COVID-19 mRNA vaccine allergy

Kimberly A. Risma

Purpose of review
A known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine is the only contraindication to coronavirus disease 2019 (COVID-19) mRNA vaccination. It is important for pediatricians to understand the likelihood of an allergic reaction to COVID-19 mRNA vaccines, including its excipients.

Recent findings
Episodes concerning for anaphylaxis were immediately reported following early administration of COVID-19 mRNA vaccines to adults. Although allergic type symptoms were reported equally in recipients of placebos and test vaccines in phase 3 clinical trials, post-authorization prospective studies state that 0.2–2% of vaccine recipients have experienced allergic reactions. Subsequent allergy testing of affected individuals has focused largely on evaluation of allergic sensitization to a novel vaccine excipient, polyethylene glycol (PEG). PEG is a polymer incorporated in numerous pharmaceutical products because of its favorable, inert properties. The results of allergy testing in adults to date indicate that IgE mediated anaphylaxis to PEG allergy is rarely identified after COVID-19 mRNA vaccine reactions. Numerous individuals with presumed anaphylaxis have tolerated a second vaccine after evaluation and testing by an allergist, suggesting either misdiagnosis or a novel immune mechanism.

Summary
Confirmed anaphylactic reactions to COVID-19 mRNA vaccines are rare, likely due to a lack of preexisting IgE against the vaccine components, including PEG.

Keywords
allergy, anaphylaxis, coronavirus disease 2019 mRNA vaccine, polyethylene glycol

INTRODUCTION

In December 2020, the United States (US) Food and Drug Administration (FDA) approved emergency use authorization (EUA) of the Pfizer-BioNTech and Moderna coronavirus disease 2019 (COVID-19) mRNA vaccines. This was a historic event, as the use of the mRNA platform had never been utilized for a global vaccine [1]. Encouraging preclinical data for the COVID-19 mRNA vaccines and remarkable phase 1–3 trial data [2–6,7,8,9] demonstrating 95% efficacy was made publicly available with expedition and great anticipation, appropriate to the public health emergency. The scientific feat would not have been possible had it not been for ongoing, extensive research for the previous two decades designing and enhancing mRNA vaccines [1]. Within 24 h of the first vaccinations administered in the United Kingdom, media reported that two individuals had developed anaphylaxis immediately after receiving the Pfizer-BioNTech COVID-19 vaccine.

REPORTING OF ALLERGIC REACTIONS: VACCINE SAFETY IN THE UNITED STATES

Prior to authorization of any medication, the FDA reviews phase 3 clinical trial data for evidence of serious adverse events. Phase 3 clinical trials for both the Pfizer BioNTech and Moderna vaccines included nearly 37 000 adults who received the vaccines and an equal number of adults who received a saline control injection (Table 1 [7,8]). Trial participants filled out surveys that solicited systemic symptoms such as headache, fatigue, chills, nausea, myalgia, arthralgia, and fever. In the Pfizer BioNTech vaccine reports, there were no cases of anaphylaxis and no...
serious allergic symptoms attributed to the vaccine. In the Moderna trial reports, unsolicited allergic reactions were reported in 1.5% of vaccine recipients and 1.1% of placebo recipients. Remarkably, a case of anaphylaxis was reported for both the vaccine and placebo arms, suggesting an alternative diagnosis.

Anaphylaxis is considered the most severe type of allergic reaction. Remarkably, there is a lack of agreement even amongst experts as to an accepted definition of anaphylaxis [10]. The simplest summary of proposed definitions includes an acute episode leading to systemic signs/symptoms that are rapid in onset, serious/severe/or potentially life threatening, and provoked by a mast cell trigger, typically immunoglobulin E (IgE). Common signs or symptoms involve pruritic rashes, flushing, mucosal angioedema (i.e., lips, tongue), wheezing, subjective dyspnea, or gastrointestinal distress. Hypotension and respiratory failure are less frequently noted but are potentially life threatening.

The differential for anaphylaxis includes vasovagal events and signs/symptoms related to anxiety. Rashes and subjective feelings of dizziness, skin tingling, pruritus, dyspnea, nausea, or dysphagia may be seen in individuals who are anxious as well, potentially explaining symptoms noted in placebo recipients of the Moderna vaccine [8]. Acknowledging the diagnostic difficulty of anaphylaxis, the Center for Disease Control and Prevention (CDC) utilizes a series of criteria to assign certainty to the diagnosis of vaccine associated anaphylaxis, called the Brighton Collaboration Criteria Definition [11].

The FDA and the Immunization Safety Office at the CDC monitor vaccine safety through several collaborative projects, including the Vaccine Safety Datalink (VSD), the Vaccine Adverse Events Reporting System (VAERS), and the Vaccine Safety DataLink (VSD). The VSD is a de-identified database of electronic health records from large health systems across the United States. The VAERS is a passive surveillance system where healthcare providers report adverse events that occur following vaccination. The VSD is a passive surveillance system where healthcare providers report adverse events that occur following vaccination.

### Table 1. Reports of allergic reactions to COVID-19 mRNA vaccines in large clinical trials

| Trial | Manufacturer (age in years of participants) | Publication date [ref] | Number of participants | Allergic symptoms reported | Solicited symptoms reported |
|-------|---------------------------------------------|------------------------|------------------------|---------------------------|-----------------------------|
| Phase 3 placebo controlled (US) | Pfizer BioNtech (≥16 years) | December 2020 [7] | 21,720 controls; 21,728 vaccine | No anaphylaxis | Solicited symptoms did not include allergic symptoms |
| Pfizer BioNtech (12–15 years) | May 2021 [9] | 1129 placebo; 1121 vaccine | No anaphylaxis or unsolicited serious allergic symptoms |
| Moderna; ≥18 years | December 2020 [8] | 15,166 controls; 15,185 vaccine | 1.5% of vaccine recipients reported hypersensitivity reaction; 1.1% in placebo group; including one case of anaphylaxis reported in each of the placebo and vaccine arms (unsolicited) |
| Healthcare workers (HCW) prospectively reporting on electronic survey (Boston, MA, USA) | Pfizer BioNtech or Moderna | May 2021 [29] | 52,805 HCW filled out survey after they received either vaccine; not placebo controlled | After first dose: 2.5% self-reported allergic symptoms | Seven individuals met criteria for anaphylaxis based on Brighton and NIAID criteria |
| Citizens self-reporting via mobile ‘app’ (UK) | Pfizer BioNtech | June 2021 [28] | 282,103 adults; not placebo controlled | Rash reported in 682 (0.2%) and/or ‘welts’ in 469 (0.2%) and/or skin burning in 2073 (0.7%) individuals | Allergic symptoms: Skin: rash or itching; Swelling: lips, eyes, tongue, face; Respiratory: wheezing, chest tightness, or shortness of breath |

COVID-19, coronavirus disease 2019.
VACCINE ADVERSE EVENTS REPORTING SYSTEM DATA FOR THE COVID-19 mRNA VACCINES

As of January 2021, the VAERS reports of anaphylaxis for adults were 47 per 9.9 million for the Pfizer-BioNTech and 19 cases per 7.6 million for the Moderna vaccine, although this data was extracted from VAERS reports when a minority of the country had been vaccinated [12]. A data search summarizing the publicly available data reporting anaphylaxis in VAERS in the age group 6–17 years as of July 30, 2021 shows 35 reports per 9.8 million children receiving their first dose of the mRNA vaccine (accessed at http://wonder.cdc.gov/vaers.html on August 11, 2021; data is unconfirmed; search term ‘anaphylaxis’ or ‘anaphylactic’ or ‘anaphylactoid’; age 6–17 years; event resulted in emergency room visit, office visit, hospitalization, or was deemed life threatening or led to permanent disability by submitter; onset 0 days).

Using the same search strategy, 539 adults were identified after Pfizer BioNTech for a total rate of all ages of 1.7 per million doses administered (333 million doses of mRNA vaccines given in the US). Thus, the rate of anaphylaxis currently appears to be comparable to historical reports from other commonly administered vaccines – Tdap (0.51 per million) and the trivalent inactivated flu vaccine (1.35 per million) with the caveat that previous estimates were based on data from the VSD and the search strategy is not identical (reviewed in [13]).

POTENTIAL MECHANISMS FOR IMMEDIATE REACTIONS TO COVID-19 mRNA VACCINES

Previous investigations into the immune mechanisms of vaccine-associated anaphylaxis have focused on IgE-mediated reactions to common excipients such as gelatin, latex or egg protein [14], none of which are found in the COVID-19 mRNA vaccines (Table 1, Supplemental Digital Content, http://links.lww.com/MOP/A64) [7*,8*]. The mRNA vaccines incorporate an ionizable lipid bearing a positive charge at low pH to neutralize the negative charge of the mRNA (Fig. 1), reviewed in [1,15]. The mRNA vaccines assemble into a lipid nanoparticle (LNP) from additional neutral lipids, cholesterol, and a phospholipid conjugated to polyethylene glycol (PEG). PEG increases the hydrophilicity of the LNP surface and historically its incorporation into pharmaceuticals has decreased the immunogenicity of proteins and nucleic acids [16]. In the COVID-19 mRNA vaccines, one form of high molecular weight (HMW) PEG (PEG 2000; the number represents the average molecular weight, determined by the length of the repeating ethylene oxide units) is incorporated. Other medications that contain other preparations of HMW PEG are summarized in Table 2, Supplemental Digital Content, http://links.lww.com/MOP/A64, including the commonly used laxative, PEG 3350.

Despite its inert properties, rare allergic reactions to HMW PEG have been described in the literature in case reports, and a previously diagnosed allergy to PEG is thus a contraindication to COVID-19 mRNA vaccination. Case reports of patients experiencing anaphylaxis after exposure to injectable medications containing PEG 3350, PEG conjugated proteins or lipids (i.e., PEGylated), or orally administered PEG 3350 have been described by allergists who have also documented positive allergy tests to these same preparations [17–22].

The manifestation of anaphylaxis upon first exposure to a novel vaccine implies either preexisting, antibody-mediated immunity (allergic, i.e., IgE mediated) or a pseudo-allergic response that does not depend upon previous exposure. Most individuals who receive the COVID-19 mRNA vaccines have never been exposed to an injectable formulation of HMW PEG or have tolerated enteral or topical medications containing HMW PEG without allergic reaction (see Table 2, Supplemental Digital Content, http://links.lww.com/MOP/A64), arguing against the likelihood of pre-existing, anti-PEG IgE.

Although the term ‘pseudo-allergy’ may suggest a tempered reaction compared to IgE-mediated anaphylaxis, the clinical presentation of these immune reactions may be indistinguishable. Mechanisms of pseudo-allergic reactions include direct activation/degranulation of mast cells (through G protein coupled receptors or complement activation) or mast cell independent mechanisms (such as mRNA stimulation of bradykinin production) causing vascular
These immune mechanisms are summarized in Fig. 1 and Figure 1, Supplemental Digital Content, http://links.lww.com/MOP/A64 and discussed extensively by separate reviews [25*,26,27]. The current document summarizes the data of allergic reactions reported in the first 7 months of mRNA vaccination and the results of allergy testing in this same period.

PROSPECTIVE EVALUATION BY DIGITAL SURVEYS SOLICITS ALLERGIC SYMPTOMS IN VACCINE RECIPIENTS

Following the early reports of anaphylaxis in the UK, allergic symptoms were solicited using an elective reporting ‘app’ from over 200,000 individuals in the UK after vaccination with the Pfizer mRNA vaccine. Minni et al. [28] reported that 0.2% experienced red welts on face/lips for both vaccines and 0.2–0.4% reported generalized rash (Table 1).

In a US study, Blumenthal et al. reported that 2.5% of healthcare workers (HCW) at a large Boston hospital system (52,805 reports) who received either the Pfizer BioNTech or the Moderna mRNA vaccines self-reported allergic symptoms by electronic survey. Most symptoms included cutaneous symptoms: i.e., itching or rash not at injection site (n = 788) and/or hives (n = 244). However, 342 individuals reported respiratory symptoms and 191 reported swelling occurring within 3 days of vaccination (Table 1; [29]). Eleven individuals reported symptoms reactions consistent with anaphylaxis when either the Brighton Criteria or a second assessment tool used by allergists was applied to increase diagnostic certainty.

Neither the UK nor US study was placebo controlled, so it is difficult to predict whether the reported allergic symptoms were related to vaccination (i.e., anxiety and/or vasovagal reactions) or a true allergic reaction. The timing of self-reported symptoms included immediate reactions (IgE mediated anaphylaxis typically occurs within 1–2 h) and delayed reactions (up to 3 days for the US and 8 days for the UK study, not typical for IgE mediated reactions).

ALLERGY TESTING AND REPEAT VACCINATION IN ADULTS SUFFERING IMMEDIATE ALLERGIC REACTIONS (<4 HOURS) AFTER COVID-19 mRNA VACCINATION SUGGEST THAT LIFE-THREATENING, IgE MEDIATED ANAPHYLAXIS IS UNCOMMON

Severe allergic reactions (i.e., anaphylaxis) to a vaccine is a contraindication to administration of a

---

**FIGURE 1.** mRNA vaccines contain unique immunostimulatory molecules. Components of COVID-19 mRNA lipid nanoparticle (LNP) include high molecular weight polyethylene glycol (PEG) to ‘protect’ the LNP from immediate degradation by macrophages; ionizable lipids to balance the negative charge of the mRNA and neutral lipids to create a viral like particle such as 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and cholesterol. COVID-19, coronavirus disease 2019; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M. Specific immune targets may include innate or adaptive immunity (IgG, IgE, IgM). To date, only preexisting IgE against high molecular weight PEG has been evaluated. Reprinted from [25*], with permission from Elsevier.
second dose of the same vaccine. Therefore, it is imperative to promptly evaluate patients presenting with a history consistent with anaphylaxis using an objective measure of allergic sensitization. Measurement of a serum tryptase within 4 h of the reaction measures systemic mast cell degranulation, consistent with anaphylaxis but is rarely obtained in the emergency department.

Skin testing is the preferred method for evaluation of IgE mediated vaccine allergy, including skin prick (scratch) and/or intradermal (ID) skin tests to the whole vaccine and typically its excipients. Generally, intradermal testing is thought to be more sensitive than skin prick testing (SPT) for detecting allergic sensitization across all allergens, but the specificity also suffers. There is limited experience using the mRNA COVID-19 vaccines for skin testing and currently there is not agreement among allergists that these should be used for allergy testing [30–32]. Three vaccine recipients with allergic symptoms tested (+) to skin testing by the mRNA vaccine [33,34]. Two had mild symptoms with the first COVID-19 mRNA dose, had (−) SPT and (+) ID testing to the mRNA vaccine; both successfully received the second dose in the allergy office [34]. The third patient was not given a second vaccine due to a (−) SPT [33]. To date, excipient skin testing after mRNA vaccine reactions has been limited to HMW PEG, summarized below.

An additional method to evaluate patients for allergy includes a basophil activation test (BAT), exposing basophils in a patient’s blood to the suspected trigger such as HMW PEG or the COVID-19 mRNA vaccine itself [35,36]. The BAT is only available in research labs, and the same caveats about sensitivity and specificity apply to interpretation of results [36].

Allergy provocation challenge (typically repeat exposure in the allergist office) is increasingly recognized as the gold standard to confirm or exclude a diagnosis of allergy. This may be done in an allergist office, prepared to treat anaphylaxis. In the event where a second vaccine is required and there is evidence of allergic sensitization, allergists may also proceed with a graded administration of the vaccine [37]. The decision to pretreat with antihistamines prior to repeat vaccination varies amongst allergists [38,39].

Two academic allergy groups have begun evaluation of the Boston HCW who reported allergic symptoms within 3 days of vaccination for evidence of allergic sensitization. Wolfson et al. [40] have reported the results of testing the first 80 individuals for HMW PEG allergy by skin testing and reported outcomes of repeat vaccine dosing. Skin testing to PEG 3350 was used as a surrogate for the PEG 2000 incorporated into the LNP of the mRNA vaccines. As shown in Fig. 2, two HCWs were recommended not to receive a second mRNA vaccine based on a concerning reaction history or positive (+) allergy test (one individual had a (+) SPT to PEG 3350). The remaining 78 individuals were offered a second vaccine and 70 proceeded with vaccination. Fifty-two individuals had no subsequent reaction on repeat dosing, including three who had (+) ID PEG skin tests (with negative SPT). Eighteen individuals did experience reproducible allergic symptoms to the vaccine upon repeat dosing, all with (−) SPT and ID skin testing to PEG 3350, calling into question the utility of the PEG 3350 testing. Vaccine allergy skin testing was not performed. It is certainly feasible that allergic reactions to the vaccines were directed at PEG 2000 displayed as a repeating structure on the vaccine LNP without detection of allergic sensitization to the surrogate, soluble PEG 3350.
To detect IgE mediated allergy, it is typical to focus on reactions occurring within hours rather than days of exposure. Five academic allergy centers in the US collaboratively reported outcomes after administering second doses to 189 individuals suffering allergic signs and symptoms within the first 4 h of their first mRNA vaccines, Fig. 3 [41**]. The report includes 32 individuals whose reactions were classified as anaphylaxis. There was overlap between previous publications— including 56 vaccine recipients (eight with anaphylaxis) previously reported in the Boston HCW study ([40] personal communication with Dr Kimberly Blumenthal) and four individuals suffering anaphylaxis, previous published in a case study highlighting findings of negative PEG 3350 skin testing ([38] personal communication with Dr Cosby Stone). Despite allergic symptoms with the first vaccine, 159 individuals (including 19 with previous diagnosis of anaphylaxis) proceeded to the second mRNA vaccine dose, and all tolerated the vaccine. Although some individuals experienced mild allergic symptoms, none were worse than the original reaction and none were thought to be IgE mediated or consistent with anaphylaxis.

Review of the literature for additional case reports published between December 2020 and July 2021 include 22 women and two men seen in consultation for PEG and/or vaccine allergy by allergists after immediate (<4 h), systemic, reactions to the first dose of COVID-19 mRNA vaccines (summarized in Table 3, Supplemental Digital Content, http://links.lww.com/MOP/A64). Seventeen of the 24 reported individuals had skin testing to PEG 3350, but only one individual had a (+) SPT and a medical history consistent with PEG 3350 allergy [20]. An additional patient was diagnosed with potential PEG allergy as she had a basophil activation test that was (+) for PEG 4000 at a range of concentrations [35] although she experienced only mild allergic symptoms with the mRNA vaccine. Twenty one of these 24 individuals who experienced immediate
Delayed allergic skin reactions may occur at injection site or may be generalized and do not prevent a second dose of the vaccine

Large, local inflammatory reactions at the site of vaccination have been reported to occur one week after injection of mRNA vaccines, nicknamed ‘COVID arm’ [45]. In addition to local site reactions and delayed large local reactions, McMahon et al. reported a variety of generalized rashes including hives, morbilliform exanthems and erythromelalgia occurring 1–12 days following vaccination. Upon second dosing, large local and systemic rashes occurred sooner after the second dose in 43% of HCW reporting rashes to a US dermatology registry [46]. None of these rashes are a contraindication to getting the second dose of the vaccine but can be quite distressing to the individual.

Conclusion: COVID-19 mRNA vaccines are unlikely to trigger an IgE mediated allergic reaction

The efficacy of mRNA LNP vaccination against COVID-19 disease in clinical trials and the expediency of production suggests the use of this technology is likely to revolutionize future vaccine approaches. Thus, it is prudent to learn from individuals experiencing allergic type symptoms and signs- not only to facilitate second dose administration following allergy consultation, but also to understand the mechanisms of reactions. The studies reported in the first 7 months of global vaccination suggest that allergic type symptoms may occur in 0.2–2.5% of vaccine recipients in the first week following vaccination. However, IgE mediated anaphylaxis is unlikely, as this mechanism is typically characterized by reproducible episodes of allergic response with repeat exposures, not observed in over 200 reported cases of immediate reactions to date. The discrepancies in the data between the reports of anaphylaxis and the tolerance of the second dose suggests either misdiagnosis or alternative, non-IgE mechanisms causing allergic type symptoms.

As most allergic data reported to date is in adults, it is prudent for pediatricians to continue to report cases of immediate reactions to vaccines occurring in children to the VAERS system and appropriate referrals made to allergists for post vaccine evaluations. Children with a previously reported severe allergic reaction to a medication containing HMW PEG (Table 2, Supplemental Digital Content, http://links.lww.com/MOP/A64) should be referred to an academic medical center for allergy testing whenever feasible to confirm the diagnosis before excluding a child from obtaining a mRNA vaccine.

Acknowledgements
Dr Kathryn Edwards and Dr Allison Norton for valuable comments

Financial support and sponsorship
K.A.R. has no external funding sources to declare. K.A.R. has served as a consultant to the CDC sponsored Clinical Immunization Safety Assessment (CISA) Project; This work was not supported by CISA.

Conflicts of interest
There are no conflicts of interest.
REFERENCES AND RECOMMENDED READING

Papers of special interest, published within the annual period of review, have been highlighted as:
• of special interest
• of outstanding interest

1. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines – a new era in vaccinology. Nat Rev Drug Discov 2018; 17:261–279.

2. Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. N Engl J Med 2020; 383:2439–2450.

3. Laczko D, Houghton MJ, Toumlin SA, et al. A single immunization with nucleoside-modified mRNA vaccines elicits strong cellular and humoral immune responses against SARS-CoV-2 in mice. Immunity 2020; 53:724–732.

4. Corbett KS, Edwards DK, Leist SR, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature 2020; 586:567–571.

5. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA vaccine against SARS-CoV-2 – preliminary report. N Engl J Med 2020; 383:1920–1931.

6. Mulligan MJ, Lyke KE, Kitchin N, et al. Phase III study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 2020; 586:589–593.

7. Polack PF, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020; 383:2603–2615.

This report describes the efficacy and safety data of the phase III clinical trial for the Pfizer BioTech COVID-19 mRNA vaccine.

8. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021; 384:403–416.

This report describes the efficacy and safety data of the phase III clinical trial for the Moderna COVID-19 mRNA vaccine.

9. Frenck RW Jr, Klein NP, Kitchin N, et al. Safety, immunogenicity, and efficacy of the BNT162b2 COVID-19 vaccine in adolescents. N Engl J Med 2021; 385:239–250.

10. Cardona V, Ansetegui U, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J 2020; 13:100472.

11. Ruggenberg JU, Gold MS, Bayas JM, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007; 25:5675–5684.

12. Shimabukuro TT,Cole M, Su JR. Reports of anaphylaxis after receipt of mRNA COVID-19 vaccine in the US – December 14, January 20, 2021. JAMA 2021; 325:1101–1102.

13. McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. J Allergy Clin Immunol 2018; 141:463–472.

14. Stone CA Jr, Rukasin CRF, Beachkofsky TM, Philips EJ. Immune-mediated adverse reactions to vaccines. Br J Clin Pharmacol 2019; 85:2694–2706.

This review focuses on the excitents that cause allergic reactions to vaccines.

15. Cullis PR, Hope MJ. Lipid nanoparticle systems for enabling gene therapies. Mol Ther 2017; 25:1467–1475.

16. Harris JM, Chess RB. Effect of pegylation on pharmaceuticals. Nat Rev Drug Discov 2005; 2:214–221.

17. Wylong K, Dole S, Worm M. Polyethylene glycol as a cause of anaphylaxis. Allergy Asthma Clin Immunol 2016; 12:67.

18. Stone CA Jr, 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; 7:1533–1540.

19. Sellaturay P, Nasser S, Ewan P. Polyethylene glycol-induced systemic allergic reactions (anaphylaxis). J Allergy Clin Immunol Pract 2021; 9:670–675.

20. Li N, Rutkowski K, Kennard L, et al. Polyethylene glycol may be the major allergen in depot medroxyprogesterone acetate. J Allergy Clin Immunol Pract 2020; 8:3194–3197.

21. Krantz MS, Liu Y, Phillips EJ, Stone CA Jr. Anaphylaxis to PEGylated liposomal echocardiogram contrast in a patient with IgE-mediated macroagglut. Allergy Clin Immunol Pract 2020; 8:1416–1419.

22. Finkelman FD, Khodoun MV, Strat R. Human IgE-independent systemic anaphylaxis. J Allergy Clin Immunol 2016; 137:1674–1680.

23. Jimenez-Rodriguez TW, Garcia-Neuer M, Alenay LA, Castells M. Anaphylaxis in the 21st century: phenotypes, endotypes, and biomarkers. J Asthma Allergy 2018; 11:121–142.

24. Risma KA, Edwards KM, Hummell DS, et al. Potential mechanisms of anaphylaxis to COVID-19 mRNA vaccines. J Allergy Clin Immunol 2021; 147:2075–2082.

This review summarizes mechanisms of allergic and pseudo allergic reactions in the context of the new COVID-19 mRNA vaccines.

25. Bruhns P, Chollet-Martin S. Mechanisms of human drug-induced anaphylaxis. J Allergy Clin Immunol Pract 2021; 14:1638–1656.

26. Greenhawt MJ, Abrams EM, Shaker M, et al. Potential mechanisms of anaphylaxis to the first dose of mRNA COVID-19 vaccines. J Allergy Clin Immunol Pract 2021; 9:2478–2477.

27. Kelso JM. Misdiagnosis of systemic allergic reactions to mRNA COVID-19 vaccines. Ann Allergy Asthma Immunol 2021; 127:133–134.

28. Perez-Codesido S, Rosado A, Alonso-Diaz-de-Durana MD, et al. Hypersensitivity to COVID-19 vaccine confirmed by a positive skin test result: a case report. J Investig Allergol Immunol 2021; 31. Online ahead of print.

29. Mustafa SS, Ramsey A, Sticau ML. Administration of a second dose of the Moderna COVID-19 vaccine after an immediate hypersensitivity reaction with the first dose: two case reports. Ann Intern Med 2021; 174:1177–1178.

30. Restivo V, Candore G, Bar nale M, et al. Allergy to polyethylene glycol of anti-SARS-CoV2 vaccine recipient: a case report of young adult recipient and the management of future exposure to SARS-CoV2. Vaccines (Basel) 2021; 9.

31. Trostnikov A, Perkins G, Yuson C, et al. Basophil reactivity to BNT162b2 is mediated by PEGylated lipid nanoparticles in patients with PEG allergy. J Allergy Clin Immunol 2021; 148:91–95.

32. Kelso JM, Greenhawt MJ, Li JT, et al. Adverse reactions to vaccines practice parameter 2012 update. J Allergy Clin Immunol 2012; 130:25–43.

33. Krantz MS, Brusgaard-Mountsea NA, Koo G, et al. Anaphylaxis to the first dose of mRNA-SARS-CoV-2 vaccines: don’t give up on the second dose! Allergy 2021; 76:2916–2920.

34. Greenhawt M, Abrams EM, Shaker M, et al. The risk of allergic reaction to SARS-CoV-2 vaccines and recommended evaluation and management: a systematic review, meta-analysis, GRADE Assessment, and International Consensus Approach. J Allergy Clin Immunol Pract 2021; 9:3546–3567.

35. Wolfson AR, Robinson LB, Li L, et al. First-dose mRNA COVID-19 vaccine allergic reactions: limited role for epinephrin skin testing. J Allergy Clin Immunol Pract 2021; 9:3308.e3–3320.e9.

36. Krantz MS, Kwah JH, Stone CA Jr, et al. Safety evaluation of the second dose of messenger RNA COVID-19 vaccines in patients with immediate reactions to the first dose. JAMA Intern Med 2021. This report describes 189 individuals from 5 medical centers in the US who have been evaluated for allergic reactions occurring within 4h of COVID-19 mRNA vaccination. It is the largest group described to date and includes 189 individuals who successfully received a 2nd dose.

37. Park HJ, Montgomery JR, Boggs NA. Anaphylaxis after the COVID-19 vaccine in a patient with cholinergic urticaria. Mil Med 2021.

38. Pitlick MM, Sitek AN, Krute SA, et al. Polyethylene glycol and polysorbate skin testing in the evaluation of coronavirus disease 2019 vaccine reactions: Early report. Ann Allergy Asthma Immunol 2021; 126:735–738.

39. Sellaturay P, Nasser S, Islam S, et al. Polyethylene glycol (PEG) is a cause of anaphylaxis to the Pfizer/BioNTech mRNA COVID-19 vaccine. Clin Exp Allergy 2021; 51:861–863.

40. Blumenthal KG, Saff RR, Freeman EE. Delayed local reactions to mRNA vaccines after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. J Am Acad Dermatol 2021; 85:46–55.

41. McNally DE, Amenson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. J Am Acad Dermatol 2021; 85:46–55.