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4. McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. *J Allergy Clin Immunol*. 2018;141(2):463–472.
5. 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):3307–3331.
6. Kozma GT, Shimizu T, Ishida T, Szebeni J. Anti-PEG antibodies: properties, formation, testing and role in adverse immune reactions to PEGylated nano-biopharmaceuticals. *Adv Drug Deliv Rev*. 2020;154–155:163–175.
7. Kohli-Pamnani A, Zapata K, Gibson T, Kwittken PL. Coronavirus disease 2019 vaccine hypersensitivity evaluated with vaccine and excipient allergy skin testing [e-pub ahead of print]. *Ann Allergy Asthma Immunol*. doi:10.1016/j.anai.2021.08.417, accessed November 18, 2021.
8. Jönsson F, de Chaisemartin L, Granger V, et al. An IgG-induced neutrophil activation pathway contributes to human drug-induced anaphylaxis. *Sci Transl Med*. 2019;11(500):eaat1479.

Coronavirus disease 2019 messenger RNA vaccine skin tests and serum histamine levels in allergic reactions



We thank de Chaisemartin et al¹ for their correspondence in regard to our manuscript, “Coronavirus disease 2019 vaccine hypersensitivity evaluated with vaccine and excipient allergy skin testing.”² De Chaisemartin et al¹ elucidate their findings of transient elevation of serum histamine levels in 1 of 5 patients with anaphylaxis after messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccine. Conversely, 4 of 5 patients had normal serum histamine and tryptase levels within 2 hours of anaphylaxis.

De Chaisemartin et al¹ reflect that their findings of transient or lack of elevated serum histamine levels after COVID-19 mRNA anaphylaxis parallel with our findings of negative excipient skin test results (polyethylene glycol [PEG], polysorbate 20 and 80) and limited positive intradermal skin test results with the vaccine. Our 4 of 39 patients with positive intradermal skin testing results to the vaccine tolerated their ensuing dose of COVID-19 mRNA vaccine. The common thread in our findings and those of de Chaisemartin et al¹ is the suggestion that antihistamine premedication may prevent some allergic reactions.³ Most patients will tolerate subsequent vaccination with the mRNA COVID-19 vaccine with or without premedication.^{1–7} In the report of de Chaisemartin et al,¹ 3 of 5 patients tolerated their consequent COVID-19 mRNA vaccine. Furthermore, 1 patient already received their second dose to which anaphylaxis had occurred. In addition, 1 patient passed away from unrelated cause before the receipt of vaccine dose 2. In our case series, 95% (n = 37) tolerated their succeeding COVID-19 vaccine without serious allergic reaction. Moreover, 92% (n = 36) received 2 doses of their COVID-19 vaccines. Of the patients who tolerated their subsequent mRNA vaccines, 62% received premedication, which could include H₁ and H₂ antihistamines and leukotriene inhibitors.

A potential explanation of transiently elevated serum histamine levels in the patient described by de Chaisemartin et al¹ could be basophil activation. Warren et al⁸ revealed that 11 patients with anaphylactic reactions to the COVID-19 mRNA vaccine had negative skin test results to the vaccine and excipients. Nevertheless, most had positive basophil activation test results to PEG. All had positive basophil activation test results to the mRNA vaccine. Notably, PEG immunoglobulin G was found despite undetectable PEG immunoglobulin E in the tested patients with allergic reactions.

In summary, de Chaisemartin et al¹ raise an interesting point on possible transient elevation of serum histamine levels. Further research is necessary to characterize skin tests with the specific vaccines and biomarkers such as serum histamine levels to evaluate which endotypes of post-COVID-19 mRNA vaccine allergic reactions may benefit from premedication or desensitization to COVID-19 mRNA vaccines.

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References

1. de Chaisemartin L, Diep A, Gonnin C, Soria A, Barbaud A, Nicaise-Roland P. Immune parameters during anaphylaxis to mRNA COVID-19 vaccines: not the usual suspects? *Ann Allergy Asthma Immunol*. Correspondence, in press.
2. Kohli-Pamnani A, Zapata K, Gibson T, Kwittken PL. Coronavirus disease 2019 vaccine hypersensitivity evaluated with vaccine and excipient allergy skin testing. *Ann Allergy Asthma Immunol*. 2022;128(1):97–98.
3. Krantz MS, Bruusgaard-Mouritsen MA, Koo G, Phillips EJ, Jr Stone CA, Garvey LH. Anaphylaxis to the first dose of mRNA SARS-CoV-2 vaccines: don't give up on the second dose! *Allergy*. 2021;76(9):2916–2920.
4. Krantz MS, Kwah JH, Stone CA Jr, et al. Safety evaluation of the second dose of messenger RNA COVID-19 vaccines in patients with immediate reactions to the first dose. *JAMA Intern Med*. 2021;181(11):1530–1533.
5. 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.
6. Kaplan B, Farzan S, Coscia G, et al. Allergic reactions to coronavirus disease 2019 vaccines and addressing vaccine hesitancy: Northwell Health experience [e-pub ahead of print]. *Ann Allergy Asthma Immunol*. 2021. doi: 10.1016/j.anai.2021.10.019. Accessed March 1, 2022.
7. Robinson LB, Landman AB, Shenoy ES, et al. Allergic symptoms after mRNA COVID-19 vaccination and risk of incomplete vaccination. *J Allergy Clin Immunol Pract*. 2021;9(8):3200–3202.e1.
8. Warren CM, Snow TT, Lee AS, et al. Assessment of allergic and anaphylactic reactions to mRNA COVID-19 vaccines with confirmatory testing in a US regional health system. *JAMA Netw Open*. 2021;4(9):e2125524.