

CORRESPONDENCE**COVID-19 vaccine anaphylaxis: PEG or not?**

To the Editor,

We read the editorial by Cabanillas et al¹ with great interest. We agree that great consideration needs to be given to the possibility that the polyethylene glycol [PEG]-2000-N,N-ditetradecylacetamide micellar carrier system for the active mRNA spike protein component of the Pfizer–BioNTech BNT162b2 mRNA vaccine, sometimes referred to as the lipid nanoparticle (LNP) delivery system, could be evoked in the recent immediate reactions post-emergency use authorization (EUA).

In our prior work, we have described patients with immediate reactions to PEG3350. These reactions were consistent with anaphylaxis to PEG3350 bowel preparations and corticosteroids containing both PEG3350 and polysorbate (PS) 80 as an excipient (Table 1). Aside from clinical presentation consistent with anaphylaxis, the case for these being IgE-mediated was supported by positive skin tests to both PEG3350 and PS80 (which we believe to be cross-reactive when primary sensitization occurs through PEG3350) as well as the presence of specific IgE (sIgE) against PEG by two independent methods.^{2,3}

We would also like to highlight a case of anaphylaxis to an intravenous medication that might be mechanistically relevant. We observed a patient with a history to suggest preexisting PEG3350 anaphylaxis who also developed anaphylaxis when later exposed to a PEGylated liposome (PEGLip) microbubble, PEGLip 5000 perflutren echocardiogram contrast (Definity[®]). This case was also skin test positive to PEG3350 and PS80 as well as having demonstrable anti-PEG sIgE.^{4,5} In post-marketing surveillance of PEGLip perflutren, first approved by the Food and Drug Administration (FDA) in 2001, a multi-center retrospective analysis observed four cases of anaphylaxis out of 66 164 doses of PEGLip perflutren administered.⁶ In this same study, an alternative formulation of perflutren conjugated to human albumin (Optison[™]), FDA approved in 1997, was also monitored and had no cases of anaphylaxis observed out of 12,219 doses administered.⁷ Both formulations of perflutren carry a FDA black box warning for the risk of severe hypersensitivity reactions, but a hypothetical mechanism underlying these reactions had not been clearly elucidated or attributed prior to our report. While anaphylactic reactions to PEGLip perflutren appears to be rare overall, occurring in 0.006% of patients in the study by Wei et al, these reactions do occur.⁶

PEG and/or lipid complexes in vitro have been shown to cause complement activation, and given the importance of these

technologies for developing new therapeutics and vaccines, there is a science behind “PEG pairing” to minimize this effect.⁸ However, our clinical and laboratory observations do support that IgE-mediated reactions can occur to a PEG-containing product presumably due to previous subclinical sensitization. These patients can notably be labeled as “idiopathic anaphylaxis” or multiple drug allergy if multiple episodes to different products occur over time without knowledge of the shared excipients. An additional observation by our group and others is that for immediate reactions associated with PEG there appears to be a molecular weight (MW) threshold.⁹ This was seen in our skin test-positive patients who were positive to PEG3350 but negative to PEG300 who then tolerated oral challenge with PEG300.^{2,9} This MW predisposition may also vary by patient. To support this hypothesis, we have observed increasing binding avidity of anti-PEG sIgG as the molecular weight of the PEG increases.²

Currently, IgE-mediated reactions associated with PEG appear to both uncommon and underrecognized.^{2,4} PEG2000 is crucial to the formation of micelles used as the delivery system for the mRNA vaccines. It will be important to determine whether PEG2000 is implicated in the IgE-mediated reactions in PEG allergic patients, both as a separate ingredient or as a lipid reagent as formulated in the Moderna, Pfizer–BioNTech, and future mRNA vaccines. Cases clinically compatible with anaphylaxis to the Pfizer–BioNTech mRNA vaccine have occurred on the first dose in the post-EUA phase of surveillance in healthcare workers. It is possible that these could be IgE-mediated reactions related to preexisting sensitization to a different PEG product. Until we understand more, patients with previous immediate reactions compatible with PEG anaphylaxis will be excluded from receiving the SARS-CoV-2 mRNA vaccines. Similarly, we need to understand the risk of immediate reactions to PEG products in those who have experienced anaphylaxis with the Pfizer–BioNTech SARS-CoV-2 mRNA vaccine and other mRNA vaccines if these occur. Until assessed by an allergist, it would be recommended that these individuals also avoid not only future vaccination with an mRNA SARS-CoV-2 vaccine but all components of the vaccine which would include PEG products (Table 1).

Understanding the mechanisms of immediate reactions associated with the Pfizer–BioNTech and any other mRNA vaccines that utilize different lipids in their PEG2000-micellar delivery system (Table 1), should they occur, will be crucial not only for the safety of the current COVID-19 mRNA vaccine program but for mRNA vaccines in earlier stages of development for other viruses and cancer.

TABLE 1 Selected vaccines (A) and medications (B) containing PEGs and polysorbates

Generic Name	Brand Name	Excipient
(A) Vaccines Containing PEGs or Polysorbates		
Vaccines		
Influenza	Flublok & Flublock quad	Polysorbate 20
Hepatitis A	Havrix	Polysorbate 20
Hepatitis A&B	Twinrix	Polysorbate 20
Tdap	Boostrix	Polysorbate 80
Influenza	Fluad	Polysorbate 80
Influenza	Fluarix quad	Polysorbate 80
Influenza	Flucelvax quad	Polysorbate 80
Influenza	Flulaval Quad	Polysorbate 80
HPV	Gardasil and Gardasil –9	Polysorbate 80
Hepatitis B	Heplisav-B	Polysorbate 80
DTaP	Infanrix	Polysorbate 80
Japanese encephalitis	JE-Vax	Polysorbate 80
DTaP+IPV	Kinrix	Polysorbate 80
DTaP+HepB+IPV	Pediarix	Polysorbate 80
DTaP+IPV+Hib	Pentacel	Polysorbate 80
Pneumococcal 13-valent	Prevnar 13	Polysorbate 80
DTaP+IPV	Quadracel	Polysorbate 80
Rotavirus	RotaTeq	Polysorbate 80
Zoster	Shingrix	Polysorbate 80
Meningococcal group B	Trumenba	Polysorbate 80
mRNA-1273 COVID-19	Moderna	Polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG] (also called PEG2000-DMG)
BNT162b2 COVID-19	Pfizer and BioNTech	2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (also called ALC-0159)
(B) Medications Reported in Association with Anaphylaxis to PEGs or Polysorbates		
Gastrointestinal disease treatments and diagnostic aids		
PEG3350	GoLytely, Miralax	PEG3350
Aluminum hydroxide, magnesium carbonate	Gaviscon	PEG20000
Infliximab	Remicade	Polysorbate 80
Adalimumab	Humira	Polysorbate 80
Ustekinumab	Stelara	Polysorbate 80
Certilizumab pegol	Cimzia	Polysorbate 80
Rheumatologic disease treatments		
Methylprednisolone acetate (injectable)	Depo-Medrol	PEG3350
Triamcinolone acetonide (injectable)	Kenalog	Polysorbate 80
Adalimumab	Humira	Polysorbate 80
Pegloticase	Krystexxa	Polysorbate 80
Cardiovascular disease treatments and diagnostic injections		
Clopidogrel	Plavix	PEG6000
Amiodarone injection	Pacerone	Polysorbate 80
PEGylated liposomal Perflutren	Definity	N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine, monosodium salt (also called MPEG5000 DPPE)
Radiologic Procedures		

(Continues)

TABLE 1 (Continued)

Generic Name	Brand Name	Excipient
Ultrasound gels with PEG	Multiple formulations	PEG8000
Gynecologic disease treatments		
Medroxyprogesterone acetate	Depo-Provera	PEG 3350, Polysorbate 80
Vaginal suppositories (European formulation)	Vagisan Zäpfchen, Vagisan Feuchtkreme	PEG 1500/6000/polysorbate 60
Hematologic/Oncologic disease treatments		
Etoposide	Toposar	PEG300, Polysorbate 80
Docetaxel	Taxotere	PEG300, Polysorbate 80
Erythropoietin	Retacrit	Polysorbate 20
Darbepoetin	Aranesp	Polysorbate 80
Pegaspargase	Oncaspar	PEG5000
PEGylated liposomal doxorubicin	Doxil, Caelyx	DSPE (1,2-distearoyl-sn-glycero-3-phosphoethanolamine- (PEG5000))
Biologic and monoclonal antibody medications used as chemotherapy	Various	Typically polysorbate 80
Infectious disease treatments		
Antibiotic tablets	Various formulations depending on country of origin	PEG400 most common, 1000, 4000, 6000
Phenoxymethylpenicillin injection (European formulation)	Generic	PEG6000
Bamlanivimab	Lilly	Polysorbate 80
Casirivimab/Imdevimab	Regeneron	Polysorbate 80
Allergic and Asthma disease treatments		
Omalizumab	Xolair	Polysorbate 20
Dupilumab	Dupixent	Polysorbate 80
Mepolizumab	Nucala	Polysorbate 80
Genetic disease treatments		
Pegvaliase	Palynziq	PEG20000

Miscellaneous Considerations on Other Drugs of Possible Concern

This table does not constitute an exhaustive list. Many film coated tablets, gels, orphan drugs and injectables (especially biologics) contain PEGs and polysorbates. For FDA approved products, the NIH Daily Med Website (<https://dailymed.nlm.nih.gov/dailymed/>) provides a rapidly searchable database of package inserts. These formulations may vary by country and manufacturer, however

Abbreviations: DTaP, diphtheria, tetanus, acellular pertussis; FDA, Food and Drug Administration; HepB, hepatitis B; Hib, *haemophilus influenzae* type B; HPV, human papillomavirus; IPV, inactivated polio vaccine; NIH, National Institutes of Health; PEG, polyethylene glycol; Tdap, tetanus, diphtheria, acellular pertussis.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

Matthew S. Krantz¹ 

Yiwei Liu²

Elizabeth J. Phillips^{3,4}

Cosby A. Stone Jr¹ 

¹Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

²Pharmaceutical Sciences Department, St. Jude Children's

Research Hospital, Memphis, TN, USA

³Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

⁴Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, USA

Correspondence

Cosby A. Stone Jr, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University Medical Center, 1161 21st Avenue South T-1218, MCN, Nashville, TN 37232-2650, USA.

Email: cosby.a.stone@vumc.org

ORCID

Matthew S. Krantz  <https://orcid.org/0000-0001-7589-9127>

Cosby A. Stone  <https://orcid.org/0000-0002-1888-4188>

REFERENCES

1. Cabanillas B, Akdis C, Novak N. Allergic reactions to the first COVID-19 vaccine: a potential role of polyethylene glycol? *Allergy*. 2021;76(6):1621-1623.
2. Stone CA, Liu Y, Relling MV, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. *J Allergy Clin Immunol Pract*. 2019;7(5):1533-1540.e8. <https://doi.org/10.1016/j.jaip.2018.12.003>
3. Zhou Z-H, Stone CA, Jakubovic B, et al. Anti-PEG IgE in anaphylaxis associated with polyethylene glycol. *J Allergy Clin Immunol Pract*. Published online November 2020:S2213219820312319. <https://doi.org/10.1016/j.jaip.2020.11.011>. [Epub ahead of print].
4. Krantz MS, Liu Y, Phillips EJ, Stone CA. Anaphylaxis to PEGylated liposomal echocardiogram contrast in a patient with IgE-mediated macrogol allergy. *J Allergy Clin Immunol Pract*. 2020;8(4):1416-1419.e3. <https://doi.org/10.1016/j.jaip.2019.12.041>
5. US Food and Drug Administration. *Prescribing Information for Definity on November 2020*. Silver Springs, MD: US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021064s024lbl.pdf. Accessed December 19, 2020.
6. Wei K, Mulvagh SL, Carson L, et al. The safety of definity and optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. *J Am Soc Echocardiogr*. 2008;21(11):1202-1206. <https://doi.org/10.1016/j.echo.2008.07.019>
7. US Food and Drug Administration. *Prescribing information for Optison on September 2016*. Silver Springs, MD: US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020899s018s019lbl.pdf. Accessed December 19, 2020.
8. Pannuzzo M, Esposito S, Wu L-P, et al. Overcoming nanoparticle-mediated complement activation by surface PEG pairing. *Nano Lett*. 2020;20(6):4312-4321. <https://doi.org/10.1021/acs.nanolett.0c01011>
9. Sellaturay P, Nasser S, Ewan P. Polyethylene glycol-induced systemic allergic reactions (anaphylaxis). *J Allergy Clin Immunol Pract*. Published online October 2020:S2213219820310072. <https://doi.org/10.1016/j.jaip.2020.09.029>. [Epub ahead of print].

How to cite this article: Krantz MS, Liu Y, Phillips EJ, Stone CA. COVID-19 vaccine anaphylaxis: PEG or not?. *Allergy*. 2021;76:1934–1937. <https://doi.org/10.1111/all.14722>