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PEG/Polysorbate Skin Testing Has No Utility in the Assessment of Suspected Allergic Reactions to SARS-CoV-2 Vaccines



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The year 2021 is becoming one of hope in overcoming this terrible SARS-CoV-2 pandemic, thanks to the development of several safe and highly effective vaccines and a rapid vaccination implementation program, which reduced the incidence of COVID-19-related fatality, severe infection, and even person-to-person transmission.¹ After 2020 bore witness to nearly 2 million fatalities and over 100 million infections at a societal cost of nearly 10 billion dollars, the success of the SARS-CoV-2 vaccines has been nothing short of a modern miracle of medical

research.² When needed the most, science once again prevailed, and rapidly.

However, despite the tremendous success and very good overall safety profile of these vaccines, concerns emerged regarding immediate and delayed SARS-CoV-2 vaccine reactions, including anaphylaxis.¹ Anxiety about these potential vaccine complications likely hampered SARS-CoV-2 immunization efforts.^{3,4} Shortly after the initial case reports of vaccine reactions, the US Centers for Disease Control and Prevention and other global health authorities acted swiftly to contraindicate the vaccine among patients with a history of an immediate allergic reaction to the first dose of the vaccine or to any of the vaccine excipients, most notably polyethylene glycol (PEG) in mRNA vaccines and polysorbate 80 in adenovirus vector vaccines.^{1,2} Still, it must be appreciated that SARS-CoV-2 vaccine anaphylaxis is a rare event, estimated at 7.9 per million doses globally, in a recent meta-analysis.¹

In an effort to provide guidance, Banerji et al⁵ published an expert-based institutional protocol recommending screening skin tests for individuals with PEG/polysorbate allergy (or a reported allergic reaction to a prior vaccine dose), advising that vaccination be withheld if PEG/polysorbate skin testing is positive but that vaccination could proceed in those with negative testing. Investigators from the same group subsequently provided a report of 472 high-risk employees who had allergist guidance before initial SARS-CoV-2 vaccination, noting that 16 underwent excipient skin testing to PEG/polysorbate, with just 1 patient showing sensitization to PEG (who tolerated the Janssen vaccine).⁶

In this issue of *J Allergy Clin Immunol Pract*, Wolfson et al⁷ update the experience of this same group with the results of excipient skin testing in their large cohort of patients with both immediate and delayed first-dose SARS-CoV-2 vaccine reactions. On the basis of the data in this report, the authors are able to refute their previous hypothesis that excipient skin testing could help to inform management of patients with reported allergy to PEG/polysorbate or the SARS-CoV-2 vaccine.^{5,7} An important finding is that excipient skin testing has very poor sensitivity.⁷ There are also concerns regarding test specificity, with Refresh Tears (the reagent used for polysorbate 80 testing) proving to have a significant irritant effect. Of 25 controls tested to Refresh Tears, an irritant response was found in 13 subjects (52%).⁷ The authors now conclude that skin testing does “not impact tolerance of a second dose in patients with immediate or delayed reactions.”⁷ In fact, of 80 patients evaluated, 88% received their second vaccine dose, and 89% of these had either no reaction or a reaction managed with antihistamines—despite the fact that 18% of this cohort had positive skin testing to PEG, polysorbate, or both.⁷

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The experience reported by Wolfson et al echoes that of a handful of other reports showing that persons with first dose reactions can safely be re-vaccinated.¹ Globally, no convincing evidence has demonstrated PEG and/or polysorbate to be the causal allergens responsible for allergic reactions to SARS-CoV-2 vaccines.¹

So, what does this mean for the clinician? The data now suggest that excipient skin testing in the context of SARS-CoV-2 vaccination is not justified when viewed through an evidence-based lens.^{1,7} If the clinician and patient nevertheless decide to pursue such testing, Wolfson et al⁷ reinforce the importance of a shared decision-making approach to either provide supervised administration of a second mRNA dose, or change the type of vaccine platform (eg, to adenovirus vector vaccine) for patients with a positive vaccine skin test. This paradigm echoes the recently published GRADE-based international consensus document.¹ In this guidance, the pooled sensitivity for PEG skin testing for suspected PEG reactions (in the non-SARS-CoV-2 vaccine context) was 58.8%, with 99.5% specificity.¹ The authors of that document make evidence-based recommendations against SARS-CoV-2 vaccine excipient testing in persons either with or without a history of a reaction to the vaccine or a vaccine excipient.¹

Although Wolfson et al suggest that more data are needed to inform the necessity of a skin testing approach for SARS-CoV-2 vaccine anaphylaxis, we must recognize that there is already sufficient evidence (which includes their data) of a lack of efficacy for such testing in patients with allergic reactions to SARS-CoV-2 vaccines.^{1,7} In the high-risk population they studied, among those PEG skin test positive patients with an immediate allergic reaction to a first dose of a SARS-CoV-2 vaccine ($n = 4$), all patients who received a second dose ($n = 2$) tolerated it.⁷ This contrasts with the results of skin test negative patients with a prior immediate first dose reaction ($n = 57$), of whom 23% experienced a second dose reaction.⁷ Although these are small numbers, and additional study would always be helpful to increase the certainty of evidence and better-informed medical decision making,² these data strongly suggest that excipient testing in the setting of allergic reactions to SARS-CoV-2 vaccines does not have efficacy.⁷ The notion that reaction severity alters PEG skin test precision (ie, sensitivity and specificity) in detection of allergen specific IgE is intriguing, but remains unproven.¹ Based on their data, an algorithm should no longer include a recommendation supporting routinely performing such testing in the context of SARS-CoV-2 vaccination.^{1,7}

Wolfson et al have advanced our understanding of SARS-CoV-2 vaccine reactions, through a comprehensive and diligent study of the performance of PEG and polysorbate skin testing,

thus helping the science surrounding the management of allergy to this vaccine to evolve.⁷ Their work echoes a similar evolution of thinking about vaccine excipient allergy that occurred in the wake of the 2009-10 H1N1 pandemic, regarding the now disproven risk of egg (ovalbumin)-containing modern influenza vaccines and risk of allergic reactions in egg-allergic individuals.⁸ It is commendable that this thought transformation with SARS-CoV-2 vaccines and PEG/polysorbate has happened within months of the first vaccine-related incidents, rather than slowly evolving over years as with ovalbumin and influenza vaccines. We are barely 6 months into the vaccine campaign, but already we have multiple high-quality research studies and a systematic review that have rapidly evolved the knowledge base regarding these vaccine reactions, and in real time we are making adjustments that, relative to other vaccines, took years.¹ That is progress, and represents the commitment of the allergy research community for high-quality, pragmatic, and timely research to make sure that we do not make the same mistake twice regarding vaccine excipient allergy and testing.

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