**Allergic Reactions to COVID-19 Vaccines**

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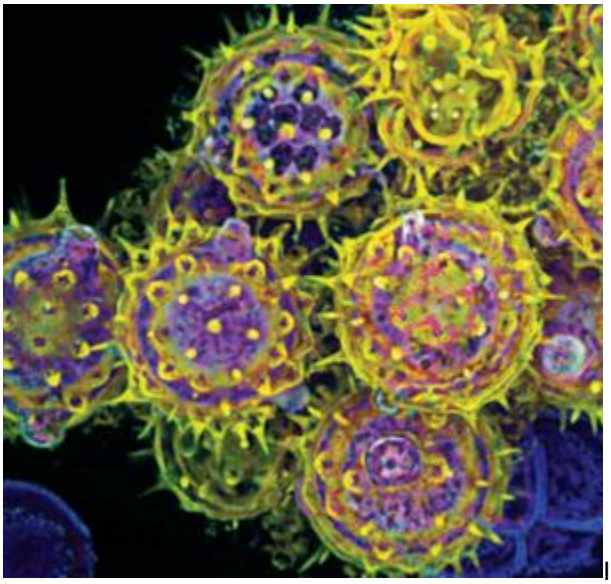

In December 2020, with great fanfare, the FDA approved for emergency authorization two highly effective mRNA COVID-19 vaccines from Pfizer-BioNTech and Moderna. These new vaccines would hold the key to finally controlling the global pandemic that has gripped us for over a year. Both mRNA vaccines have shown outstanding efficacy (94% for Pfizer and 95% for Moderna) in preventing COVID infections and near 100% efficacy in preventing severe infections.Â

However, reports of anaphylactic reactions in the UK and United States within days of administration for the Pfizer-BioNTech vaccine sparked public concern. The United Kingdomâ€™s Medicines and Healthcare Products Regulatory Agency (MHRA) subsequently released an advisory statement to avoid vaccinating anyone with a history of anaphylaxis to a vaccine, drug or food. Meanwhile, governing bodies in the United States (FDA and CDC) advised only patients with a history of anaphylaxis to a previous COVID vaccine or components of COVID vaccines to avoid vaccination. TheyÂ also recommended that all vaccine recipients should be monitored for 15 minutes following vaccination.[1]Â

Subsequent surveillance data between Dec. 14, 2020, and Jan 18, 2021, found the incidence of anaphylaxis to mRNA vaccines to be only 4.7 cases per million for the Pfizer-BioNTech and 2.5 cases per million for the Moderna vaccine. The adenovirus vector-based Janssen/Johnson & Johnson vaccine was approved by the FDA for emergency use on February 27, 2021.[2]Â The anaphylaxis rate for the Janssen/ J&J vaccine has not been reported but is also thought to be extremely rare.Â

**Components of mRNA Vaccines That Could Cause Allergic Reactions**

Adverse reactions to vaccines, including arm soreness, large local reactions, fever and malaise, are common and a result of the normal immune response. However, anaphylaxis to vaccines is exceedingly rare, occurring in approximately 1.31 per million doses.[3Â]

The components potentially responsible for anaphylaxis in the recently approved COVID-19 vaccines have not yet been confirmed. However, the lipid nanoparticle polyethylene glycol (PEG), present in both the Pfizer-BioNTech and Moderna vaccines, has been known to cause immediate hypersensitivity reactions and is thought to be the most likely cause of the allergic reactions with mRNA vaccines.[4]

**History of Reactions to PEG and Polysorbates**
Polyethylene glycols are used widely in medicines (such as MiraLAX), household products, cosmetics and as food additives. PEG nanoparticles are used in mRNA vaccines to encapsulate the mRNA to avoid degradation and promote water solubility. PEG allergy is very uncommon, but there are several case reports in the literature.[4]Â

Most allergic reactions to PEG are due to high molecular weight PEG, such as the PEG 2000 found in both mRNA vaccines. Although rare, the cases of anaphylaxis to PEG have been severe, with several requiring multiple doses of epinephrine. The mechanism of the anaphylactic reactions is not fully understood and may include both IgE mediated mechanisms as well as complement-related pseudo allergic reactions.Â

Several non-mRNA vaccines, including the Janssen/J&J vaccine, contain polysorbate 80. Polysorbates are derivatives of PEG and cross-react with PEG but are much lower molecular weight and theoretically should be less allergenic. Polysorbate 80 is widely used in most vaccines and injectable medications. Most patients with a PEG allergy tolerate polysorbate 80, including in vaccines.[1Â]

**Types of Reactions Post COVID-19 Vaccination Non-Allergic Reactions:**
Vasovagal reactions typically occur within 15 minutes following vaccination but are not associated with rash. The skin typically becomes cold and clammy, and patients can feel symptoms of dizziness, nausea, weakness and changes in vision. Respiratory and cardiac effects are variable but are often associated with bradycardia. Vasovagal reactions typically resolve quickly without treatment unlike immediate allergic reactions, which can last several hours.

Panic attacks and anxiety may also mimic allergic reactions with tachycardia, flushing and lightheadedness.Â

Â Vaccine side effects (local or systemic) occur due to the bodyâ€™s immune response to the vaccine and typically appear 1-3 days after vaccination. Symptoms include tenderness and swelling at the site of injection, lymphadenopathy, fatigue, malaise, headache, nausea, vomiting, fever and chills. These symptoms are not a contraindication or a precaution to future COVID vaccinations.[5]Â Infrequently, patients who have previously received dermal fillers may develop swelling at or near the site of dermal filler injections after a mRNA COVID-19 vaccination. This swelling is temporary and resolves with corticosteroid therapy. A history of previous dermal filler injection is not a contraindication to COVID-19 vaccination, but patients should be notified of this potential side effect.[6]

**Allergic Reactions:**
Delayed rashes, including maculopapular and urticarial rashes, occurring over 4 hours since vaccination typically are not IgE mediated. These reactions can be treated with antihistamines and, if severe, oral corticosteroids. These reactions are not a contraindication to future COVID vaccination. If there are any questions about the timing or management of these rashes, patients may be referred to an allergist.Â

Immediate allergic reactions including urticaria and anaphylaxis primarily occur within 30 minutes of vaccination and almost always within 4 hours. Anaphylaxis typically involves more than one body system and skin reactivity (hives/angioedema). However, anaphylaxis can occur with a single body system if it involves respiratory or cardiac involvement.Â

Allergic reactions following COVID vaccine administration should be reported to VAERS.

**Treating Anaphylactic Reactions**
Patients with suspected anaphylactic reactions to COVID-19 vaccines should be immediately placed supine and treated with intramuscular epinephrine. The anaphylactic reactions reported thus far have responded to epinephrine, although many have needed more than one dose. Staff should be trained in how to treat anaphylaxis.[7]

**Diagnostic Testing and Management of Patients After an Immediate Reaction**
If possible, patients with suspected anaphylactic reactions should have blood drawn between 30 to 90 minutes of the reaction for a serum tryptase level (a marker of mast cell activation) as well as C3a, C3b, C5a and SC5b-9 (the terminal complement complex as markers of complement activation), which may be elevated in anaphylaxis.Â According to the CDC, the following laboratories can do the above tests: Tryptase â€“ ARUP Laboratories, Labcorp and Quest Diagnostics; SC5b-9 â€“ Quest Diagnostics and Clinical Laboratory Clinic at National Jewish Hospital.[8]

Patients with a history of an immediate or severe reaction to a PEG or polysorbate-containing vaccine or injectable medication should be referred to an allergist to review the clinical history and determine if further skin testing to PEG and polysorbates is needed. There is a skin-testing protocol that has been published in the medical literature for the evaluation of IgE mediated allergy to PEG and polysorbates. This protocol involves prick testing to PEG 3350 (i.e., MiraLAX), methylprednisolone acetate (contains PEG 3350), Refresh Eye Drops (contains polysorbate 80), triamcinolone acetonide or Prevnar (contains polysorbate 80) as well as the Hepatitis A or TwinRix vaccine (contains polysorbate 20).Â

If prick testing is negative, intradermal testing with dilutions of these products are performed (excluding MiraLAX since it is not sterile). Patients negative to prick and intradermal testing then undergo COVID-19 vaccination under the supervision of an allergist with a 30-minute observation period. This protocol has not been standardized, and the positive and negative predictive values have not been established. Therefore, it should only be performed by a board-certified allergist/immunologist.Â

This author has performed this protocol in clinical practice on a patient who is an emergency room nurse with previous anaphylaxis to a vaccine containing polysorbate 80. Patient was negative to skin testing and subsequently received bothÂ doses of the Moderna vaccine 4 weeks apart successfully with no allergic reactions.Â

Split dose challenges (giving 10% of a dose followed by the remaining 90% 30 minutes later) is not recommended for mRNA COVID vaccines since there is no data on the efficacy or safety. Skin testing to the actual COVID-19 vaccine is also not recommended due to the limited vaccine supply, lack of information on sensitivity and specificity, and lack of safety data.[9]

**Current Guidance for People with a History of Allergic Reactions to Previous Vaccines or Vaccine Components**
All subjects receiving mRNA or adenovirus vector COVID-19 vaccines should be screened prior to

vaccination for their risk of allergic reactions. These three screening questions were modified from the ACAAI websiteÂ *Guidance on Risk of Allergic Reactions to COVID-19 VaccinesÂ* and Banerji A et al.Â The Journal of Allergy and Clinical Immunology: In PracticeÂ (2021).[6]

- Â Do you have a history of an immediate (<4 hr.) or severe allergic reaction to an injectable medication (intravenous, intramuscular or subcutaneous)?
- Â Do you have a history of an immediate (<4 hr.) or severe allergic reaction to a prior vaccine?
- Â Do you have a history of an immediate (<4 hr.) or severe allergic reaction to polyethylene glycol (PEG), a polysorbate or polyoxyl 35 castor oil (e.g., paclitaxel) containing injectable or vaccine?

If yes to any of these answers, the subject should be referred to a board-certified allergist/immunologist for further evaluation prior to COVID-19 vaccination.

COVID-19 vaccines should be administered by healthcare personnel with medical personnel available nearby who can recognize and treat anaphylaxis. All individuals vaccinated should be observed for 15-30 minutes post-vaccination for adverse effects or allergic reactions. Patients with a history of anaphylaxis or allergic reactions to any injectable medications should be monitored for 30 minutes.Â

Current CDC guidelines list a history of a severe allergic reaction (i.e., anaphylaxis) or history of an immediate (<4 hr.) allergic reaction to a previous mRNA vaccine (Moderna or Pfizer) or component of the vaccine as a contraindication to future mRNA vaccines. Polyethylene glycol (PEG) is the primary component in mRNA vaccines thought to be most likely to trigger allergic reactions. However, the Janssen/J&J COVID vaccine contains polysorbate 80 but not PEG. Current CDC guidance states patients with a contraindication to mRNA vaccines (such as a PEG allergy) could potentially receive the Janssen J&J vaccine in consultation with an allergist.Â

Polysorbate allergy is no longer a contraindication to receiving the mRNA vaccines but is a precaution. Polysorbate allergy is a contraindication to receiving the Janssen/J&J vaccine. Any patients with an immediate hypersensitivity reaction to any previous COVID-19 vaccine, PEG or polysorbate should be referred to an allergist.[5]

The CDC guidelines list a previous history of immediate reaction to any previous vaccine or injectable therapy (excluding subcutaneous immunotherapy for allergies,i.e., â€œallergy shotsâ€) as a precaution but not a contraindication to receiving COVID-19 vaccination. These patients should also be referred to an allergist for evaluation and, if deemed necessary, skin testing to COVID-19 vaccine components to determine if they are able to receive COVID-19 vaccination.[5]

A history of immediate allergic reactions not related to a COVID-19 vaccine or injectable medications including anaphylaxis to food, pets, venom, environmental allergies, latex and oral medications are not considered contraindications or precautions to COVID-19 vaccination. These patients may receive any COVID-19 vaccination as normal, but patients with a history of anaphylaxis should be observed for 30 minutes instead of the normal 15 minutes following vaccination.

In summary, allergic reactions to the three available COVID-19 vaccines are extremely rare. However, those reactions can be severe and are thought to be due to the polyethylene glycol or polysorbate components in these vaccines. Any patient with an immediate allergic reaction to a COVID-19 vaccine or

component, previous vaccine or other injectable medication should be referred to an allergist for further evaluation.Â

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