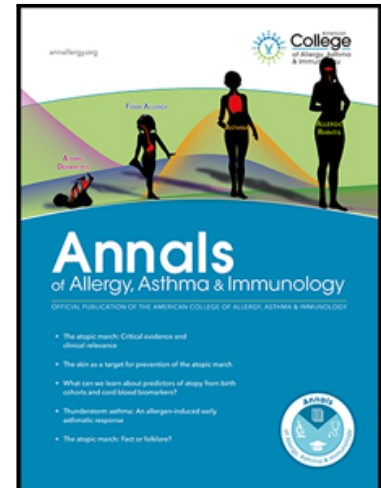


COVID-19 Vaccine Hypersensitivity Evaluated with Vaccine and Excipients Allergy Skin Testing

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**Conflicts of Interest:**

Anita Kohli-Pamnani MD reports consulting and speaking for Pfizer outside the submitted work.

Pamela L. Kwittken MD consulted on an Advisory Board Meeting for EyeVance

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Polyethylene glycol; Polysorbate

**Abbreviations:** CBC, Complete blood count; H1, Type 1 Histamine Receptor; H2, Type 2 Histamine Receptor; IgE, Immunoglobulin E; mg, milligrams; mRNA, messenger Ribonucleic Acid; PEG, Polyethylene Glycol; SC5B-9, Soluble Terminal Complement Complex

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**Tables:** 1

Since COVID-19 mRNA vaccines became available, VAERS data and early reports identified rare cases of anaphylaxis.<sup>1</sup> Banerji et al<sup>2</sup> proposed a suggested approach to skin test for COVID-

19 vaccine excipients, specifically polyethylene glycol (PEG), polysorbate 80 and polysorbate 20. Utilizing this algorithm, and skin testing with COVID-19 mRNA vaccine leftover from vial overfill, we report findings in a case series of 39 patients referred to an Allergy and Immunology practice for possible COVID-19 vaccine hypersensitivity January through May 2021.

Expanded skin testing for COVID-19 vaccine excipients was performed as previously published.<sup>2</sup> Additionally, percutaneous and intradermal skin tests (1:10 dilution and full strength both for pricks and intradermals) with Moderna/Pfizer COVID-19 vaccines were completed. We recorded whether premedication was used and analyzed available laboratory data (serum tryptase, SC5B-9, CBC with differential). Premedication could consist of H1/H2 blockers and/leukotriene antagonists. An example regimen was Cetirizine 20 mg, Famotidine 40 mg and Monteleukast 10 mg daily starting three days before vaccine. Patient outcome, or vaccine tolerance was assessed through follow up and/chart review.

Patient characteristics and atopic conditions are shown, Table 1. 77% (n=30) of patients were referred for reactions to COVID-19 mRNA vaccine. The remaining 23% (n=9) were referred for other high risk history for potential reaction to vaccine. The most common clinical presentation (Table I.) was urticaria and/or angioedema, immediate (within 4 hours) in 36% of patients (n=14) and delayed (beyond 4 hours) in 28% of patients (n=11). Overall, 46% of reactions were immediate (n=18), mean time to occurrence was 32 minutes. 31% of reactions were delayed (n=12), average time to manifestation was 3.8 days. Such designation was not applicable in 23% (n=9) referred for other high risk history.

None of the patients had positive percutaneous or intradermal skin tests for COVID-19 vaccine excipients. 11% of patients (n=4) had positive intradermal skin testing to COVID-19 vaccines of unclear clinical significance (3 patients with immediate positive intradermal skin testing to

Moderna vaccine, 1 patient with delayed full strength positive intradermal to Pfizer vaccine).

The skin test positive patients also tolerated subsequent vaccine.

95% of patients (n=37) tolerated their succeeding COVID-19 vaccine without serious allergic reaction. 92% (n=36) have received two doses of COVID-19 vaccines. One patient pre screened due to severe chronic idiopathic urticaria and angioedema elected to receive Janssen vaccine.

62% of the patients (n=23) who tolerated their subsequent COVID-19 vaccine received premedication.

One patient with initial reaction to Moderna experienced nausea and pruritus during skin testing similar but milder than initial reaction. Despite negative skin test results, this necessitated intramuscular Epinephrine. An elevated serum tryptase level (11.6 ug/L) was obtained with 24 hour delay (basal/post unavailable). Subsequently, the patient tolerated Janssen vaccine without incident in lieu of the second Moderna dose. Another patient with chronic urticaria starting four days after Moderna had an elevated serum tryptase level obtained weeks after his vaccine (25.7 ug/L). Subsequent bone marrow and diagnostic criteria confirmed indolent systemic mastocytosis.

16% (n=6) of patients who tolerated their following dose of COVID-19 vaccine did experience mild allergic symptoms that were self-limited or treatable with antihistamines. 5% (n=2) were either unreachable for follow up, or the patient declined the ensuing dose.

Our data in a private practice setting exhibits similarities to the findings of Banerji et al in 16 health care employees of a large university hospital system.<sup>3</sup> They completed pre-mRNA vaccination excipient skin testing and demonstrated an 88% tolerance of first dose COVID-19 vaccine in individuals with a high risk allergy history. Our population differs in that a high percentage (77%, n=30) of patients in our report had vaccine reactions as their referral reason.

Three case reports of 4-14 patients demonstrated negative vaccine/excipient skin tests and tolerance of consequent mRNA COVID-19 vaccine in patients with first dose reactions or other high risk history.<sup>4-6</sup> Recently, Robinson et al<sup>7</sup> published prospective data from 1,261 Mass General Brigham employees with self-reported COVID-19 mRNA vaccine allergic symptoms. Most of the patients with mild hypersensitivity or non-immediate symptoms safely completed the two dose vaccine series. To our knowledge, we report the first large series of COVID-19 vaccine hypersensitivity referrals in a private Allergy and Immunology practice.

Since private practices did not have access to full vials of vaccine for administration during the period of study, there was not an option of graded challenge. Some patients with more severe symptoms of immediate hypersensitivity reactions with or without positive skin tests to vaccine may have benefitted from graded dose challenge or desensitization.<sup>8</sup> Our findings, though, suggest a simpler paradigm in that most individuals with prior reactions would be able to receive their subsequent COVID-19 vaccine dose with or without premedication, or by treating through mild to moderate allergic symptoms.

A limitation was that non-irritant skin test concentrations of COVID-19 vaccine have not yet been established. We did skin test control individuals on our health care team, and skin tests were negative, suggesting positive immediate intradermal skin tests at 1:10 and full strength were likely non-irritant. A study of 131 patients with idiopathic anaphylaxis found negative pre screening percutaneous tests for COVID-19 mRNA vaccines and excipients including trometamol (buffer in Moderna vaccine associated with anaphylaxis to gadolinium contrast).<sup>9</sup> However, intradermal skin testing was not performed.

Our findings did not demonstrate an IgE mediated pathogenesis for immediate type COVID-19 vaccine hypersensitivity, given vastly negative skin tests. There may be non-specific mast cell

histamine release which can be countered with premedication or treating through the reactions.

Other researchers espoused that theory based on their clinical findings and experience with premedication for possible allergic reactions to COVID-19 mRNA vaccine.<sup>6</sup> We could not confirm whether CARPA (complement activation related pseudoallergy) was a putative mechanism but found no evidence of abnormal complement levels in the few patients where SC5B-9 was obtained.

A systematic review cites overall utility of skin testing for COVID-19 vaccine and excipients to be of uncertain diagnostic value.<sup>10</sup> However, there are limited patients with COVID-19 vaccine hypersensitivity skin tested with vaccine in the published literature to guide decision making. Further research in this area is urgently warranted.

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**Table 1. Patient Characteristics, COVID-19 Vaccine Hypersensitivity**

|                                                            |                                                                 |
|------------------------------------------------------------|-----------------------------------------------------------------|
| Age, Mean (SD), y                                          | 56 (16)                                                         |
| Gender, No. (%)                                            | Female 34 (87) , Male 5 (13)                                    |
| Ethnicity, No. (%)                                         | Caucasian 34 (87), African American 3 (8), Hispanic 2 (5)       |
| Vaccine, No. (%)                                           | Moderna 19 (47.5), Pfizer 19 (47.5), Janssen 2 (5) <sup>a</sup> |
| Patients On Baseline Antihistamine, No. (%)                | 14 (36)                                                         |
| Patients On Baseline Monteleukast, No. (%)                 | 8 (21)                                                          |
| Peripheral Eosinophilia, No. (%)                           | 3 (8)                                                           |
| Elevated Serum Tryptase, No. (%)                           | 2 (5)                                                           |
| Atopic, No. (%)                                            | 37 (95)                                                         |
| <b>Concomitant Allergic Disorders, No. (%)<sup>b</sup></b> |                                                                 |
| Allergic Rhinitis                                          | 21 (54)                                                         |
| Antibiotics Allergy                                        | 21 (54)                                                         |
| Asthma/COPD                                                | 12 (31)                                                         |
| Food Allergy                                               | 8 (21)                                                          |
| Chronic Idiopathic Urticaria and/Angioedema                | 16 (41)                                                         |

|                                                                                                     |                     |
|-----------------------------------------------------------------------------------------------------|---------------------|
| Mastocytosis                                                                                        | 1 (3)               |
| <b>Most Common Reactions, No. (%)</b>                                                               |                     |
| Immediate Urticaria and/Angioedema (< 4 hours following vaccine)                                    | 14 (36)             |
| Delayed Urticaria and/Angioedema (> 4 hours following vaccine)                                      | 11 (28)             |
| Asthma/COPD/Chest tightness/Shortness of breath                                                     | 3 (8)               |
| Syncopal/Vasovagal                                                                                  | 2 (5)               |
| <b>Concerning High Risk History for Potential to Have Allergic Reaction Upon Receipt of Vaccine</b> |                     |
| Allergy to Meds/Other High Risk Allergy History (Includes Latex/Hymenoptera)                        | 5 (13)              |
| Reaction to Other Vaccines/Injectables                                                              | 6 (15) <sup>c</sup> |
| Clinical History of Concern for Polyethylene Glycol (PEG) Allergy                                   | 2 (5)               |
| <b>Treatments of Acute Vaccine Reactions Requiring IM Epinephrine And/Systemic Corticosteroids</b>  |                     |
| Received IM Epinephrine and Systemic Corticosteroids, No. (%)                                       | 2 (5)               |
| Received Systemic Corticosteroids Only, No. (%)                                                     | 2 (5)               |

<sup>a</sup> 40 vaccines, 39 patients (One received Moderna then Janssen)

<sup>b</sup> Total percentages exceed 100% due to overlap.

<sup>c</sup> 4 patients/influenza vaccine; 2/omalizumab

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; IM, Intramuscular; No., Number; SD, Standard Deviation; y, years