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Development of a screening checklist to identify individuals with suspected allergy to polyethylene glycol

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Abstract

Background Polyethelene glycol (PEG) is a key component of several ultrasound enhancing agents (UEA) but has been recognized as contributing to anaphylactoid reactions, resulting in new contraindications to use in those with known or suspected PEG allergy. Despite these recommendations, no clinical tools currently exist to screen for those with suspected PEG-allergy in echocardiography laboratories.

Methods We developed a screening survey to identify patients with potential PEG allergy and prospectively implemented it in a pilot study involving 8 patients with confirmed PEG allergy by skin prick testing and 50 prospectively enrolled patients undergoing clinically-indicated echocardiography without known PEG allergy, June – July 2025.

Results All patients completed the survey. A positive response to at least 2 of the first 4 questions on the screening survey had a sensitivity of 100% (95% CI 67.6–100%), specificity of 100% (95% CI 92.9–100%), positive predictive value of 100% (95% CI 67.6–100%), and a negative predictive value of 100% (95% CI 92.9–100%) to identify individuals with known PEG allergy.

Conclusions In this pilot multicenter study, a brief screening survey identified all patients with proven allergy to PEG, suggesting possible utility to its use to identify those with potential PEG allergy who would benefit from a non-PEGylated UEA, though further clinical validation is needed.

Keywords Polyethelene glycol, Ultrasound enhancing agents, Safety, Allergy

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Polyethylene glycol (PEG) is a key component of several liposomal echocardiographic enhancing agents (UEAs), helping to stabilize the lipid shell and reduce microbubble opsonization and inter-cellular interactions [1]. At the same time, PEG, particularly high-molecular weight PEG, has been recently recognized as a key contributor to anaphylactoid reactions observed in individuals receiving such agents [1, 2], resulting in changes in labeling to include new contraindications to use of PEG-containing UEAs in those with known or suspected PEG-hypersensitivity [3]. While overall, the serious adverse event rate with receipt of UEAs remains low (~ 1:10,000) in contemporary practice [4], identifying the small number with suspected PEG-allergy represents a challenge given the ubiquity of PEG in thousands of enteral and parenteral drugs, many cosmetics and household products, and certain vaccines like the mRNA COVID-19 vaccines, with up to 24% of the population having been exposed to PEG [5]. As such, some individuals with PEG-allergy could be inadvertently administered PEGylated UEAs if prior allergic reactions are not recognized as being due to PEG.

As such, in this study, we sought to develop and prospectively validate a screening survey that could be administered to patients awaiting echocardiograms to identify those possibly requiring a non-PEGylated UEA. A checklist (Fig. 1) to screen for PEG allergy was developed in consultation with allergists with expertise in PEG allergy at Vanderbilt University Medical Center, Nashville, TN, USA (VUMC; RL, CAS) and echocardiographers with expertise in UEAs at Beth Israel Deaconess Medical Center, Boston, MA, USA (BIDMC; JBS, NS, JLS, MW).

Delayed adverse cutaneous reactions to household products and cosmetics containing PEG were not considered as felt to occur via a different pathophysiologic pathway to PEG-mediated reactions to UEAs (which is felt to be either IgE-mediated or related to complement activation related pseudoallergy [CARPA]) [6]. This checklist was prospectively administered by front desk staff to 50 consecutive patients undergoing echocardiography at BIDMC and 8 patients with confirmed PEG allergy at VUMC [7] via telephone call and responses recorded, including one patient with a previous anaphylactoid reaction to PEGylated UEA [2]. No clinical details or identifying information was collected. The data collected from this study are available from the authors upon request.

A total of 58 individuals were administered the checklist between June 16, 2025 and July 3, 2025. All patients completed the survey and none declined participation. As written, those who answer "No" to the first survey question were instructed not to continue completing the survey. All except one patient at BIDMC answered "No" to question 1 with this patient responding "No" to questions 2–4. Of the eight PEG-allergic patients, 6 (75%) responded "Yes" to question 4 and all eight (100%) responded "Yes" to questions 1–3. A positive response to question 1 had a sensitivity of 100% (95% CI 67.6–100%), specificity of 94.0% (95% CI 83.8–79.7%), positive predictive value (PPV) of 72.7% (95% CI 43.4–90.3%), and negative predictive value (NPV) of 100% (95% CI 92.4–100%). A positive response to at least 2 of the first 4 questions had a sensitivity of 100% (95% CI 67.6–100%), specificity of 100% (95% CI 92.9–100%), PPV of 100% (95% CI 67.6–100%), and a NPV of 100% (95% CI 92.9–100%) to identify PEG allergy.

In this case-control study, a positive response to at least 2 of the first 4 questions on a screening survey identified all individuals with confirmed PEG allergy and none of those without PEG allergy. As PEG is present in two of three commercially available UEAs [1], either as an excipient (Lumason/Sonovue®, Bracco Diagnostics, Milan, Italy) or integrated into the microbubble shell (Definity®, Lantheus Medical Imaging, Billerica, MA), use of this survey in the waiting room could be used to screen patients presenting for echocardiography or contrast-enhanced radiologic ultrasounds who benefit from a non-PEGylated agent. Similar safety screens are utilized to evaluate for imaging-related risk in radiologic settings such as magnetic resonance imaging and computed tomography [3]. As no clinical information was acquired other than the questions in the survey, it is not possible to evaluate how this survey works across subgroups of interest. Moreover, as this represents a pilot study, further prospective clinical validation is needed. However, as UEAs remain underutilized in echocardiography [8, 9], administration of this survey could help promote broader adoption and safe use of this vital technology.

ID	Have you experienced any of the following during your lifetime?	Yes	No
1	Have you experienced anaphylaxis or a systemic immediate reaction to any medication (i.e. occurring within one hour of receipt)?	☐	☐
	If No, STOP. Checklist is complete. If Yes, continue.		
2	Do you have a known allergy to polyethylene glycol (PEG)?	☐	☐
3	Have you ever had an immediate reaction after receiving a steroid injection or bowel preparations, or ultrasound gels?	☐	☐
4	Have you ever experienced serious immediate reactions to different medications (different in either type, e.g. MiraLAX® and Adagen® [two distinct medications], or formulation, e.g. MoviPrep® and Klean Prep® [two formulations of the same medication, PEG-3350])?	☐	☐
ID	**Have you experienced an immediate reaction (within 1 hour of receipt) or any symptoms (e.g. feeling warm, lightheadedness or passing out, rash, difficulty breathing, chest discomfort, swelling of the lips, tongue or other areas, throat tightness, low blood pressure, blurred vision, sneezing, runny nose) in the past within 24 hours after receiving any of the following products? OR Have you ever been told you had an allergy to any of the following specific products?**	**Yes**	**No**
5	Bowel Preparations or Constipation Treatments: • MoviPrep® (osmotic laxative PEG-3350), • Klean Prep® (osmotic laxative, PEG-3350), • Motilium Suppository® (domperidone, PEG-400 and 1000), • MiraLAX® (PEG 3350), • Golytely (PEG 3350 plus electrolytes)	☐	☐
6	Steroid injections: • Depo-Medrol (Methylprednisolone acetate)	☐	☐
7	Vaccines: • COVID-19 mRNA vaccine (Moderna or Pfizer/BioNTech)	☐	☐
8	Drugs for Enzyme or Hormone or Blood Factor Replacement: • Adagen® (adenosine deaminase) • Somavert® (human growth hormone) • Rebinyn® (recombinant coagulation factor IX) • Jivi® (recombinant antihemophilic factor VIII) • Palynziq® (recombinant phenylalanine ammonia lyase) • Esperoct ® (recombinant antihemophilic factor VIII) • Skytrofa ® (human growth hormone) • Mircera® (erythropoietin) • Krystexxa® (recombinant uricase)	☐	☐
9	Chemotherapy, Anti-vascular, or Anti-Inflammatory Drugs: • Doxil® (PEGylated liposomal doxorubicin, • Asparlas® (L-asparaginase) • Ziextenzo® or Udenyca® or Nyvepria® (granulocyte colony stimulating factor [G-CSF]) • Besremi® (Interferon) • Empaveli® (Pentadecapeptide) • Neulasta® (pegfilgrastim) • Oncaspar® (pegaspargase) • Cimzia® (anti-tumor necrosis factor antibody) • Macugen® (anti-vascular endothelial growth factor [VEGF]) • Onpattro® (Patisiran)- amyloidosis treatment	☐	☐
10	Contraceptives • Depo-Provera® (medroxyprogesterone PEG-3350)	☐	☐
11	Non-steroidal anti-inflammatory drugs (NSAIDs) • Vimovo® (esomeprazole and naproxen) • Nurofen® (Ibuprofen, PEG-6000) • Voltorol Oral® (diclofenac, PEG-8000)	☐	☐
12	Vitamins and Electrolytes: • Phosphate Sando® (effervescent phosphate, PEG-4000), • Effervescent vitamin C® (effervescent vitamin C: high molecular weight PEG)	☐	☐
13	Topical Cleansers, Gels, or Implanted Spacer Gels: • Betadine® (Povidone-iodine, PEG-400, 6000) • Ultrasound gels or surgical lubricant gels • SpaceOAR Hydrogel (PEG containing prostate hydrogel)	☐	☐

Fig. 1 Survey questions to screen patients for allergy to polyethlene glycol. LEGEND: Shown are the survey questions administered to patients in the study to screen for allergy to polyethlene glycol (PEG). Questions are listed in order by identification (ID) number. For specific medications or agents, both brand name and generic name are provided with the list of agents included derived from prior publication (Stone CA, 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(5):1533–1540). Numbers following PEG (e.g. PEG-4000) represent the molecular weight with higher numbers indicating a greater number of ethylene glycol repeats

Abbreviations

BIDMC	Beth Israel Deaconess Medical Center
CARPA	Complement Activation Related Pseudoallergy
NPV	Negative Predictive Value
PEG	Polyethylene Glycol
PPV	Positive Predictive Value
UEA	Ultrasound Enhancing Agent
VUMC	Vanderbilt University Medical Center

Author contributions

J.B.S. and C.A.S. conceived of the study and provided funding. J.B.S. wrote the main manuscript text. All authors assisted in prospective patient enrollment, provided critical edits to the manuscript, and approved of the final manuscript.

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Data availability

The data collected from this study are available from the authors upon request.

Declarations

Ethics, consent to participate, and consent to publish

The study was performed in accordance with the Declaration of Helsinki and approved by the institutional review boards at both BIDMC (Federal Wide Assurance # 00003245) and VUMC (Federal Wide Assurance #00005756) with verbal consent from patients for participation.

Competing interests

Dr. Strom reports research grants from the National Heart, Lung, and Blood Institute (1R01HL169517, 1R01HL173998), Edwards Lifesciences, EchoIQ, Anumana, Viz.ai, EVERSANA Lifesciences; consulting for Bracco Diagnostics, Edwards Lifesciences, Philips Healthcare, General Electric Healthcare, and EVERSANA, and is a member of the scientific advisory boards for Ultromics, HeartSciences, Bristol Myers Squibb, Alnyam, Ultrasight, and EchoIQ. Dr. Stone received funding from the American Academy of Allergy, Asthma, and Immunology Foundation which supported this research. He reports additional grant support from AHRQ R01HS030234, NIAID U01AI181927, NIAID 1U01AI184071-01 and a pilot award for chemotherapy allergy research from the Vanderbilt Ingram Cancer Center/Chic Awearness. Funders played no role in any aspect of this manuscript. Dr. Stone reports consulting work for Larimar Therapeutics and Stallergenes Greer which is unrelated to the current work. All other authors report no relevant disclosures.

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