

COVID-19 Vaccination in Patients With Inflammatory Bowel Disease and History of Reaction to Injectable Therapies

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With the Emergency Use Authorization (EUA) and initial distribution of the novel mRNA coronavirus disease 2019 (COVID-19) vaccines produced by Pfizer-BioNTech and Moderna, there have been reports of hypersensitivity or anaphylactic reactions after vaccination. This has prompted concern among patients, physicians, and other health care providers regarding the safety of vaccination, including in those who have a history of reaction to polyethylene glycol (PEG) or an injectable therapy, such as the biologics used in treatment of inflammatory bowel disease (IBD). Based on Centers for Disease Control and Prevention (CDC) and additional expert recommendations, we aim to provide clarity for physicians and other health care providers regarding current recommendations for COVID-19 vaccination in patients with a history of reaction to common therapies used in the management of IBD.

Drug hypersensitivity reactions (DHR) are adverse effects of a drug, including allergic reactions, and are classified as immediate or nonimmediate/delayed.¹ Immediate reactions occur within 1 to 6 hours after administration, typically within the first hour and most often present with hives, lip or tongue swelling, nasal congestion or rhinorrhea, wheezing, or gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain).¹ Anaphylaxis is a severe systemic, potentially fatal immediate hypersensitivity reaction.² Allergic reactions to vaccines overall are generally uncommon, occurring at a rate of 1.31 cases per million vaccine doses and are more often identified to be caused by inactive ingredients or excipients within the vaccine.³

Hypersensitivity-related adverse events were also relatively rare in the mRNA COVID-19 vaccine trials, with a rate

of 0.63% in Pfizer-BioNTech vaccine recipients and 1.5% in Moderna vaccine recipients. There was 1 case of anaphylaxis and 1 drug hypersensitivity reaction in the Pfizer-BioNTech trial and 2 delayed hypersensitivity reactions in a vaccine recipient of the Moderna trial.³ Only 1 serious hypersensitivity reaction, not classified as anaphylaxis, was reported in the Janssen (Johnson & Johnson) adenovirus vector vaccine trial.⁴ With the widespread release of the Pfizer-BioNTech and subsequent Moderna COVID-19 vaccines, there have been additional reports of immediate hypersensitivity or anaphylactic reactions to these vaccines. An analysis of The Vaccine Adverse Event Reporting System (VAERS) through January 18, 2021, identified 47 cases of anaphylaxis out of 9,943,247 doses of the Pfizer-BioNTech vaccine (a rate of 4.7 cases of anaphylaxis/million doses) and 19 cases out of 7,581,249 doses of the Moderna vaccine (a rate of 2.5 cases of anaphylaxis/million doses).⁵ Twenty-one (32%) of the cases had a prior history of anaphylaxis, including to “unspecified infusions.”⁵ Since the EUA and release of the Janssen viral vector COVID-19 vaccine, there has not been a significant increase in immediate, allergic reactions to this vaccine reported, as of yet.

Though the exact cause for these reactions has not been determined, there is a concern that PEG, which is a component of the lipid nanoparticle carrier system of the mRNA vaccines, may be to blame. Polyethylene glycol is a rare, but known, cause of immediate allergic reactions including anaphylaxis to medications. Stone et al reported that after review of FDA reports between 1989 to 2017, they identified 53 reactions suggestive of anaphylaxis or anaphylactic shock to a PEG-containing bowel preparation or laxative.⁶ In addition to PEG-containing bowel preparations, case reports of anaphylaxis to PEG-containing injectables, such as methylprednisolone acetate, have been reported and PEG identified as the likely cause of reaction.⁶ Polyethylene glycol has also been implicated as a cause of infusion-related, non-IgE mediated reactions with pegylated medications, such as liposomal doxorubicin in up to 40% of recipients, which improves with subsequent injections.² Polyethylene glycol is structurally similar to polysorbate, which is a common inactive ingredient in many injectable therapies and vaccines, including the Janssen COVID-19 vaccine, raising the concern for cross-reactive hypersensitivity reactions.⁶ The majority of injectable therapies used for the treatment of IBD contain polysorbate 80 (Table 1). A National Institute of

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TABLE 1. IBD Injectable Therapies With PEG or Polysorbate⁷

Monoclonal Antibody	Excipient
Adalimumab	polysorbate 80
Certolizumab pegol	Lyophilized powder: polyethylene glycol and polysorbate
	Prefilled syringe: polyethylene glycol
Golimumab	polysorbate 80
Infliximab	polysorbate 80
Natalizumab	polysorbate 80
Ustekinumab	polysorbate 80
Vedolizumab	polysorbate 80

Health-sponsored website with a quick reference of excipients of medications may be accessed at <http://dailymed.nlm.nih.gov/dailymed/>.⁷

Immediate hypersensitivity reactions to biologic medications are not uncommon. In large randomized controlled trials and cohorts of patients with inflammatory bowel disease treated with infliximab, immediate hypersensitivity reactions were reported in 5%–23% of patients.⁸ The most common symptoms reported with immediate infusion reactions included pruritus, flushing, and shortness of breath. Several mechanisms for these reactions have been proposed, such as cytokine-release syndrome, complement activation, and IgE-mediated reactions.⁸ A reaction to the initial infusion or injection of a medication is not typical for IgE-mediated allergy which requires prior exposure, unless there is preexisting sensitization to a component of the injectable therapy, such polysorbate.² Evidence of IgE-mediated allergy to biologics, including infliximab, has been identified with evidence of drug-specific IgE antibodies and/or positive skin testing,⁹ but component testing to identify if polysorbate is the primary culprit within these medications has not often been performed. There have only been a few cases in which polysorbate 80 has been indicated as the allergen causing hypersensitivity reactions to vaccines, injectable therapies, or other biologics, despite its widespread use.^{3,6} It should also be noted that there does not seem to be a significantly increased rate of vaccination reactions to the influenza vaccine, which contains polysorbate 80.³ Therefore, the possible link between PEG or polysorbate allergy and COVID-19 vaccine reactions requires additional research.

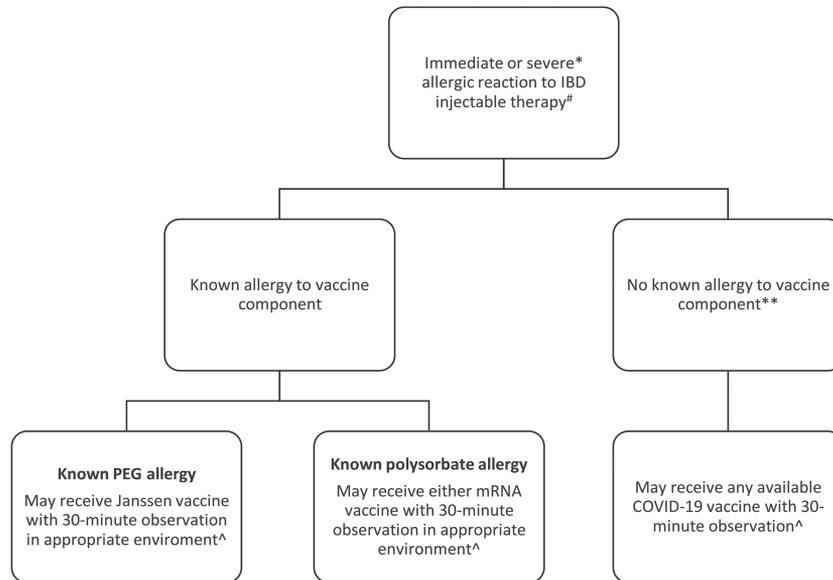
Skin testing to PEG and polysorbate can be performed to identify if there is a potential risk of IgE-mediated reaction to this inactive ingredient.³ Symptoms suggestive of an immediate, IgE-mediated reaction to an injectable therapy includes hives or angioedema distant from the site of injection, respiratory distress such as shortness of breath/stridor/wheezing, nausea/vomiting, and in severe cases, anaphylaxis, within the first 1 to 6 hours after administration.¹ In patients with a history

of immediate or severe hypersensitivity reaction to an injectable therapy that contains polysorbate or PEG, referral to an allergist/immunologist can be considered. Though if the patient is known to have tolerated a subsequent injectable therapy or vaccine that contains the component of concern (PEG or polysorbate), then IgE-mediated allergy is unlikely and skin testing is not necessary.

To provide clinical decision-making support, the CDC has issued guidelines regarding conditions/allergies to consider before vaccination.¹⁰ The only current contraindications to COVID-19 vaccination are history of severe or immediate allergic reaction to a prior dose of a COVID-19 vaccine or known allergic reaction to a vaccine component, particularly PEG for the mRNA vaccines or polysorbate for the Janssen vaccine. Of note, PEG allergy is not a contraindication, rather a precaution, to vaccination with the Janssen vaccine, and polysorbate allergy is not a contraindication to mRNA vaccines despite the possible cross-reactivity. If there is concern for allergy to both components, then patients should defer vaccination and referral to an allergist/immunologist be considered. In patients with a history of immediate allergy to another vaccine or injectable therapy, even if it contained PEG or polysorbate but it is not known to be cause of the reaction, vaccination may proceed with precaution and risk assessment, followed by 30-minute observation in a facility able to treat anaphylaxis. Therefore, after discussion of potential risks, patients with IBD who have had a reaction to an injectable therapy that contained polysorbate, may receive any COVID-19 vaccine with 30-minute observation. If the patient has tolerated another injectable therapy or vaccine that contains polysorbate without issue, they can be considered not allergic to this component. But if a patient, physician, or other health care provider has concern due a history of immediate or severe, anaphylactic reaction to a vaccine or injectable therapy that contained PEG, polysorbate, or polyoxyl 35 castor oil (eg, paclitaxel), a referral to an allergist/immunologist can be considered for skin testing to PEG and polysorbate before receiving a COVID-19 vaccine.³

Patients with a history of anaphylaxis due to any cause should be observed for 30 minutes after vaccination. Those with a history of allergies to food, medications, environmental allergens, venom, etc., but no prior anaphylaxis may receive the vaccine with the standard 15-minute observation period. All patients should be monitored in a clinical setting equipped to manage vaccine reactions, including anaphylaxis.¹⁰ Eighty-nine percent of anaphylactic reactions to the Pfizer-BioNTech and Moderna vaccines have occurred within 30 minutes or less after vaccination, and the majority occurred within 15 minutes (76% for Pfizer-BioNTech and 84% for Moderna), thus the current CDC guidelines for monitoring patients for 15 to 30 minutes post-vaccination should capture the majority of reactions.⁵

These guidelines are subject to continued evolution as further information regarding the reactions to COVID-19



*Immediate allergic reaction: hives, angioedema distant from the site of injection, respiratory distress such as shortness of breath/stridor/wheezing or anaphylaxis occurring within 4 hours after administration¹

#Consider referral to allergist-immunologist for further testing

^Vaccination should be undertaken in an appropriate setting under the supervision of a health care provider experienced in the management of severe allergic reactions.

**Can be considered not allergic if has tolerated alternate form of polysorbate or PEG: such as vaccine with polysorbate (yearly flu), Miralax or colonoscopy prep (PEG), or other IBD injectable therapy (see Table 1)

FIGURE 1. Flowchart for vaccination in patients with reaction to injectable therapy.

vaccines are obtained. Physicians and health care providers are urged to monitor the CDC guidelines for updates, but **Figure 1** is provided for reference regarding current recommendations for COVID-19 vaccination in patients with a history of reaction to injectable therapies, including polysorbate-containing monoclonal antibodies for IBD. It is important for gastroenterologists treating patients with IBD with a history of reaction to an injectable therapy to be aware of the concern for polysorbate or PEG allergy relating to hypersensitivity reactions to the currently available mRNA COVID-19 vaccines that contain PEG or the Janssen (Johnson & Johnson) vaccine that contains polysorbate 80.

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