



Anaphylaxis associated with the mRNA COVID-19 vaccines: Approach to allergy investigation

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ABSTRACT

Reports about cases of anaphylaxis to mRNA vaccines have created anxiety in the community and could increase vaccine hesitancy in the population. There are no standardized protocols for allergy testing to mRNA vaccines. PEG is currently the only excipient in both vaccines with recognized allergenic potential. Allergy to PEG has been reported with increasing frequency over recent years, often in patients who had repeated systemic allergic reactions/anaphylaxis to several classes of drugs before diagnosis. Proposed protocols are based on current knowledge about potential mechanisms of anaphylaxis associated with the mRNA vaccines, and the assumption that polyethylene glycol (PEG) is the most likely culprit. Allergy testing to PEGs and mRNA vaccines is complex and carries the risk of anaphylaxis and should be conducted in a specialist drug allergy center. Appropriate PEG-free emergency medical treatment and supervision should be readily available.

1. Introduction

1.1. The COVID-19 mRNA vaccines

With the introduction of vaccination programs with the new Pfizer/BioNTech's and Moderna's mRNA vaccines, more allergic reactions including vaccine-associated cases of anaphylaxis are reported, but overall remain rare. However, the information has created anxiety in the community. Allergies in general are so common (10–40%) that this could increase the vaccine hesitancy or resistance against the vaccines in the population [1,2]. Conversely, patients with allergies are concerned about the possibility that they may not be able to get vaccinated. Anaphylactic reactions can occur with any vaccine but are usually extremely rare—about one per 1 million doses [3]. The U.S. Centers for Disease Control and Prevention (CDC) reported a rate of 11.1 per million doses administered for Pfizer/BioNTech's mRNA vaccine [4]; however, new data indicate a lower rate of 5.5 per 1 million doses for the COVID-19 vaccines (29 cases out of more than 5.3 million doses that have been administered as of Jan 5, 2021) [5]. The reported rate for the Moderna COVID-19 vaccine is 2.5 per million doses administered [6].

1.2. Is polyethylene glycol the culprit?

The COVID-19 mRNA vaccines consist of non-infectious, non-replicating RNA in a lipid-based formulation, which delivers the RNA to cells in the immunized person. The lipid nanoparticles are chemically attached to polyethylene glycol (PEG) molecules (PEGylated) that cover the outside of the particles and increase their stability and life span. Protein expression from the RNA is transient, and as is RNA itself. The vaccines do not contain adjuvants and the vaccine vials do not contain latex [7].

PEG is currently the only excipient in both vaccines with recognized allergenic potential [8]. PEGs, also called macrogols, are hydrophilic polymers with molecular weight (MW) in the 300–35,000 g/mol range. They are found in everyday products such as cosmetics, and medications, industrial and food products. PEGylation is a process used to extend half-life and limit volume of distribution of nucleic acid, peptide, and small molecule therapeutics. In pharmaceuticals, the number included in the name indicates the average molecular weight (e.g., PEG4000) but in the cosmetics industry, the number refers to the average number of ethylene oxide units in each molecule (e.g., PEG40). Cross-reactivity exists with polysorbates [9]. Allergy to PEG has been reported with increasing frequency over recent years, often in patients

Abbreviations: PEG, polyethylene glycol; MW, molecular weight; SPT, skin prick test; IDT, intradermal test.

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who had repeated systemic allergic reactions/anaphylaxis to several classes of drugs before diagnosis [10,11]. No studies to date examine the prevalence of PEG hypersensitivity, although occurrence is likely underestimated. The onset of serious hypersensitivity reactions and anaphylaxis to PEG is typically rapid and severe. Symptoms include pruritus, flushing, urticaria, and angioedema. Hypotension occurs in severe cases with airway symptoms of chest tightness and dyspnea. The presence of lipid PEG2000 in the mRNA vaccines has led to assumption about its involvement in anaphylaxis.

1.3. The mechanism of PEG-associated hypersensitivity

The mechanism of PEG-induced hypersensitivity reactions is poorly understood. Investigations for allergy to PEG currently include skin testing which is usually useful in the diagnosis of IgE-mediated allergy. However, some researchers believe that PEG-induced anaphylaxis is mediated by IgM and IgG antibodies against PEG, leading to complement activation and mediators release. This type of hypersensitivity reaction, called a complement activation-related pseudoallergy (CARPA), is proposed as a major mechanism of infusion reactions to a variety of nanoparticulate drugs and agents [12]. Most reported adverse events occurred on an apparent first exposure to a parenteral version of a specific-PEG containing product, suggesting previous sensitization to PEG [13,14]. This opinion is supported by results of clinical studies that found IgG and IgM antibodies against PEG in a significant proportion of the population without known prior exposure to PEGylated products (up to 25%), and in up to 89% of patients with known prior exposure to PEGylated products [15,16]. At least three PEGylated nanomedicines were withdrawn from clinical use because of severe hypersensitivity reactions; pegnivacogin, pegloticase and peginesatide. The strong association of IgG anti-PEG antibodies with severe allergic reactions was found in clinical trials with pegnivacogin, a PEGylated IXa blocker RNA aptamer, and pegloticase, a PEGylated recombinant porcine uricase for treatment of refractory gout [17–19]. No investigations were conducted to clarify the mechanisms of anaphylaxis related to peginesatide, a PEGylated EPO-mimetic peptide [20]. However, it remains unknown to which extend positive anti-PEG IgG antibodies predisposes a person to a hypersensitivity reaction.

Literature data regarding PEG-associated anaphylaxis confirmed by skin testing, oral challenge, and/or the detection of specific IgE antibodies to PEG, suggest the importance of IgE-mediated mechanisms for some hypersensitivity reactions [9–11,21–25]. Positive skin reactions were more frequent with high MW PEGs (>4000), independently of the PEG MW in the culprit product. Furthermore, patient's history of PEG-containing product exposures and oral challenge findings indicate that PEG dose may be a critical factor in triggering a hypersensitivity reaction [11]. The MW and dose thresholds are not known, but it is likely that patients have an individual reactivity-threshold for both dose and MW. An IgE-related mechanism is further supported by positive basophil activation and basophil histamine release tests, and suppression of histamine release through the utilization of omalizumab (anti IgE monoclonal antibodies) and both mono- and dimeric fractions of PEGs [24–27]. Recently, a study was published by Zhou and colleagues [28] who developed a Dual Cytometric Bead Assay for anti-PEG IgG, IgM, and IgE; samples for PEG-associated anaphylaxis cases were positive for anti-PEG IgE, confirming the long-considered hypothesis of IgE-mediated type 1 hypersensitivity. Interestingly, subjects positive for anti-PEG IgE also had high anti-PEG IgG titers.

Given the evidence for both IgE-mediated and non-IgE-mediated mechanisms, further research is needed to explore the possibility of their coexistence in PEG-associated anaphylaxis [29,30].

1.4. The need for standardized allergy protocols

Prevention of anaphylaxis may not be possible, particularly with the 1st dose of a mRNA vaccine; therefore, healthcare professionals

administering the vaccine must be vigilant for early signs and symptoms. Appropriate medical treatment and supervision should be readily available on vaccination site. Anaphylaxis should be managed with PEG-free medications.

There are no standardized protocols for allergy testing to mRNA vaccines. Recommendations for allergy investigations are based on current but limited knowledge, and the assumption that PEG is the implicated in anaphylaxis. Future research will provide clarifications regarding the culprit and mechanisms of the reaction, the most appropriate methods of diagnosis and risk factors, enabling safer use of mRNA vaccines in the future.

2. Allergy investigations

2.1. Individuals eligible for allergy investigations

Pre-vaccination allergy work-up is not feasible, due the rarity of the event, uncertainties regarding the culprit and mechanism behind anaphylaxis associated with mRNA vaccines. Currently, contraindication to vaccination with an mRNA vaccine is a known severe immediate-type allergy/anaphylaxis to components of the vaccine (e.g., PEG or polysorbate) or to the first vaccine dose [7]. For all other individuals with history of allergic reactions, observation for 15 or 30 min after the receipt of the vaccine is recommended, depending on their history of allergic reactions [31,32]. However, in individuals with a history of immediate onset allergic reactions or anaphylaxis to multiple classes of drugs, or an unexplained anaphylaxis, skin testing for PEG sensitization may be considered as this is a shared feature of many cases of PEG hypersensitivity [11].

So, the proposed criteria for pre-vaccination allergy investigations are severe immediate-type allergy/anaphylaxis to the first vaccine dose or to components of the vaccine, and history suggestive for PEG hypersensitivity. In test-negative individuals, vaccination with an alternative non-mRNA vaccine may be recommended in these patients, if available and not otherwise contraindicated. Ideally, the alternative vaccine should be PEG/polysorbate free.

2.2. Proposed protocol for allergy investigation

The proposed approach is based on published cases and review of cases investigating allergy to PEGs/polysorbate80; however, the uncertainties regarding the culprit and mechanism behind anaphylaxis associated with mRNA vaccines, have been considered (Fig. 1).

Individuals who have had severe allergic reaction/anaphylaxis to an mRNA vaccine should be urgently investigated to determine the mechanisms behind the reactions and the potential involvement of PEG. Other potential allergens should be excluded (e.g., disinfectants, other medications taken before vaccination, etc.), or if there is suspicion, included in the testing panel.

To characterize the acute phase of the reaction, two laboratory tests are recommended by the CDC: tryptase (a mast cell marker whose increase is suggestive for IgE-mediated allergy) and SC5b-9 (terminal complement complex whose increase is suggestive of non-IgE mediated allergy) [33]. If available, extended laboratory testing may be considered with measurements of other mediators of anaphylaxis (e.g., histamine, complement components, etc.).

Following a reaction, in vitro tests, skin tests, as well as provocation tests if necessary, are used to identify the trigger and to characterize the reaction [34]. These should ideally be performed 4 weeks at the earliest, but not later than 6 months after the reaction, due to increased risk of false positive or false negative results, respectively [35]. The in vitro diagnosis of IgE-mediated allergic diseases is useful in the identification of the causative allergen [36]. Due to current unavailability of an assay for the measurement of anti-PEG IgE antibodies, basophil tests can be used: the basophil activation test and/or the basophile histamine release test. Assays to detect PEG-specific IgG and IgM antibodies are

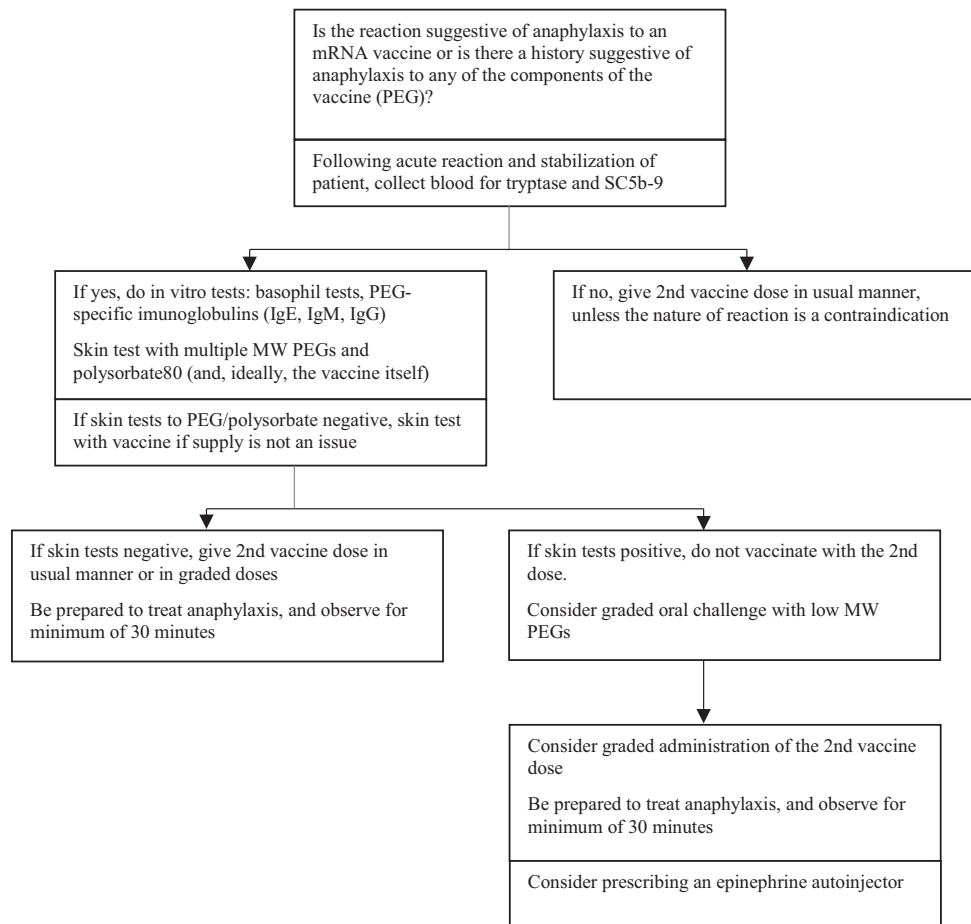


Fig. 1. Suggested approach to suspected anaphylaxis to an mRNA vaccine.

commercially available.

Skin prick testing (SPT) is the most frequently used method for the detection of IgE antibodies, due to its rapidity, simplicity, and low cost. In SPT negative patients, intradermal tests (IDTs) can be performed. Standardized methods and appropriate positive and negative controls should be used [34]. Of note, atypically high rate of systemic hypersensitivity reactions including anaphylaxis have been reported with both SPT and IDTs; so, patients should provide a written consent.

In addition to PEG2000 contained in the mRNA vaccines, skin testing should include numerous MWs when investigating suspected immediate-type PEG hypersensitivity with the aim to establish a PEG MW threshold: the lowest MW tested positive. Published data suggest the absence of an upper limit for MW regarding reactivity [9,10]. Due to the possibility of systemic reactions with skin testing, a stepwise approach using dilute solutions is recommended. The readings for SPT should take place after 30 min, and readings for IDTs should take place after 45–60 min because of slow evolution of test results. In PEG-sensitized patients, positive tests tend to occur at very low concentrations. The proposed dilutions for SPT are 0.0001%–10%; SPT with lower MW PEGs may require comparatively greater test concentrations to show a response. IDTs should only be performed in SPT-negative patients and using dilute solutions; proposed dilutions are 0.0001%–1% (Table 1). Due to possible cross-sensitivity with PEGs, skin tests with polysorbate80 should be included in the panel.

In SPT- and IDT-negative patients, skin testing with the mRNA vaccine should be considered if the supply is not an issue, although the culprit in the vaccine would not be identified. Ideally, skin testing with the mRNA vaccine should be conducted in all individuals who experienced anaphylaxis to the first vaccine dose. Standard skin testing to vaccines involves the use of both SPT and IDs at varying concentrations

[37]. However, the interpretation of these skin test results is complicated in many instances by irritant reactions. Generally, SPTs are done with the undiluted vaccine, but if the previous reaction with the vaccine was life-threatening it is appropriate to use dilute vaccine for the SPT. The IDTs are done with dilutions 1:100. At the 1:10 and full-strength concentrations, irritant reactions are quite common for some vaccines [38]. The sensitivity is higher with a higher dilution, but higher rate of false negatives. With lower dilutions the specificity is higher but also the false positive rate. However, protocols should be validated because the skin reactivity to various dilutions of the new mRNA vaccines is not known. If skin testing using the vaccine is negative, the vaccine can be administered in the usual manner, but under close observation, with epinephrine and other treatments available. For safety reasons, graded administration of the vaccine can be considered [37]. However, no data are available on the efficacy of graded administration of mRNA vaccines. Alternatively, the second mRNA vaccine dose could be waived, if future research shows sufficient efficacy a single mRNA vaccine dose. The proposed PEG MWs and dilutions for skin tests and graded vaccine administration are shown in Table 1.

If a PEG MW threshold is established with skin testing, oral challenge may be considered with PEGs with MWs below the threshold level to enable safer recommendations concerning future exposures to PEG-containing products. However, the safety of this approach is not established, and the risks of cross-sensitization between PEGs of various MW, PEGylated drugs as well as PEG derivatives, are unknown. Thus, for patients with confirmed PEG sensitization, prescription of an epinephrine autoinjector may be considered.

Testing for PEG sensitization should be conducted in a specialist drug allergy center due to associated risk of anaphylaxis. PEG- and polysorbate-free emergency medication for management of systemic

Table 1
Proposed protocol for allergy testing to PEGs and mRNA vaccines.

Allergen ^a	SPT ^b	SPT- number of steps	IDT ^b	IDT- number of steps
PEG300	0,001%– 10%	4	0,0001%– 1%	5
PEG400	0,001%– 10%	4	0,0001%– 1%	5
PEG2,000	0,0001%– 10%	5	0,0001%– 1%	5
PEG3,350	0,0001%– 10%	5	0,0001%– 1%	5
PEG4000	0,0001%– 10%	5	0,0001%– 1%	5
PEG6,000	0,0001%– 10%	5	0,0001%– 1%	5
PEG8,000	0,0001%– 10%	5	0,0001%– 1%	5
PEG20,000	0,0001%– 10%	5	0,0001%– 1%	5
Polysorbate 80	0,001%– 10%	4		
Comirnaty	1:10- undiluted	2	1:100	2
Comirnaty graded administration	The full normal dose volume is 0.3 mL; give the following doses at 15-min intervals as tolerated: 0.03 mL 1:10 dilution 0.03 mL full-strength 0.06 mL full-strength 0.09 mL full-strength 0.12 mL full-strength			
Moderna COVID-19 Vaccine	1:10- undiluted	2	1:100	2
Moderna COVID-19 Vaccine graded administration	The full normal dose volume is 0.5 mL; give the following doses at 15-min intervals as tolerated: 0.05 mL 1:10 dilution 0.05 mL full-strength 0.1 mL full-strength 0.15 mL full-strength 0.2 mL full-strength			

^a Bolded text- recommended minimum of allergens that should be included in the testing panel.

^b Stepwise approach from lower to higher concentrations multiplied by 10; stop at positive result.

reactions/anaphylaxis should be available on site.

3. Conclusion

The risk of anaphylaxis to mRNA vaccines is present but extremely low and is offset by the benefits of the vaccine; however, it could negatively impact the growing vaccine hesitancy.

The proposed protocols are based on current knowledge about potential mechanisms of anaphylaxis associated with the mRNA vaccines, the assumption that PEG is the most likely culprit, and the author's extensive experience in drug allergy testing. However, they are open for discussion within experts or expert groups in the field, and for subsequent adjustments or corrections.

An efficient risk minimization strategy coupled with management algorithms for individuals experiencing an anaphylactic reaction to an mRNA vaccine or those at risk, is important to reassure people that the risks are manageable, and that the use of the new mRNA vaccines is safe.

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Declaration of Competing Interest

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References

- [1] R. Pawankar, S.T. Holgate, G.W. Canonica, R.F. Lockey, M.S. Blaiss, The WAO White Book on Allergy (Update 2013). <https://www.worldallergy.org/UserFiles/file/WhiteBook2-2013-v8.pdf>, 2021 (accessed 11 January 2021).
- [2] J.V. Lazarus, S.C. Ratzan, A. Palayew, L.O. Gostin, H.J. Larson, K. Rabin, S. Kimbal, A. El-Mohandes, A global survey of potential acceptance of a COVID-19 vaccine, *Nat. Med.* (2020) 1–4, <https://doi.org/10.1038/s41591-020-1124-9>.
- [3] M.M. McNeil, E.S. Weintraub, J. Duffy, L. Sukumaran, S.J. Jacobsen, N.P. Klein, S. J. Hambidge, G.M. Lee, L.A. Jackson, S.A. Irving, J.P. King, E.O. Kharbanda, R. A. Bednarczyk, F. DeStefano, Risk of anaphylaxis after vaccination in children and adults, *J. Allergy Clin. Immunol.* 137 (2016) 868–878, <https://doi.org/10.1016/j.jaci.2015.07.048>.
- [4] CDC COVID-19 Response Team, Food and Drug Administration, Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine— United States, December 14–23, 2020, *M.M.W.R* 70, 2021, pp. 46–51.
- [5] Centers for Disease Control and Prevention Newsroom, Transcript: CDC Update on COVID-19, Press Briefing Transcript, January 6, 2021. <https://www.cdc.gov/media/releases/2021/t0106-cdc-update-covid-19.html> (accessed on 11 January 2021).
- [6] CDC COVID-19 Response Team, Food and Drug Administration, Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine — United States, December 21, 2020–January 10, M.M.W.R 70, 2021, pp. 125–129.
- [7] Centers for Disease Control and Prevention, U.S. COVID-19 Vaccine Product Information. <https://www.cdc.gov/vaccines/covid-19/info-by-product/index.html>, 2021 (accessed on 12 January 2021).
- [8] R.P. Garay, J.P. Labeaune, Immunogenicity of polyethylene glycol (PEG), *Open Conf. Proceed. J.* 2 (2011), <https://doi.org/10.2174/2210289201102010104>.
- [9] C.A. Stone Jr., Y. Liu, M.V. Relling, M.S. Krantz, A.L. Pratt, A. Abreo, J.A. Hemler, E.J. Phillips, Immediate hypersensitivity to polyethylene glycols and Polysorbates: more common than we have recognized, *J Allergy Clin Immunol Pract* 7 (2019) 1533–1540, <https://doi.org/10.1016/j.jaip.2018.12.003>.
- [10] P. Sellaturay, S. Nasser, P. Ewan, Polyethylene glycol-induced systemic allergic reactions (anaphylaxis), *J Allergy Clin Immunol Pract* S2213-2198 (20) (2020), <https://doi.org/10.1016/j.jaip.2020.09.029>, 31007–2.
- [11] E. Wenande, L.H. Garvey, Immediate-type hypersensitivity to polyethylene glycols: a review, *Clin. Exp. Allergy* 46 (2016) 907–922, <https://doi.org/10.1111/cea.12760>.
- [12] G.T. Kozma, T. Meszaros, I. Vashegyi, T. Fulop, E. Orfi, L. Dezsi, L. Rosivall, Y. Bavli, R. Urbanics, T.E. Mollnes, Y. Barenholz, J. Szebeni, Pseudo-anaphylaxis to polyethylene glycol (PEG)-coated liposomes: roles of anti-PEG IgM and complement activation in a porcine model of human infusion reactions, *ACS Nano* 13 (2019) 9315–9324, <https://doi.org/10.1021/acsnano.9b03942>.
- [13] S.H. Lee, J.M. Cha, J.I. Lee, K.R. Joo, H.P. Shin, I.H. Baek, J.W. Jeon, J.U. Lim, J. L. Lee, H.M. Lee, Y.H. Cho, Anaphylactic shock caused by ingestion of polyethylene glycol, *Intest. Res.* 13 (2015) 90–94, <https://doi.org/10.5217/ir.2015.13.1.90>.
- [14] C.L. Bennett, S. Jacob, J. Hymes, L.A. Usyat, F.W. Maddux, Anaphylaxis and hypotension after administration of peginesatide, *N. Engl. J. Med.* 370 (2014) 2055–2056, <https://doi.org/10.1056/nejmc1400883>.
- [15] R.P. Garay, R. El-Gewely, J.K. Armstrong, G. Garratty, P. Richette, Antibodies against polyethylene glycol in healthy subjects and in patients treated with PEG conjugated agents, *Expert. Opin. Drug. Deliv.* 9 (2012) 1319–1323, <https://doi.org/10.1517/17425247.2012.720969>.
- [16] Q. Yang, T.M. Jacobs, J.D. McCallen, D.T. Moore, J.T. Huckaby, J.N. Edelstein, S. K. Lai, Analysis of pre-existing IgG and IgM antibodies against polyethylene glycol (PEG) in the general population, *Anal. Chem.* 88 (2016) 11804–11812, <https://doi.org/10.1021/acs.analchem.6b03437>.
- [17] N.J. Ganson, T.J. Povsic, B.A. Sullenger, J.H. Alexander, S.L. Zelenkofske, J. M. Sailstad, C.P. Rusconi, M.S. Hershfield, Pre-existing anti-polyethylene glycol antibody linked to first-exposure allergic reactions to pegnivacogin, a PEGylated RNA aptamer, *J. Allergy Clin. Immunol.* 137 (2016) 1610–1613, <https://doi.org/10.1016/j.jaci.2015.10.034>.
- [18] M.S. Hershfield, N.J. Ganson, S.J. Kelly, E.L. Scarlett, D.A. Jagers, J.S. Sundry, Induced and pre-existing anti-polyethylene glycol antibody in a trial of every 3-week dosing of pegloticase for refractory gout, including in organ transplant recipients, *Arthritis Res. Ther.* 7 (2014) R63, <https://doi.org/10.1186/ar4500>.
- [19] T.J. Povsic, M.G. Lawrence, A.M. Lincoff, N.F. Adkinson, A.I. Levinson, Pre-existing anti-PEG antibodies are associated with severe immediate allergic reactions to pegnivacogin, a PEGylated aptamer, *J. Allergy Clin. Immunol.* 136 (2016) 1712–1715, <https://doi.org/10.1016/j.jaci.2016.04.058>.
- [20] T. Hermanson, C.L. Bennett, I.C. Macdougall, Peginesatide for the treatment of anemia due to chronic kidney disease - an unfulfilled promise, *Expert Opin. Drug Saf.* 15 (2016) 1421–1426, <https://doi.org/10.1080/14740338.2016.1218467>.
- [21] M.S. Krantz, Y. Liu, E.J. Phillips, C.A. Stone Jr., Anaphylaxis to PEGylated liposomal echocardiogram contrast in a patient with IgE-mediated macrogl allergy, *J Allergy Clin Immunol Pract* 8 (2020) 1416–1419, <https://doi.org/10.1016/j.jaip.2019.12.041>.

- [22] B.D. Jakubovic, C. Saperia, G.L. Sussman, Anaphylaxis following a transvaginal ultrasound, *Allergy Asthma Clin. Immunol.* 12 (2016) 3, <https://doi.org/10.1186/s13223-015-0106-9>.
- [23] V. Jover Cerdá, R. Rodríguez Pacheco, J. Doménech Witek, F.M.M. de la Calle, M. L. de al Sen Fernandez, Immediate hypersensitivity to polyethylene glycols in unrelated products: when standardization in the nomenclature of the components of drugs, cosmetics, and food becomes necessary, *Allergy Asthma Clin. Immunol.* 15 (2019) 9, <https://doi.org/10.1186/s13223-019-0327-4>.
- [24] N.A. Oyarzabal, N.L. Areso, N.B. Belar, I.G. Popolizio, A.V. Arregui, O.V.B. de Vallejo, Anaphylactic shock due to allergy to macrogol 4000 contained in SonoVue®, *Case Rep. Clin. Med.* 6 (2017) 143–147, <https://doi.org/10.4236/crcm.2017.66014>.
- [25] N. Giangrande, J.M. García-Menaya, M. Marcos-Fernández, C. Cámara-Hijón, P. Bobadilla-González, Anaphylaxis due to macrogol in a laxative solution with a positive basophil activation test, *Ann. Allergy Asthma Immunol.* 123 (2019) 302–304, <https://doi.org/10.1016/j.anai.2019.07.002>.
- [26] L. Bommarito, S. Mietta, F. Nebiolo, M. Geuna, G. Rolla, Macrogol hypersensitivity in multiple drug allergy, *Ann. Allergy Asthma Immunol.* 107 (2011) 542–543, <https://doi.org/10.1016/j.anai.2011.08.008>.
- [27] E.C. Wenande, P.S. Skov, H. Mosbech, L.K. Poulsen, L.H. Garvey, Inhibition of polyethylene glycol-induced histamine release by monomeric ethylene and diethylene glycol: a case of probable polyethylene glycol allergy, *J. Allergy Clin. Immunol.* 131 (2013) 1425–1427, <https://doi.org/10.1016/j.jaci.2012.09.037>.
- [28] Z.H. Zhou, C.A. Stone Jr., B. Jakubovic, E.J. Phillips, G. Sussman, J. Park, U. Hoang, S.L. Kirshner, R. Levin, S. Kozlowski, Anti-PEG IgE in anaphylaxis associated with polyethylene glycol, *J Allergy Clin Immunol Pract* S2213–2198 (20) (2020) 31231–31239, <https://doi.org/10.1016/j.jaip.2020.11.011>.
- [29] F.D. Finkelman, M.V. Khodoun, S.R. Strait, Human IgE-independent systemic anaphylaxis, *J. Allergy Clin. Immunol.* 137 (2016) 1674–1680, <https://doi.org/10.1016/j.jaci.2016.02.015>.
- [30] M.C. Castells, E.J. Phillips, Maintaining safety with SARS-CoV-2 vaccines, *N. Engl. J. Med.* 384 (2021) 643–649, <https://doi.org/10.1056/NEJMr2035343>.
- [31] ACAAI Updates to Guidance on Risk of Allergic Reactions to COVID-19 Vaccines. <https://acaai.org/news/acaai-updates-guidance-risk-allergic-reactions-covid-19-vaccines>, 2021 (accessed on 26 April 2021).
- [32] American Academy of Allergy Asthma and Immunology, An Update on COVID-19 for the Practicing Allergist/Immunologist. https://education.aaaai.org/resource-s-for-a-i-clinicians/Update-for-AI_COVID-19, 2021 (accessed on 12 January 2021).
- [33] Centers for Disease Control and Prevention, Lab Tests to Collect Shortly After Severe Allergic Reaction/Anaphylaxis Following COVID-19 Vaccination. <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/testing-after-allergic-reaction.html>, 2020 (accessed on January 11, 2021).
- [34] Joint Task Force on Practice Parameters, American Academy of Allergy A, Asthma and Immunology, American College of Allergy Asthma and Immunology, Joint Council of Allergy Asthma and immunology, Drug allergy: an updated practice parameter, *Ann. Allergy Asthma Immunol.* 105 (2010) 259–273, <https://doi.org/10.1016/j.anai.2010.08.002>.
- [35] World Allergy Organization, IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper, *World Allergy Organ. J* 13 (2020), 100080, <https://doi.org/10.1016/j.waojou.2019.100080>.
- [36] C. Mayorga, G. Celik, P. Rouzaire, P. Whitaker, P. Bonadonna, J. Rodrigues-Cernadas, A. Vultaggio, K. Brockow, J.C. Caubet, J. Makowska, A. Nakonechna, A. Romano, M.I. Montañez, J.J. Laguna, G. Zanoni, J.L. Gueant, H. Oude Elberink, J. Fernandez, S. Viel, P. Demoly, M.J. Torres, In vitro tests for Drug Allergy Task Force of EAACI Drug Interest Group. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper, *Allergy* 71 (2016) 1103–1134, <https://doi.org/10.1111/all.12886>.
- [37] J.M. Kelso, M.J. Greenhawt, J.T. Li, R.A. Nicklas, D.I. Bernstein, J. Blessing-Moore, L. Cox, D. Khan, D.M. Lang, J. Oppenheimer, J.M. Portnoy, C.R. Randolph, D. E. Schuller, S.L. Spector, S.A. Tilles, D. Wallace, Adverse reactions to vaccines practice parameter 2012 update, *J. Allergy Clin. Immunol.* 130 (2012) 25–43, <https://doi.org/10.1016/j.jaci.2012.04.003>.
- [38] R.A. Wood, R. Setse, N. Halsey, Clinical Immunization Safety Assessment (CISA) Network Hypersensitivity Working Group. Irritant skin test reactions to common vaccines, *J. Allergy Clin. Immunol.* 120 (2007) 478–481, <https://doi.org/10.1016/j.jaci.2007>.