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Cohort experience of second messenger RNA vaccine dose tolerance after an initial-dose reaction



Concern arose on the increased rates of anaphylaxis for the 2 messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccines.^{1–3} The initial concern was that a history of allergy to food, medication, venom, or polyethylene glycol (PEG) increased this risk, but this has not been substantiated.^{3,4} Both mRNA vaccines require 2 doses to achieve optimal protection against infection.⁵ There is limited guidance on how to evaluate and proceed with the second dose in patients with reactions to the first.⁴ Owing to earlier vaccine supply issues, testing to the vaccine itself was not feasible, and graded dosing protocols or testing with similar excipients was proposed.^{6,7} The validity and necessity of such testing have been questioned and refuted recently.^{7,8}

This is a single-center, retrospective chart review of all patients evaluated for a possible allergic reaction to the first dose of Pfizer or Moderna COVID-19 vaccines in the allergy department of a large tertiary medical center from December 2020 through May 2021. All patients who received a vaccine within the medical system were sent a postvaccine symptom survey. Anyone with symptoms within 4 hours who were potentially allergic was referred for further evaluation.¹ In addition, referrals were made by primary care physicians. Patients who received a second dose after evaluation were contacted. This study aimed to characterize considerable adverse symptoms after the first dose and outcomes of second doses. The study protocol was approved by the Spectrum Health Institutional Review Board.

A total of 72 patients were evaluated for possible reactions to either the Pfizer or Moderna vaccines. We excluded 6 patients given

that their symptoms were not consistent with a reaction to the vaccine on the basis of unrelated symptoms with delayed onset. Of the 66 patients who were included, 56 (84.8%) were women, 90% were White, and the average age was 42 (range, 19–69 years). A total of 22 had reported a history of anaphylaxis (food or medicine) and none had a history of PEG or polysorbate allergy. Fifty-three patients (80.3%) successfully received their second vaccination (48 with known symptom outcomes [Table 1]), 12 (18.2%) refused as per patient choice (including the only person treated with epinephrine for a dose 1 reaction), and 1 (1.5%) did not receive dose 2 as per allergist recommendation.

A total of 18 patients had hives or angioedema with no respiratory, cardiac, or gastrointestinal symptoms after their first dose (Table 1). Five of these had preexisting long-term hives and experienced worsening after the vaccine. Nine patients with no history of urticaria experienced hives, with a median onset of 1 hour after vaccination (range, 15 minutes to 5 days) and a duration of 3 days (range 6 hours to 60 days) after dose 1. Four patients had periorbital or facial angioedema with a median onset of 4 hours after vaccination (range 30 minutes to 1 day) and duration of 1 day (1 had a duration of 7 days) after dose 1. Thirteen of these patients received a second dose; only 5 had a recurrence of symptoms with none being more severe, with no cases of anaphylaxis. Nonurticarial rashes were seen in 5 patients after dose 1, with 2 having delayed onset (both at 8 days) at the site of injection, 1 with lip dermatitis (history of dermal filler use), and 2 with viral exanthem. A total of 3 patients, including the

Table 1
Summary of Symptoms After Dose 1 and Outcomes of Second Doses

Symptom	Dose 1			Dose 2			
	N (%)	Pfizer (N)	Moderna (N)	Received second dose (N), if symptoms known ^a	Same symptoms recurred, if known (N)	Pfizer (N)	Moderna (N)
Hives or angioedema	18 (26.1%)	16	2	13 ^b	5 (38%)	4	1
New onset hives	9	9	0	5	1 (20%)	1	0
New onset angioedema	4	4	0	4	1 (25%)	1	0
Flaring long-term hives	5	3	2	4	3 (75%)	2	1
Anaphylaxis ^c	2 (2.9%)	1	1	2	Both desensitized, ^d no adverse events		
Delayed onset rash	5 (7.2%)	3	2	3	0 (0%)		
Large local reaction	2	1	1	0			
Lip dermatitis	1	1	0	1	0 (0%)		
Viral exanthem	2	1	1	2	0 (0%)		
Subjective itching, warmth, SOB, palpitations, and/or throat tightness	22 (31.9%)	15	7	18 (6 supervised, 2 by graded challenge)	8 (44%)	7	1
Dizziness, numbness, tingling, tinnitus, and/or vision changes	11 (16.6%)	8	3	7	1 (17%)	0	1
Loss of smell/taste	1 (1.4%)	1	0	0			
GI symptoms	1 (1.4%)	0	1	1	0 (0%)		
Expected symptoms including headache, fever, body aches	6 (8.7%)	5	1	4	3 (75%)	2	1
Total	66	49 (74%)	17 (26%)	48 (72.7%) ^e	17 (36%)	13 (76%)	4 (24%)

Abbreviations: GI, gastrointestinal; SOB, shortness of breath.

^aPatients were contacted after their second dose to assess the recurrence of symptoms. Those that responded are summarized here. None developed a different type of symptom. None had anaphylaxis.

^bFour pretreated with antihistamines.

^cBoth patients developed hives, flushing, shortness of breath, and feeling of impending doom within 30 minutes.

^dA 6-step graded-dose protocol with Pfizer vaccine (0.003 mL, 0.009 mL, 0.018 mL, 0.04 mL, 0.08 mL, 0.15 mL; final volume 0.3 mL).

^eFive additional patients received the vaccine but could not be reached; recurrence of symptoms is unknown.

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patient with lip dermatitis, received their second vaccination, with no recurrence of symptoms.

Two patients had symptoms consistent with anaphylaxis (within 30 minutes, developed hives, flushing, shortness of breath, feeling of impending doom) after dose 1. Neither received epinephrine. Both underwent successful desensitization procedures for their second dose (Table 1, footnote d).² Of the patients with a history of anaphylaxis unrelated to the vaccine, 18 received their second dose. Seven of them had symptoms, with 2 patients having hives and 5 with subjective shortness of breath or itching. None required epinephrine.

Twenty-two patients had subjective symptoms including shortness of breath, palpitations, feeling warm, or throat tightness after dose 1; 10 had a previous history of unrelated anaphylaxis. Because of the unclear symptom causation, the initial 6 patients were observed by an allergist for their second dose by means of either a graded vaccine challenge (10% and 90%) or direct challenge, and no patients had a reaction. The rest were instructed to get their second dose normally with no additional observation. Overall, 18 received their second dose. Eight (44%) had a recurrence of symptoms, but all were deemed to be less severe than the initial symptoms with no resultant anaphylaxis.

Subjective neurologic complaints of dizziness, vision changes, numbness, or tingling of mouth or extremities occurred in 10 patients after dose 1. The median onset was 30 minutes (range 15 minutes to 5 days) and duration of 14 hours (range 45 minutes to several weeks), with all symptoms resolved. Seven received their second dose and only 1 had a recurrence of symptoms. One patient with a history of COVID-19 infection causing loss of smell and taste had symptom recurrence after the initial Pfizer vaccine; it was recommended this patient not receive a second dose. One patient with a history of hyperemesis gravidarum had a recurrence of repetitive vomiting the day of the first dose, but no recurrence with the second.

All 51 patients (77.3%) tolerated the second dose and none had what would be considered dose-limiting symptoms that would preclude future vaccine administration. No severe reactions or new cases of anaphylaxis were observed. Patients with nonanaphylactic reactions after dose 1, but with symptoms concerning immunoglobulin E (IgE)-mediated reactions including hives and angioedema, successfully received their second dose without preceding skin testing for risk stratification. The 2 patients with anaphylaxis tolerated their second dose with a graded-dose protocol. Neurologic and gastrointestinal symptoms were also mild and temporary. Our experience does

not support extensive skin testing to aid in the decision to give a second dose to patients with mild to moderate symptoms, similar to what others have found.^{8–10} The mechanisms of these reactions are unknown, although immediate reactions may be related to non-IgE-mediated mechanisms, whereas delayed symptoms may be owing to vaccine-induced immune response. This presents an opportunity for shared decision-making when discussing the second dose of mRNA vaccine in a patient who had a reaction to the first dose.

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Atopic comorbidity has no impact on severity and course of Coronavirus disease 2019 (COVID-19) in adult patients



In the beginning of the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, chronic airway diseases were discussed to be risk factors for a severe outcome of COVID-19, as epithelial barrier dysfunction in allergic rhinitis or asthma was suspected to increase susceptibility for SARS-CoV-2 infection, potentially leading to increased symptoms or prolonged recovery.^{1,2}

This was based on previous investigations revealing pollen exposure can decrease immune defense against respiratory viruses.^{3,4} Moreover, high airborne pollen concentrations were correlated with

increased SARS-CoV-2 infection rates, whereas pollen or particulate matter was not found to serve as transmitters for viral particles.^{4,5} Studies have revealed that T_H2-dominated diseases are associated with lower viral defense mechanisms owing to a reduced antiviral interferon response, altogether increasing the susceptibility for respiratory viral infections or even systemic infections in patients with atopy.^{1,3,4} Several international studies, however none from Germany, have investigated possible effects of atopic disorders on COVID-19 disease and recently even a protective effect was suggested.^{6,7}

In a retrospective, questionnaire-based study, we aimed at analyzing the impact of atopic diseases on the course and severity of COVID-19 in adult patients with confirmed SARS-CoV-2 infection in our

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