

Expert Consensus Statement from the American Society of Echocardiography on Hypersensitivity Reactions to Ultrasound Enhancing Agents in Patients with Allergy to Polyethylene Glycol (PEG)

Jonathan R. Lindner, MD, FASE (chair)^a

Todd Belcik, RDCS, ACS, FASE^a

Michael L. Main, MD, FASE^b

Anthony Montanaro, MD^c

Sharon L. Mulvagh, MD, FASE^d

Joan Olson, ACS, RDCS, RVT, FASE^e

Ali Olyaei, PharmD^f

Thomas R. Porter, MD, FASE^e

Roxy Senior MD, FRCP^g

From the ^aKnight Cardiovascular Institute and the ^cDivision of Immunology and Allergy, Oregon Health & Science University, Portland, OR; ^bSaint Luke's Mid America Heart Institute, Kansas City, MO; ^dMaritime Heart Center, Dalhousie University, Halifax, Nova Scotia, Canada; Division of ^eCardiovascular Medicine, University of Nebraska Medical Center, Omaha, NE; ^fDepartment of Pharmacy Practice, Oregon State University, Corvallis, OR; and ^gNational Heart and Lung Institute, Imperial College, London, UK.

The American Society of Echocardiography (ASE) is composed of healthcare providers and scientists committed to the well-being of patients through excellence in cardiovascular imaging. In alignment with ASE's mission to provide education that improves clinical outcomes, this Consensus Statement has been generated to provide our members and all practitioners of echocardiography with information and recommendations that will benefit the safety of patients receiving ultrasound enhancing agents (UEAs). Specifically, this document provides expert opinion on the clinical impact of the recent alert from *MedWatch*, the U.S. Food and Drug Administration (FDA) product safety reporting system, on presumed Type I immediate hypersensitivity reactions to the polyethylene glycol (PEG) component of UEAs.

The UEAs that are approved for use by the FDA include perfluorocarbon or sulfur hexafluoride microbubbles stabilized with "shells" composed of albumin or lipid.¹ These agents can interact with immune cells of the monocytic/phagocytic system via opsonization involving the complement (C') system, or interaction with specific immune cell surface receptors.² These interactions contribute to the **normal and uneventful** mechanism for clearance of UEAs from the circulation by the reticuloendothelial (mononuclear phagocyte) system. **Serious immune-related reactions to UEAs are rare** and have been attributed largely to C' activation-related pseudoallergy (CARPA) reactions which are known to also occur with liposomal drug preparations.^{1,3-6} The lipid-based UEAs approved for human use by the FDA contain PEG either in the excipient (vehicle or inactive ingredient) alone (Lumason, Sonovue; Bracco Diagnostics), or in the microbubble shell and the lipid excipient (Definity, Definity RT, Luminity; Lantheus Medical Imaging). The PEG components not only stabilize the agents, but when incorporated in the shell can also reduce microbubble opsonization and interaction with cells.⁷ The potential for rare IgE-mediated Type I hypersensitivity reactions to PEG components has been recently recognized after publication of case reports implicating PEG allergy.^{8,9} The *MedWatch* alert is based on post-marketing pharmacovigilance from over two decades which identified eleven cases of anaphylaxis, including two deaths, related to the administration of UEAs in patients with pre-existing PEG hypersensitivity.

The comments below provide expert opinion on the impact of newly-recognized PEG hypersensitivity. We believe it is important to recognize the potential for reactions to the PEG component of lipid UEAs. Our recommendations also take into account that

these reactions remain extremely rare, and that UEAs provide vital information that improves patient outcomes based on the ability of UEAs to detect or exclude life-threatening conditions or to stratify patients to life-saving therapies.¹

Key Background Information

- PEG is also known as macrogol or polyoxyethylene. It is a poly-ether compound that is commonly used in a multimeric form (H-[O-CH₂-CH₂]_n-OH) with designation according to its molecular weight (e.g. PEG-5000 which contains 113 ethylene glycol repeats).
- **PEG is a component (excipient) in thousands of enteral and parenteral drugs**, including commonly used medications in cardiovascular medicine. It is also a component in COVID-19 vaccines based on mRNA technology, and is present in many skin creams, cosmetics, and household products.
- Although rare, PEG allergy is established in the scientific literature.^{10,11} It is unknown how often allergies to the thousands of drugs that contain PEG occur from IgE-mediated reaction to the active drug versus reactions to excipients including PEG. The most commonly used agents that contain solely PEG as an active ingredient are certain bowel preps used prior to colonoscopy and certain laxatives containing PEG or macrogol.
- Of the FDA-approved UEAs, only lipid-based agents (Definity, Definity RT, Luminity, Lumason, Sonovue) contain PEG or PEGylated lipids.
- For Definity preparations and Luminity, PEG is a component of an amphiphilic "PEGylated" phospholipid (DPPE-PEG-5000) that becomes incorporated in the lipid monolayer shell, and represents 8% molar fraction of all lipid content in the vial. The amount of DPPE-PEG-5000 per vial is 0.304 mg for Definity, and 1.52 mg for Definity RT. For Lumason and Sonovue, PEG-4000 is in the excipient and is not incorporated into the shell. The amount of PEG-4000 per vial of Lumason is 24.56 mg.
- The *MedWatch* alert refers to eleven cases presumed to be Type I immediate hypersensitivity reactions to PEG based on anaphylactic reactions in patients with known PEG hypersensitivity. The alert does not provide confirmatory data, such as subsequent hypersensitivity testing, that are helpful for confirming that these events were IgE-mediated reactions to PEG.

- The period over which these presumed PEG-related anaphylactic reactions occurred has not yet been publicly reported. However, the alert was the result of pharmacovigilance programs that span several decades. It appears that these cases accumulated over 10 years, resulting in an incidence of reported reactions at **less than once per million doses of lipid-stabilized UEA administered**. Because reactions are reported on a voluntary basis, it is not always possible to reliably estimate the true frequency or their causal relationship to UEA.
- In the absence of post-reaction specialized testing by experts in allergy and immunology, **the clinical differentiation of CARPA and Type I hypersensitivity reactions is extremely difficult**.
- The treatment of severe CARPA and Type I hypersensitivity reactions is similar and includes epinephrine, steroids, antihistamines, bronchodilators, and other supportive measures. The alert from the FDA does not indicate that any changes in therapy or monitoring for severe reactions to UEA should be enacted.
- Before the *MedWatch* alert, package inserts for the lipid-based UEA had already cautioned against their use in patients with hypersensitivity to any of the components of the agent. The package inserts for the relevant UEA have been updated to specifically caution against their use in patients with hypersensitivity reactions to PEG.

Recommendations for Laboratory Policies on UEA

1. The *MedWatch* alert provides additional insight into mechanisms by which serious reactions to lipid-based UEA can occur; it does not change the known incidence of these reactions which occur in approximately 1 out of every 10,000 administrations,^{3,4} making UEA amongst the safest contrast agents used in medical imaging. Accordingly, we do not recommend any changes to laboratory policy with respect to indications for their use. In other words, UEA have an extremely low risk-to-benefit ratio and their use should be continued in situations where they have been shown to be impactful.¹
2. Lipid-based UEA (Definity, Definity RT, Luminity, Lumason and Sonovue) are contraindicated in patients who have had a known or suspected hypersensitivity to these UEA or their components (**established recommendation**); they are also contraindicated in patients with known hypersensitivity to PEG (**new recommendation**). Because patients may be unaware of products that contain PEG, health care providers should inquire about hypersensitivity to agents that contain PEG or macrogol as their active ingredient including certain bowel preps used for colonoscopy and laxatives.
3. Recommendations for counseling patients on the frequency of severe reactions (1 in 10,000) should not change.
4. All sonographers, nurses, and physicians who routinely administer UEA should be trained in the recognition of hypersensitivity reactions; cardiopulmonary resuscitation equipment must be readily available for use by trained personnel (**established recommendation**).
5. The FDA alert does not contain any information that would justify changes in laboratory policy for patient monitoring or treatment algorithms for hypersensitivity reactions.

SUMMARY

- The FDA alert enhances our understanding of the mechanism of severe reactions to UEA. The known incidence of these reactions remains low and unchanged (1 in 10,000 administrations). Because the risk-to-benefit ratio for UEA remains extremely low, we do not recommend any changes to laboratory policy regarding indications for their use. The use of these agents should continue in situations where they have been shown to be impactful.
- Lipid-based UEA (Definity and Lumason) are contraindicated in patients who have a history of prior hypersensitivity to these UEA, to PEG (macrogol), or to PEG-containing products such as certain bowel preps for colonoscopy or laxatives.

REFERENCES

1. Porter TR, Mulvagh SL, Abdelmoneim SS, Becher H, Belcik JT, Bierig M, et al. Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update. *J Am Soc Echocardiogr*. 2018;31:241-274.
2. Lindner JR, Coggins MP, Kaul S, Klibanov AL, Brandenburger GH and Ley K. Microbubble persistence in the microcirculation during ischemia/reperfusion and inflammation is caused by integrin- and complement-mediated adherence to activated leukocytes. *Circulation*. 2000;101:668-75.
3. Wei K, Mulvagh SL, Carson L, Davidoff R, Gabriel R, Grimm RA, 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;21:1202-6.
4. Muskula PR and Main ML. Safety With Echocardiographic Contrast Agents. *Circ Cardiovasc Imaging*. 2017;10.
5. Szebeni J. Complement activation-related pseudoallergy: a new class of drug-induced acute immune toxicity. *Toxicology*. 2005;216:106-21.
6. Main ML, Hibberd MG, Ryan A, Lowe TJ, Miller P and Bhat G. Acute mortality in critically ill patients undergoing echocardiography with or without an ultrasound contrast agent. *JACC Cardiovasc Imaging*. 2014;7:40-8.
7. Fisher NG, Christiansen JP, Klibanov A, Taylor RP, Kaul S and Lindner JR. Influence of microbubble surface charge on capillary transit and myocardial contrast enhancement. *J Am Coll Cardiol*. 2002;40:811-9.
8. Krantz MS, Liu Y, Phillips EJ and Stone CA, Jr. Anaphylaxis to PEGylated liposomal echocardiogram contrast in a patient with IgE-mediated macrogol allergy. *J Allergy Clin Immunol Pract*. 2020;8:1416-1419 e3.
9. Oyarzabal NA, Areso NL, Belar NB, Popolizio IG, Arregui AV and de Valejo OVB. Anaphylactic shock due to allergy to macrogol 4000 contained in SonoVue. *Case Reports Clin Med*. 2017;6:143-147.
10. Stone CA, Jr., Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, et al. Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized. *J Allergy Clin Immunol Pract*. 2019;7:1533-1540 e8.
11. Sellaturay P, Nasser S and Ewan P. Polyethylene Glycol-Induced Systemic Allergic Reactions (Anaphylaxis). *J Allergy Clin Immunol Pract*. 2021;9:670-675.

DISCLOSURES

The following authors do have financial relationships with industry/commercial supporters to disclose:

- Jonathan R. Lindner, MD, FASE - Boston Scientific (Research Grant Support), Lantheus Medical Imaging (Research Grant Support), GE Healthcare (Research Grant Support)
- Thomas R. Porter, MD, FASE - Northwest Imaging Forums (Speaker/Speaker's Bureau), Lantheus Medical Imaging (Consultant/Advisor)

The following authors do not have any relationship with industry/commercial supporters to disclose:

- Todd Belcik, RDCS, ACS, FASE
- Anthony Montanaro, MD
- Joan Olson, ACS, RDCS, RVT, FASE
- Roxy Senior MD, FRCP
- Michael L. Main, MD, FASE
- Sharon L. Mulvagh, MD, FASE
- Ali Olyaei, PharmD