28.6)	1 (8.3)	.92
Treatment received (%)				
None	15 (41.7)	2 (28.6)	0 (0)	.68
Antihistamines	20 (55.6)	5 (71.4)	11 (91.7)	.68
Corticosteroids	8 (22.2)	3 (42.9)	7 (58.3)	.35
IM epinephrine	7 (19.4)	0 (0)	3 (25.0)	.58
Emergency department visit	10 (27.8)	1 (14.3)	7 (58.3)	.66
Hospitalization	1 (2.8)	0 (0)	0 (0)	.66

Abbreviations: COVID-19, coronavirus disease 2019; GI, gastrointestinal; IM, intramuscular; mRNA, messenger RNA; PEG, polyethylene glycol.
[a]Tolerance: No allergic symptoms experienced. In 7 patients who had allergic symptoms, none required epinephrine.
[b]*P* values represent comparison between the "tolerated vaccine dose" group and "symptoms with vaccine dose" group.
[c]Includes systemic mastocytosis, monoclonal mast cell activation syndrome, and hereditary alpha tryptasemia.
[d]Cutaneous: Pruritus, rash (urticarial and nonurticarial), lip angioedema, and flushing.
[e]Upper airway: Throat swelling, hoarse voice, and globus sensation.
[f]Lower airway: Wheezing, dyspnea, and cough.
[g]Cardiovascular: Tachycardia and hypotension.
[h]Gastrointestinal: Nausea, vomiting, abdominal pain, and diarrhea.
[i]Other: Headache, extremity tingling, lightheaded, abnormal taste, hearing or vision decrease, rhinorrhea, and palpitations without heart rate change.
[j]Brighton classification[26]: All cases of anaphylaxis (represented by classes 1-3) must have sudden onset of symptoms and rapid symptom progression with classification based on a certain combination of symptoms as follows (see reference for list of symptoms that fulfill major and minor criteria):
Class 1: ≥1 major dermatologic criterion AND ≥1 cardiac or respiratory major criterion.
Class 2: Four ways to meet class 2:
1. ≥1 Dermatologic major criterion AND ≥1 cardiac or respiratory minor criterion.
2. ≥1 Respiratory major criterion AND ≥1 cardiac major criterion.
3. ≥1 Respiratory major criterion AND ≥1 minor criterion from a different system (dermatologic, cardiac, GI, laboratory).
4. ≥1 Cardiac major criterion AND ≥1 minor criterion from a different system (dermatologic, respiratory, GI, laboratory).
Class 3: Two ways to meet class 3:
1. ≥1 Respiratory minor criterion AND ≥1 minor criterion from at least 2 different systems (dermatologic, cardiac, GI, laboratory).
2. ≥1 Cardiac minor criterion AND ≥1 minor criterion from at least 2 different systems (dermatologic, respiratory, GI, laboratory).
Class 4: Reported anaphylaxis with insufficient evidence to meet any levels of diagnostic certainty.
Class 5: Not a case of anaphylaxis.
[k]Immediate: Symptom onset <4 hours after vaccination; delayed: symptom onset ≥4 hours after vaccination.

Table 3
Evaluation and Outcomes of Patients With First-Dose Messenger RNA Coronavirus Disease 2019 Vaccine Reactions

Evaluation and outcomes	Tolerated[a] second vaccine dose, n = 36	Symptoms[a] with second vaccine dose, n = 7	Deferred second vaccine dose, n = 12	*P* value[b]
Skin test performed[c]				
PEG (%)				
MiraLAX (PEG3350)	36 (100)	7 (100)	12 (100)	.99
Methylprednisolone acetate	18 (50)	4 (57.1)	10 (83.3)	.73
Methylprednisolone sodium	16 (44.4)	5 (71.4)	8 (66.7)	.24
Polysorbate 80 (%)				
Triamcinolone acetonide	10 (27.8)	3 (42.9)	7 (58.3)	.66
Prevnar-13	7 (19.4)	3 (42.9)	3 (25.0)	.32
Polysorbate 20 (%)				
Flublok	0 (0)	0 (0)	2 (16.7)	.99
Havrix	6 (16.7)	2 (28.6)	3 (25.0)	.60
Polysorbate 20 compound	9 (25.0)	3 (42.9)	5 (41.7)	.38
Pfizer-BioNTech vaccine (%)	6 (16.7)	1 (14.3)	1 (8.3)	.86
Moderna vaccine (%)	1 (2.8)	1 (14.3)	1 (8.3)	.30
Average days from index reaction to skin test (SD)	28.9 (18.2)	24.4 (11.5)	49.2 (27.1)	.12
Positive skin test results (total, %)	2 (5.6)	1 (14.3)	1 (8.3)	.42
PEG	0 (0)	0 (0)	0 (0)	
Polysorbate	2 (5.6)[d]	1 (14.3)[e]	1 (8.3)[f]	
Vaccine	0 (0)	(0)	0 (0)	
Vaccine received (%)				
Pfizer-BioNTech	26 (72.2)	5 (71.4)	N/A	.99
Moderna	10 (27.8)	2 (28.6)	N/A	.99
Janssen	0 (0)	0 (0)	N/A	.99
Average days between first and second vaccine doses (SD)	39.7 (18.4)	35.3 (13.3)	N/A	.55

Abbreviations: COVID-19, coronavirus disease 2019; ID, intradermal; F, flare; IM, intramuscular; mRNA, messenger RNA; N/A, not available; PEG, polyethylene glycol; W, wheal.
[a]Tolerance: No allergic symptoms experienced. In 7 patients who had allergic symptoms, none required epinephrine.
[b]*P* values represent comparison between the "tolerated vaccine dose" group and "symptoms with vaccine dose" group.
[c]See Table 1 for concentrations used.
[d]Patient 1: Triamcinolone acetonide 1:100 ID (5×5W, 15×10F). Patient 2: triamcinolone acetonide 1:1 ID (3×3W, 8×8F).
[e]Triamcinolone acetonide 1:10 ID (4×3W, 15×10F).
[f]Flublok: 1:100 ID (10×11W, 35×55F).

11 received the Janssen COVID-19 vaccine. A total of 93.1% (54 of 58) of the patients tolerated their first dose with no allergic symptoms. Of the 4 patients who experienced allergic symptoms with their first dose, none had a positive skin test result or received any treatment beyond antihistamines. Furthermore, 3 of those 4 were able to receive their second dose of the same vaccine with no allergic symptoms, with the remaining patient opting to undergo graded vaccine administration when it is able to be arranged. Of the 11 patients who received the Janssen vaccine, 10 were recommended to do so because of their reported history of PEG allergy, with 2 of those patients having a positive result for a PEG or Pfizer-BioNTech COVID-19 vaccine skin test. None of these patients experienced allergic symptoms with vaccination. There was no substantial difference in vaccine tolerance between any of the groups.

Discussion

This is one of the largest reports to date of utilization of excipient and vaccine skin testing in the evaluation of both mRNA COVID-19 vaccine reactions and patients who have deferred vaccination owing to a previously reported history of PEG or polysorbate allergy. Previous reports have provided suggestions for excipient skin testing in these groups, but subsequent reports have largely been confined to the use of excipient skin testing in those with reactions to the first dose of an mRNA COVID-19 vaccine, the utility of which is questionable.[9,23,24] This report is unique in its evaluation of skin testing in patients who have yet to receive a vaccine but report a PEG or polysorbate allergy and in its use of vaccine for skin testing.

Several findings from this study deserve attention. First, in 129 patients tested, there were only 12 who had positive skin test results (9.3%). In addition, of the 101 patients who proceeded with receiving a vaccine dose subsequent to testing, 90 were able to tolerate it without allergic symptoms with the other 11 patients experiencing mild symptoms that were either self-limited or treated with antihistamines. The overall rate of tolerance was slightly higher in those with a previous PEG or polysorbate allergy compared with those with reactions to the first dose of an mRNA COVID-19 vaccine (93.1% vs 83.7%). These findings are similar to a recent report of 80 patients with first vaccine dose reactions where 14 had positive skin test results (18%) and 62 of 70 (88.6%) were able to tolerate a subsequent vaccine dose without considerable allergic symptoms.[24] In our cohort, patients with positive PEG skin testing results were able to tolerate a subsequent mRNA vaccine dose with no symptoms, but some patients with negative skin testing results had symptoms with subsequent vaccine doses. This raises concerns regarding the sensitivity and specificity of excipient skin testing in this population and the role of PEG in adverse reactions to the mRNA vaccines. Allergy to PEG-containing laxatives and medications confirmed by skin testing has previously been reported in the past, with a recent review revealing an estimate of 4 cases of PEG anaphylaxis per year between 2005 and 2017.[14,15,28,29] Although an early single case report revealed positive PEG skin testing result in a patient with anaphylaxis to the Pfizer-BioNTech COVID-19 vaccine, larger cohorts, including this one, have revealed extremely low rates of PEG skin test positivity in patients with reactions to mRNA COVID-19 vaccines, including those with anaphylaxis.[13,23,24] This suggests that non–PEG- or non–IgE-mediated mechanisms, such as complement activation-related pseudoallergy, may account for some of these reactions.[11,22]

In addition to the overall low rate of skin test positivity, another interesting aspect of this report is that 8 of the 12 patients who tested positive did so only for polysorbate-containing products. Polysorbates are derived from PEGs and found in a large number of injectable medications and existing vaccines.[9,30,31] Furthermore, polysorbate 80 is an excipient in the Janssen COVID-19 vaccine, but not in the mRNA COVID-19 vaccines from Pfizer-BioNTech or Moderna. Given previous

Table 4
Demographic Characteristics and Reaction Details of Patients With Polyethylene Glycol or Polysorbate Allergy Before COVID-19 Vaccination

Demographics and reaction details	Tolerated[a] first vaccine dose, n = 54	Symptoms[a] with first vaccine dose, n = 4	Deferred first vaccine dose, n = 16	*P* value[b]
Age, mean (SD)	60.2 (14.6)	47.3 (9.9)	54.9 (13.4)	.24
Sex (female, %)	46 (85.2)	4 (100)	15 (93.8)	.81
Race (%)				.89
White	51 (94.4)	4 (100)	13 (81.3)	
African American	0 (0)	0 (0)	1 (6.3)	
Asian	1 (1.9)	0 (0)	1 (6.3)	
Other	2 (3.7)	0 (0)	1 (6.3)	
Nonatopic comorbidities (%)				
Obesity	21 (38.9)	1 (25)	8 (50)	.58
Hypertension	20 (37.0)	0 (0)	4 (25)	.29
Diabetes	8 (14.8)	0 (0)	3 (18.8)	.85
Chronic obstructive pulmonary disease	3 (5.6)	0 (0)	0 (0)	.99
Previous COVID-19 disease	4 (14.8)	0 (0)	2 (12.5)	.73
Allergic and atopic comorbidities (%)				
Allergic rhinitis	17 (31.5)	2 (50)	4 (25)	.58
Asthma	16 (29.6)	2 (50)	4 (25)	.58
Mast cell disease[c]	1 (1.9)	0 (0)	1 (6.3)	.99
Non–COVID-19 vaccine allergy	17 (31.5)	3 (75)	6 (37.5)	.11
Chronic spontaneous urticaria	0 (0)	0 (0)	2 (12.5)	
Food allergy	7 (13.0)	1 (25)	4 (25)	.46
Anaphylaxis	13 (24.1)	2 (50)	9 (56.3)	.27
Drug allergy	54 (100)	4 (100)	16 (100)	
History of PEG allergy	29 (53.7)	1 (25)	7 (43.8)	.34
History of polysorbate allergy	12 (22.2)	2 (50)	3 (18.8)	.24
Venom allergy	2 (3.7)	0 (0)	1 (6.3)	.70
Prior tolerance of polysorbate containing vaccines (%)	27 (50)	1 (25)	6 (37.5)	.61
Reaction symptoms (%)				
Cutaneous[d]	38 (70.4)	4 (100)	9 (56.3)	.57
Upper airway[e]	11 (20.4)	1 (25)	7 (43.8)	.83
Lower airway[f]	10 (18.6)	2 (50)	6 (37.5)	.19
Cardiovascular[g]	4 (14.8)	0 (0)	1 (6.3)	.57
Gastrointestinal[h]	6 (11.1)	1 (25)	1 (6.3)	.41
Other[i]	12 (22.2)	1 (25)	4 (25)	.90
Brighton classification[j] (%)				
1	3 (5.6)	1 (25)	1 (6.3)	.25
2	5 (9.3)	1 (25)	4 (25)	.36
3	0 (0)	0 (0)	0 (0)	
4	1 (1.9)	0 (0)	2 (12.5)	.78
5	45 (83.3)	2 (50)	9 (56.3)	.16
Reaction timing[k] (%)				
Immediate	33 (61.1)	3 (75)	8 (50)	.58
Delayed	6 (11.1)	0 (0)	1 (6.3)	.48
Unknown	15 (27.8)	1 (25)	7 (43.8)	.90
Treatment received (%)				
None	13 (24.1)	0 (0)	1 (6.3)	.57
Unknown	21 (38.9)	2 (50)	11 (68.8)	.66
Antihistamines	19 (35.2)	1 (25)	3 (18.8)	.68
Corticosteroids	10 (18.6)	0 (0)	2 (12.5)	.34
IM epinephrine	5 (9.3)	1 (25)	1 (6.3)	.36
Emergency department visit	17 (31.5)	0 (0)	2 (12.5)	.31
Hospitalization	2 (3.7)	0 (0)	3 (18.8)	.70

Abbreviations: COVID-19, coronavirus disease 2019; GI, gastrointestinal; PEG, polyethylene glycol.
[a]Tolerance: No allergic symptoms experienced. In 4 patients who had allergic symptoms, none required epinephrine.
[b]*P* values represent comparison between the "tolerated vaccine dose" group and "symptoms with vaccine dose" group.
[c]Includes systemic mastocytosis, monoclonal mast cell activation syndrome, and hereditary alpha tryptasemia.
[d]Cutaneous: Pruritus, rash (urticarial and nonurticarial), lip angioedema, and flushing.
[e]Upper airway: Throat swelling, hoarse voice, and globus sensation.
[f]Lower airway: Wheezing, dyspnea, and cough.
[g]Cardiovascular: Tachycardia and hypotension.
[h]Gastrointestinal: Nausea, vomiting, abdominal pain, and diarrhea.
[i]Other: headache, extremity tingling, lightheaded, abnormal taste, hearing or vision decrease, rhinorrhea, and palpitations without heart rate change.
[j]Brighton classification[26]: all cases of anaphylaxis (represented by classes 1-3) must have sudden onset of symptoms and rapid symptom progression with classification based on a certain combination of symptoms as follows (see reference for list of symptoms that fulfill major and minor criteria):
Class 1: ≥1 Major dermatologic criterion AND ≥1 cardiac or respiratory major criterion.
Class 2: Four ways to meet class 2:
1. ≥1 Dermatologic major criterion AND ≥1 cardiac or respiratory minor criterion.
2. ≥1 Respiratory major criterion AND ≥1 cardiac major criterion.
3. ≥1 Respiratory major criterion AND ≥1 minor criterion from a different system (dermatologic, cardiac, GI, laboratory).
4. ≥1 Cardiac major criterion AND ≥1 minor criterion from a different system (dermatologic, respiratory, GI, laboratory).
Class 3: Two ways to meet class 3:
1. ≥1 Respiratory minor criterion AND ≥1 minor criterion from at least 2 different systems (dermatologic, cardiac, GI, laboratory).
2. ≥1 Cardiac minor criterion AND ≥1 minor criterion from at least 2 different systems (dermatologic, respiratory, GI, laboratory).
Class 4: Reported anaphylaxis with insufficient evidence to meet any levels of diagnostic certainty.
Class 5: Not a case of anaphylaxis.
[k]Immediate: Symptom onset <4 hours after vaccination; Delayed: symptom onset ≥4 hours after vaccination.

Table 5
Evaluation and Outcomes of Patients With Polyethylene Glycol or Polysorbate Allergy Before COVID-19 Vaccination

Evaluation and outcomes	Tolerated[a] first vaccine dose, n = 54	Symptoms[a] with first vaccine dose, n = 4	Deferred first vaccine dose, n = 16	*P* value[b]
Skin test performed[c] (%)				
PEG				
MiraLAX (PEG3350)	50 (92.6)	3 (75)	15 (93.8)	.31
Methylprednisolone acetate	33 (61.1)	2 (50)	12 (75)	.66
Methylprednisolone sodium	32 (59.3)	1 (25)	6 (37.5)	.31
Polysorbate 80				
Triamcinolone acetonide	17 (31.5)	2 (50)	8 (50)	.59
Prevnar-13	17 (31.5)	2 (50)	5 (31.3)	.59
Polysorbate 20				
Flublok	1 (1.9)	1 (25)	6 (37.5)	.13
Havrix	17 (31.5)	2 (50)	5 (31.3)	.59
Polysorbate 20 compound	12 (35.3)	0 (0)	3 (18.8)	.57
Pfizer-BioNTech vaccine	8 (14.8)	0 (0)	1 (6.3)	.41
Moderna vaccine	2 (3.7)	0 (0)	0 (0)	.70
Janssen vaccine	1 (1.9)	0 (0)	1 (6.3)	.78
Positive skin test results (%)	3 (5.6)	0 (0)	5 (31.3)	.63
PEG	2 (3.7)[d]	0 (0)	1 (6.3)[f]	
Polysorbate	0 (0)	0 (0)	4 (25)[g]	
Vaccine	1 (1.9)[e]	0 (0)	0 (0)	
Vaccine received (%)				
Pfizer-BioNTech	32 (59.2)	3 (75)	NA	.64
Moderna	11 (20.4)	1 (25)	NA	.83
Janssen	11 (20.4)	0 (0)	NA	.32

Abbreviations: COVID-19, coronavirus disease 2019; F, flare; ID, intradermal; IM, intramuscular; PEG, polyethylene glycol; W, wheal.
[a]Tolerance: No allergic symptoms experienced. In 4 patients who had allergic symptoms, none required epinephrine.
[b]*P* values represent comparison between the "tolerated vaccine dose" group and "symptoms with vaccine dose" group.
[c]See Table 1 for concentrations used.
[d]Patient 1: PEG 1:1 SP (5×5 W, 10×10F), methylprednisolone acetate 1:10 ID (6×6W, 8×8F). Patient 2: PEG 1:100 SP (5×7W, 25×30F) 1:10 SP (10×10W, 18×40F) 1:1 SP (9×10W, 22×30F), methylprednisolone acetate 1:1 SP (6×10W, 25×30F).
[e]Pfizer-BioNTech vaccine 1:1 SP (7×7w, 10×10f).
[f]PEG 1:1 SP (3×4W, 6×7F).
[g]Patient 1: FluBlok 1:100 ID (10×11W, 15×20F). Patient 2: FluBlok 1:100 ID (8×8W, 20×25F). Patient 3: Flublok 1:100 ID (4×5W, 19×20F), triamcinolone acetonide 1:10 ID (3×3W, 20×30F). Patient 4: Flublok 1:100 ID (5×5W, 8×7F), triamcinolone acetonide 1:100 ID (5×6W, 8×9F) 1:10 ID (5×5W, 4×4F).

reports of skin test cross-reactivity to polysorbate 80 in patients with PEG allergy, there was initial concern and caution from the Centers for Disease Control and Prevention regarding administration of PEG-containing mRNA vaccines to patients with polysorbate allergy.[15,32] Nevertheless, clinical reactivity to polysorbate 80 is uncommon, with only 1 report of skin test-proven hypersensitivity to a polysorbate 80-containing vaccine previously reported.[33] We have previously reported a case of biphasic anaphylaxis after the first dose of the Pfizer-BioNTech COVID-19 vaccine in a patient with positive skin testing results to multiple polysorbate-containing products, but negative testing results to PEG and the Pfizer-BioNTech COVID-19 vaccine.[34] In our current report, 2 patients with positive polysorbate skin testing results tolerated a subsequent mRNA COVID-19 vaccine dose with no symptoms and another experienced minor symptoms treated with antihistamines, but the remaining 5 deferred additional vaccine. Given the lack of knowledge regarding the sensitivity, specificity, and predictive values of skin testing as it pertains to COVID-19 vaccine hypersensitivity and what is likely a low rate of clinical cross-reactivity between PEG and polysorbate, this deferral rate is concerning. Expanded skin testing with polysorbate-containing products in both the evaluation of mRNA COVID-19 vaccine reactions and as a screening tool before vaccination may result in positive test results of unclear significance that generate more anxiety and hesitation in patients. Limited use of this particular testing may be the optimal route moving forward.

Aside from excipient skin testing, this report is one of the largest to date on the use of COVID-19 vaccine skin testing. Although nonirritating concentrations for intradermal testing with the Pfizer-BioNTech COVID-19 vaccine have been reported, our report primarily used skin prick testing (only 2 patients underwent intradermal vaccine testing) owing to institutional restrictions.[16] Of the 24 skin prick tests performed (17 Pfizer-BioNTech, 5 Moderna, 2 Janssen), only 1 test result to the Pfizer-BioNTech COVID-19 vaccine was positive. This patient had not yet received any COVID-19 vaccine and after testing received the Janssen vaccine without any allergic symptoms. Choosing or altering a vaccine platform based on skin testing either as a screening tool before vaccination or in response to a first dose vaccine reaction has been suggested and reported, although the necessity and efficacy of it have not been proven.[3,9,24,30] An overemphasis on this technique may result in delayed vaccination in resource-limited areas. Although general practice parameters exist regarding the use of vaccine skin prick and intradermal testing in the evaluation of vaccine hypersensitivity, the validity of these modalities for mRNA COVID-19 vaccines remains unproven and will require further evaluation.[35]

It should be noted that even in the case of true COVID-19 vaccine or excipient hypersensitivity with positive skin testing results, subsequent vaccination can still be possible. Although using an alternative vaccine platform (ie, Janssen vaccination in a patient with mRNA vaccine hypersensitivity) is a previously discussed option, using a graded dosing regimen for a subsequent dose of the same vaccine that may have caused a reaction is also an option, as discussed in vaccine allergy practice parameters.[35] Given the lack of knowledge regarding efficacy of mixed vaccine platform use, graded dosing using the same vaccine may be an attractive option, although the efficacy of this is also unproven in terms of vaccine response. Graded dosing regimens for the Moderna vaccine in patients who experienced an allergic reaction with their first dose have been published, and 1 of the authors has also used graded dosing regimens for the Pfizer-BioNTech vaccine in 2 patients with Pfizer-BioNTech COVID-19 vaccine-induced anaphylaxis (AGE, unpublished data, August 24, 2021).[36] Although this strategy may be limited by patient access to an allergist, it is important to stress that excipient and vaccine skin testing, when used, should not be to label patients as unable to receive a vaccine but to potentially identify those who require an alternative dosing scheme or vaccine type.

Our data are similar to a recent multicenter study that evaluated 189 patients with an immediate hypersensitivity (including anaphylaxis) to their first dose of an mRNA COVID-19 vaccine and revealed that all 159 patients that chose to receive their next dose were able to tolerate it, with only 32 experiencing minor self-limited allergic symptoms.[25] These reports revealing a high rate of subsequent mRNA COVID-19 vaccine tolerance despite immediate hypersensitivity or anaphylaxis with the first dose are encouraging and should be included in the medical decision-making discussion with patients when contemplating vaccine doses. An emphasis should be placed on the high tolerance rate of subsequent vaccine doses in our COVID-19 vaccine reaction cohort even when most of the immediate reactions occurred within 1 hour, a time frame that may be more concerning to some individuals. These data can be used to address COVID-19 vaccine hesitancy that may still exist in both patients and health care providers.

Weaknesses of our study include its retrospective nature and limited standardization in the approach of different providers to the use of skin testing in these clinical situations, which limits our ability to provide a robust, systematic review of its utility. In addition, there is the potential for recall bias among the patients, particularly among those who presented for evaluation owing to a previous PEG or polysorbate allergy before receiving any vaccine.

In summary, we revealed a low rate of skin test positivity in patients evaluated for potential allergic reactions to the first dose of an mRNA COVID-19 vaccine and in patients with a previous history of PEG or polysorbate allergy before receiving any COVID-19 vaccine. There was a high rate of COVID-19 vaccine tolerance after evaluation, regardless of skin test result. This report reveals that excipient skin testing may be of minimal value in the evaluation of these patients. COVID-19 vaccine skin testing with offering of subsequent graded vaccine dosing according to established vaccine allergy guidelines may be the most reasonable and cost-effective strategy moving forward, although more study is needed to determine this.

References

1. Shimabukuro T, Nair N. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine. *JAMA*. 2021;325(8):780–781.
2. Shimabukuro TT, Cole M, Su JR. Reports of anaphylaxis after receipt of mRNA COVID-19 vaccines in the US-December 14, 2020-January 18, 2021. *JAMA*. 2021;325(11):1101–1102.
3. Greenhawt M, Abrams EM, Shaker M, et al. The risk of allergic reaction to SARS-CoV-2 vaccines and recommended evaluation and management: a systematic review, meta-analysis, GRADE assessment, and international consensus approach. *J Allergy Clin Immunol Pract*. 2021;9(10):3546–3567.
4. Dreskin SC, Halsey NA, Kelso JM, et al. International Consensus (ICON): allergic reactions to vaccines. *World Allergy Organ J*. 2016;9(1):32.
5. McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. *J Allergy Clin Immunol*. 2018;141(2):463–472.
6. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed large local reactions to mRNA-1273 vaccine against SARS-CoV-2. *N Engl J Med*. 2021;384(13):1273–1277.
7. Johnston MS, Galan A, Watsky KL, Little AJ. Delayed localized hypersensitivity reactions to the moderna COVID-19 vaccine: a case series. *JAMA Dermatol*. 2021;157(6):716–720.
8. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. *J Am Acad Dermatol*. 2021;85(1):46–55.
9. Banerji A, Wickner PG, Saff R, et al. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. *J Allergy Clin Immunol Pract*. 2021;9(4):1423–1437.
10. Garvey LH, Nasser S. Anaphylaxis to the first COVID-19 vaccine: is polyethylene glycol (PEG) the culprit? *Br J Anaesth*. 2021;126(3):e106–e108.
11. Klimek L, Novak N, Cabanillas B, Jutel M, Bousquet J, Akdis CA. Allergenic components of the mRNA-1273 vaccine for COVID-19: possible involvement of polyethylene glycol and IgG-mediated complement activation. *Allergy*. 2021;76(11):3307–3313.
12. 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.
13. 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.
14. Broyles AD, Banerji A, Barmettler S, et al. Practical guidance for the evaluation and management of drug hypersensitivity: specific drugs. *J Allergy Clin Immunol Pract*. 2020;8(9S):S16–S116.
15. Stone CA, Jr 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.
16. Marcelino J, Farinha S, Silva R, Didenko I, Proenca M, Tomaz E. Nonirritant concentrations for skin testing with SARS-CoV-2 mRNA vaccine. *J Allergy Clin Immunol Pract*. 2021;9(6):2476–2477.
17. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med*. 2021;384(7):643–649.
18. Greenhawt M, Abrams EM, Oppenheimer J, et al. The COVID-19 pandemic in 2021: avoiding overdiagnosis of anaphylaxis risk while safely vaccinating the world. *J Allergy Clin Immunol Pract*. 2021;9(4):1438–1441.
19. Kim MA, Lee YW, Kim SR, et al. COVID-19 vaccine-associated anaphylaxis and allergic reactions: consensus statements of the KAAACI Urticaria/Angioedema/Anaphylaxis Working Group. *Allergy Asthma Immunol Res*. 2021;13(4):526–544.
20. Klimek L, Jutel M, Akdis CA, et al. ARIA-EAACI statement on severe allergic reactions to COVID-19 vaccines - an EAACI-ARIA position paper. *Allergy*. 2021;76(6):1624–1628.
21. Murphy KR, Patel NC, Ein D, et al. Insights from American College of Allergy, Asthma, and Immunology COVID-19 vaccine task force: allergic reactions to mRNA SARS-CoV-2 vaccines. *Ann Allergy Asthma Immunol*. 2021;126(4):319–320.
22. Turner PJ, Ansotegui IJ, Campbell DE, et al. COVID-19 vaccine-associated anaphylaxis: a statement of the World Allergy Organization Anaphylaxis Committee. *World Allergy Organ J*. 2021;14:(2) 100517.
23. 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.
24. Wolfson AR, Robinson LB, Li L, et al. First-dose mRNA COVID-19 vaccine allergic reactions: limited role for excipient skin testing. *J Allergy Clin Immunol Pract*. 2021;9(9). 3308-3320.e3.
25. Krantz MS, Kwah JH, Stone Jr CA, et al. Safety evaluation of the second dose of messenger RNA COVID-19 vaccines in patients with immediate reactions to the first dose. *JAMA Intern Med*. 2021;181(11):1530–1533.
26. Gold MS, Gidudu J, Erlewyn-Lajeunesse M, Law B. Brighton Collaboration Working Group on Anaphylaxis. Can the Brighton Collaboration case definitions be used to improve the quality of Adverse Event Following Immunization (AEFI) reporting? Anaphylaxis as a case study. *Vaccine*. 2010;28(28):4487–4498.
27. Ruggeberg JU, Gold MS, Bayas JM, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007;25(31):5675–5684.
28. Sellaturay P, Nasser S, Ewan P. Polyethylene glycol-induced systemic allergic reactions (anaphylaxis). *J Allergy Clin Immunol Pract*. 2021;9(2):670–675.
29. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. *Clin Exp Allergy*. 2016;46(7):907–922.
30. 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.
31. Shelley WB, Talanin N, Shelley ED. Polysorbate 80 hypersensitivity. *Lancet*. 1995;345(8960):1312–1313.
32. Centers for Disease Control and Prevention. Interim Clinical Considerations for use of COVID-19 vaccines currently approved or authorized in the United States. 2020. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Accessed August 8, 2021.
33. Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. *BMJ Case Rep*. 2012;2012. bcr0220125797.
34. Pitlick MM, Park MA, Gonzalez-Estrada A, Chiarella SE. Biphasic anaphylaxis after first dose of messenger RNA coronavirus disease 2019 vaccine with positive polysorbate 80 skin testing. *Ann Allergy Asthma Immunol*. 2021;127(4):498–499.
35. Kelso JM, Greenhawt MJ, Li JT, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol*. 2012;130(1):25–43.
36. Mustafa SS, Ramsey A, Staicu ML. Administration of a second dose of the Moderna COVID-19 vaccine after an immediate hypersensitivity reaction with the first dose: two case reports. *Ann Intern Med*. 2021;174(8):1177–1178.