

VIEWPOINT

Hypersensitivity Reactions to COVID-19 Vaccines—Identify High-risk Children and Vaccinate the Rest

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COVID-19 vaccines are highly effective in preventing severe COVID-19 disease and hospitalization in adults and adolescents aged 12 to 15 years.¹ Recently, the BNT162b2 (Pfizer-BioNTech) vaccine was granted emergency use authorization for children aged 5 to 11 years, and the vaccine has shown to be 90.7% effective in preventing symptomatic COVID-19 in children of this age group. Although highly efficacious in preventing COVID-19 disease, hypersensitivity reactions associated with the COVID-19 vaccines have been reported since the December 2020 vaccine rollout. To date, the pooled prevalence of COVID-19 vaccine hypersensitivity reactions is an estimated 5.58 cases per million doses administered.² Although these hypersensitivity reactions are rare, with the current rollout of COVID-19 vaccine emergency use authorization for children aged 5 to 11 years it will be more important for the pediatric medical community to (1) recognize who is at risk of COVID-19 vaccine hypersensitivity reactions and (2) distinguish who should receive additional COVID-19 vaccine doses after a reaction from those who should be referred to an allergist.

Potential Causes for Vaccine Reactions

Vaccine hypersensitivity reactions are typically associated with excipients within vaccines, such as egg, gelatin, milk, alpha-gal, or polysorbate 80 (PS-80).³ The cause of the COVID-19 vaccine reactions was initially suggested to be an IgE-mediated response to the vaccine excipients polyethylene glycol (PEG) 2000 or PS-80. PEGs are hydrophilic polymers of varying molecular weight used as excipients in various products, such as cosmetics and drugs. The molecular weight of PEG can range from 300 g/mol to 10 000 000 g/mol. A commercially available PEG 2000 preparation suitable for skin testing is currently not available; however, PEG 3350, used in laxatives (eg, MiraLAX; Bayer), is available and has been used for PEG skin testing. Interestingly, IgE-mediated anaphylaxis to PEG-containing products is extremely rare. The US Food and Drug Administration has reported that anaphylaxis to PEG occurs in an average of 4 cases per year.⁴ Both the Pfizer-BioNTech and the mRNA-1273 (Moderna) COVID-19 vaccines contain PEG 2000 as a vaccine excipient in conjugation with lipid nanoparticles for improved messenger RNA (mRNA) delivery into cells. The Ad26.COV2.S (Johnson & Johnson [J&J]) adenoviral vector COVID-19 vaccine contains PS-80. Although cross-reactivity between PEG and PS can occur as a result of the shared polyether structure derived from the ethylene oxide group, patients with PEG allergies can usually tolerate the PS-80-containing COVID-19 vaccine.³ Although, IgE-mediated reactions to PEG 2000 have been suggested as the cause of reactions, most COVID-19 vaccine reactions are believed to be non-IgE mediated.⁵⁻⁷

The non-IgE hypersensitivity mechanism has been proposed to occur through either direct mast cell activation, activation of the contact system by nucleic acid in the mRNA-containing vaccines, or complement recognition of vaccine-activating allergic effector cells.⁸ Recent studies also have revealed evidence of the possibility of PEG-lipid conjugate being more immunoreactive than PEG alone.^{6,7} This new evidence questions the utility of skin testing with PEG 3350 in patients with previous COVID-19 vaccine reactions.

Who Should and Should Not Receive the COVID-19 Vaccine?

The current Centers for Disease Control and Prevention interim clinical recommendations for COVID-19 vaccination state that individuals with a history of a severe allergic reaction not related to vaccines or injectable medications, a history of allergies to oral medications that do not contain PEG, or a family history of allergies may receive the COVID-19 vaccine. However, an individual with a history of a PEG allergy should avoid the mRNA COVID-19 vaccines and discuss with their medical provider (eg, family practitioner, pediatrician, nurse practitioner) about receiving the J&J COVID-19 vaccine, if eligible. The same applies to individuals with a history of a PS-80 allergy, for which the Centers for Disease Control and Prevention recommends avoidance of the J&J COVID-19 vaccine and consultation with a medical provider about receiving an mRNA vaccine.⁹

Recommendations on COVID-19 Vaccinations

With reports of allergic reactions after COVID-19 vaccination, combined with vaccine hesitancy among some families, international evidence-based guidance for the diagnosis and management of severe allergic reactions to the COVID-19 vaccine was recently published.¹⁰ The guidelines were based on a systematic review and meta-analysis, and the recommendations were based on the Grading of Recommendation, Assessment, Development, and Evaluation approach. The recommendations included the following: (1) patients with a history of severe allergic reactions (including anaphylaxis) unrelated to the COVID-19 vaccine or its excipients (PEG or PS) are eligible for and encouraged to receive a COVID-19 vaccine, and prolonged observation would not be necessary following vaccination; (2) patients with a history of an immediate severe allergic reaction (≤ 4 hours) to the COVID-19 vaccine/excipient should be referred to an allergist for consultation regarding full or graded dosing or changing the vaccine to another platform; and (3) additional research is needed to clarify COVID-19 vaccine/excipient skin testing in patients who have reacted to the COVID-19 vaccine or its excipients. Pa-

tients with a history of PEG allergic reactions may actually benefit from PEG skin testing and oral PEG 3350 challenge.¹⁰

Managing COVID-19 Vaccine-Related Reactions

An allergy referral and evaluation are warranted in children presenting with symptoms of anaphylaxis (ie, generalized hives, lip and/or tongue edema, difficulty breathing, wheezing, coughing, repetitive vomiting, severe abdominal pain, hypotension) within 4 hours of receiving the COVID-19 vaccine. When examining a child who reports an immediate (≤ 4 hours) allergic reaction to the COVID-19 vaccine, a thorough history is important to characterize the reaction, including the nature and timing of the symptoms and interventions given. Furthermore, a review of medications and vaccine history will provide additional details on whether previous PEG and/or PS-80 tolerance exists. A recent study⁵ examined the outcomes of PEG 3350 and PS-80 skin testing and subsequent COVID-19 vaccine tolerance in 80 adult patients reporting an allergic reaction after their first dose of an mRNA COVID-19 vaccine (65 patients with immediate reactions, ie, in ≤ 4 hours; 15 patients with delayed reactions, ie, in > 4 hours). The study authors concluded that most individuals (75%) who report immediate or delayed allergic reactions to the first dose of the mRNA COVID-19 vaccine, regardless of skin test findings, were able to tolerate the second dose safely without reaction.⁵ In children without an immediate allergic reaction other than anaphylaxis

after vaccination (> 4 hours), shared decision-making with a patient's medical provider is recommended with regard to administration of the second dose. In general, children who present with large local reactions, delayed reactions after 4 hours, nonallergic signs and symptoms (eg, headache, nausea, myalgia, fever, chills), and subjective symptoms after vaccination should be encouraged to receive subsequent doses of the mRNA COVID-19 vaccine.⁵

Conclusions

Immediate (≤ 4 hours) allergic reactions to COVID-19 vaccines are extremely rare. Individuals with a history of food, venom, latex, and/or environmental allergies should receive the COVID-19 vaccine without further referral or evaluation. In patients with a history of anaphylaxis unrelated to a COVID-19 vaccine or its excipients (PEG or PS), prolonged observation time is not necessary. Referral to an allergist is recommended for children with a history of PEG and/or PS-80 allergy or a history of an immediate severe reaction (≤ 4 hours) after the administration of a COVID-19 vaccine. It is important to note that most patients who react to the first COVID-19 vaccine dose will be able to tolerate the second dose. Because COVID-19 vaccines are safe and effective and severe allergic reactions are rare, it is important to encourage patients to get vaccinated against COVID-19 and avoid booster delays and to refer high-risk children to an allergist.

ARTICLE INFORMATION

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