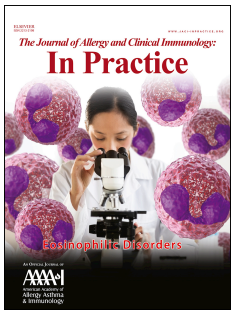

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COVID-19 Vaccination in Patients with Reported Allergic Reactions: Updated Evidence and Suggested Approach

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Centers for Disease Control and Prevention, CDC
Mass General Brigham, MGB
Polyethylene glycol, PEG

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Conflicts of Interest

None.

Background

As of March 25, 2021, over 124 million people globally have been diagnosed with a COVID-19 infection and almost 2.7 million have died from COVID-19.[1] This international pandemic was met with the rapid development and Food and Drug Administration (FDA) approval under Emergency Use Authorization (EUA) of two effective COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) in December 2020. Unfortunately, within days, severe allergic reactions to the COVID-19 mRNA vaccines occurred creating a potential barrier to large-scale vaccination efforts. To address this unmet need amidst great uncertainty, in December 2020, we published initial algorithms to help the allergist guide safe vaccination in individuals with allergy histories.[2]

Since then, more than 46 million individuals have been fully vaccinated and more than 2 million additional Americans receive their vaccinations daily.[3] The Centers for Disease Control and Prevention (CDC), using VAERS and V-safe voluntary reporting data, described the rate of anaphylaxis after receipt of the mRNA COVID-19 vaccines as 4.5 cases per million doses administered with 89% occurring within the 15 to 30 minute observation period.[4-6] This is comparable to anaphylaxis rates with other vaccines including the inactivated influenza vaccine (1.4 per million), pneumococcal polysaccharide vaccine (2.5 per million), and the live attenuated herpes zoster vaccine (9.6 per million).[4] However, prospective cohort data from over 60,000 Mass General Brigham (MGB) employees found a higher incidence rate of anaphylaxis to the mRNA COVID-19 vaccines at 2.47 per 10,000 vaccinations.[7] The marked difference in observed incidence rates likely relates to incomplete CDC capture of cases, although the MGB cohort may have a higher rate than some US populations because of demographic or geographic effects.

Janssen COVID-19 Vaccine

On February 27, 2021, the FDA issued EUA approval for a third COVID-19 vaccine from Janssen (Johnson and Johnson) in individuals $\geq$18 years of age. This is an adenovirus type 26

vectored vaccine encoding a stabilized variant of the SARS-CoV-2 spike protein showing high efficacy with 100% protection from death or hospitalization (similar to the mRNA COVID-19 vaccines available under EUA in the United Sates) following the currently recommended single dose. The pivotal phase III trial data reported urticaria in five vaccinated individuals and one individual who received placebo in the 7 days following vaccination. One hypersensitivity reaction deemed likely related to vaccine, not classified as anaphylaxis, was reported in one vaccinated individual with urticaria beginning two days following vaccination and angioedema of the lips without respiratory distress beginning four days following vaccination.[8] Additionally, one case of anaphylaxis among 110,000 in an ongoing open-label study in South Africa has been reported following the Janssen COVID-19 vaccine administered in clinical studies.[9]

Updated CDC Vaccination Guidance

Despite increasing knowledge, the mechanism of allergic reactions to any of the COVID-19 vaccines remains unclear but the excipients within these vaccines remain a possibility. Polyethylene glycol (PEG) is the common excipient in both mRNA COVID-19 vaccines while polysorbate 80 is the excipient in the Janssen COVID-19 vaccine. PEG and polysorbate are structurally related, and skin testing have shown cross-reactive hypersensitivity in rare cases when evaluation to both excipients has been pursued. Polysorbate 80 as an excipient cause of anaphylaxis is extremely rare with just one case report of vaccine anaphylaxis thought to be related to polysorbate 80 in the literature.[10]

At the time of publication, updated CDC guidance[11] states (1) if you are allergic to PEG, you should not receive an mRNA COVID-19 vaccine and instead speak to your physician about receiving the Janssen COVID-19 vaccine; (2) if you are allergic to polysorbate 80, you should not receive the Janssen COVID-19 vaccine and instead speak to your physician about receiving the mRNA COVID-19 vaccines; (3) a history of polysorbate allergy is a precaution rather than a contraindication to mRNA vaccination;[13] and (4) vaccination of these individuals (i.e., those with PEG or polysorbate allergy histories) should only be undertaken under the supervision of a health care provider experienced in the management of severe allergic reactions.[13] Therefore, the CDC suggests that individuals with a contraindication to the mRNA COVID-19 vaccines (due to a history of possible PEG allergy) may be considered for the Janssen COVID-19 vaccine and

similarly, individuals with a contraindication to the Janssen COVID-19 vaccine (due to a history of possible polysorbate allergy) may be considered for the mRNA COVID-19 vaccines. The CDC also provides guidance around use of Janssen COVID-19 vaccine if the recipient develops a severe allergic reaction to dose one of an mRNA COVID vaccine, allowing for Janssen vaccination provided a delay between mRNA and Janssen vaccination of at least 28 days.[11] There are currently no efficacy data on this "mix and match" approach and we do not know the long-term durability of protection from any of the current COVID-19 vaccines.

Pre-Vaccine Risk Stratification: Outcomes

Since vaccination efforts were initiated at MGB, 16 employees with high-risk allergy histories were referred to Allergy/Immunology and underwent risk stratification prompting skin testing prior to initial COVID-19 vaccination (**Figure 1**). Our prior protocols were used.[2] Referral reasons included a history of a severe allergic reaction to: a vaccine or injectable with PEG/polysorbate (n=8), oral PEG (n=4), other vaccine or injectable (n=3), and food, drug, venom or latex (n=1). Only one employee, with a history of oral PEG allergy, was skin test positive to methylprednisolone acetate (4 mg/mL intradermal, 10x30mm), which contains PEG as an excipient. This employee subsequently tolerated the Janssen COVID-19 vaccine. Among the skin test negative individuals (n=15) that received the first dose (n=13), no allergic reactions were observed (9 Pfizer-BioNTech, 2 Moderna, 2 Janssen). At the time of publication, two employees with negative skin testing, await COVID-19 vaccination.

Pre-Vaccine Risk Stratification: Algorithm

With additional clinical data and approval of the third COVID-19 vaccine in the United States, we now propose modified approaches to the evaluation of patients with reported allergy histories that remain consistent with CDC guidance (**Figure 2**). While these algorithms provide guidance, until COVID-19 vaccine supply increases, the primary role of the allergist is to enable patients to safely receive the first vaccine available to them. This may require allergist evaluation for PEG and/or polysorbate allergy depending on vaccine availability.

Similar to our initial algorithm,[2] individuals with any history of anaphylaxis should continue to be monitored for 30 minutes after receiving an mRNA COVID-19 vaccine. Following current

CDC guidance,[11,13] individuals who self-report a PEG allergy only can be considered for Janssen COVID-19 vaccine while individuals who self-report with a polysorbate only allergy can be considered for mRNA COVID-19 vaccines after shared decision making with their physician. For COVID-19 vaccine naïve individuals, clarification of polysorbate allergy can be easily assessed by asking about tolerance of other common vaccines with polysorbate 80 (**Table 1**). In patients with history of PEG anaphylaxis, cross-reactivity to polysorbate 80 and other PEG derivatives may be a significant problem[12] and more data are needed to assess whether these individuals will tolerate the low concentrations of polysorbate 80 present in the Janssen vaccine (and other SARS-CoV-2 vaccines in development).

Conclusions

Severe allergic reactions to COVID-19 vaccines remain exceedingly rare and the mechanism of these reactions requires further investigations. All vaccine sites should continue to observe higher risk individuals following CDC guidelines and have staff trained in recognizing and managing anaphylaxis. As our experience and knowledge with COVID-19 variants vaccines increases, we must continue to remain flexible with our approach. Our updated pre-vaccine risk stratification algorithm can be used in conjunction with the previously published skin testing guidance.[2] In the meantime, the potential life-saving benefit of vaccination makes it essential that Allergists continue to carefully evaluate and advise all patients with allergy histories and prevent denying access to the vaccine unnecessarily.

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Polysorbate	Vaccine Name	Vaccine Type	Total mg per dose
Polysorbate 20	Havrix (adult)	HepA	0.050
Polysorbate 20	Flublok	Influenza	0.028
Polysorbate 20	Flublok Quad	Influenza	0.028
Polysorbate 20	Havrix (child)	HepA	0.025
Polysorbate 20	Sanofi*	Sars-CoV-2**	unknown
Polysorbate 20	Twinrix	HepA+HepB	Not specified
Polysorbate 80	Flucelvax Quad	Influenza	≤1.50
Polysorbate 80	Fluad	Influenza	1.18
Polysorbate 80	Flulaval Quad	Influenza	≤0.887
Polysorbate 80	Fluarix Quad	Influenza	≤0.55
Polysorbate 80	**Jansen COVID-19**	**Sars-CoV-2**	**0.16**
Polysorbate 80	Boostrix	Tdap	≤0.10
Polysorbate 80	Infanrix	DTaP	≤0.10
Polysorbate 80	Kinrix	DTaP+IPV	≤0.10
Polysorbate 80	Pediarix	DTaP+HepB+IPV	≤0.10
Polysorbate 80	Prevnar 13	Pneumococcal 13-valent	≤0.10
Polysorbate 80	Shingrix	Zoster	0.080
Polysorbate 80	Gardasil	HPV	0.050
Polysorbate 80	Gardasil 9	HPV	0.050
Polysorbate 80	Heplisav-B	HepB	0.050
Polysorbate 80	Vaxelis	Dtap-IPV-Hib-HepB	≤0.030
Polysorbate 80	Trumenba	Meningococcal Group B	0.018
Polysorbate 80	AstraZeneca	Sars-CoV-2†	≤0.007 mg
Polysorbate 80	Sanofi*	Sars-CoV-2†AS03 adjuvant	4.86 mg
Polysorbate 80	JE-Vax	Japanese Encephalitis	≤0.0074
Polysorbate 80	Pentacel	DTaP+IPV+Hib	0.0050
Polysorbate 80	Quadracel	DTaP+IPV	0.0050
Polysorbate 80	RotaTeq	Rotavirus	Not specified

Table 1: Select Vaccines Containing Polysorbate Excipients

*The Sars-CoV-2 Sanofi vaccine contains polysorbate 20 (unknown mg/dose) with polysorbate 80 in the AS03 adjuvant (4.86 mg/dose)

†Not yet FDA approved

FIGURE LEGENDS

Figure 1: Pre-Vaccine Allergy Risk Stratification and Subsequent Vaccination Outcomes (n=16)
Among the 16 individuals requiring skin testing after risk stratification, only one individual was skin test positive (oral PEG severe allergic reaction, tolerated Janssen vaccine). 13 of the 15 skin test negative individuals tolerated the initial dose of COVID-19 vaccine.
*Two skin test negative individuals are awaiting dose 1 of the COVID-19 vaccine: 1 employee with a history of severe allergic reaction to vaccine or injectable containing PEG/Polysorbate and 1 employee with a history of severe allergic reaction to vaccine or injectable.
[†]1 employee experienced pruritus on lower back immediately after Pfizer dose 1, was given 10 mg cetirizine with complete resolution of symptoms in 30 minutes. Tolerated Pfizer dose 2 without any allergic symptoms.
PEG: Polyethylene Glycol

Figure 2: Risk Stratification Pathways for COVID-19 Vaccination in Patients with Possible PEG or Polysorbate Allergy
The primary role of the allergist is to enable patients to safely receive the first vaccine available to them. This may require allergist evaluation for PEG and/or polysorbate allergy depending on vaccine availability. Individuals with any history of anaphylaxis, per CDC guidance would be monitored for 30 minutes after mRNA COVID-19 vaccination. Individuals without a PEG or polysorbate allergy are eligible to receive all COVID-19 vaccines and observation time would depend on which vaccine was being given and if there was a prior history of anaphylaxis. Individuals with a polysorbate 80 only allergy would be further assessed by asking “Did you tolerate a polysorbate 80 vaccine after your initial reaction” to a polysorbate 80 injectable or vaccine. Individuals with PEG only allergy are eligible to receive Janssen COVID-19 vaccine without allergy evaluation.
*mRNA COVID-19 vaccines from Pfizer-BioNTech and Moderna.
[†]See Table 1: Select Vaccines Containing Polysorbate Excipients.
[‡]Consider allergy evaluation of polysorbate allergy history if patient preference is for the Janssen vaccine
[§]Polysorbate allergy evaluation may be useful in guiding future use of injectables and vaccines with polysorbate

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