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mRNA COVID-19 Vaccine Anaphylaxis: Epidemiology, Risk Factors, and Evaluation

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Abstract

Purpose of Review The COVID-19 vaccines have proved essential in our defense against the COVID-19 pandemic. However, concerns regarding allergic reactions to the vaccines persist to this day. Herein, we review the data regarding the frequency of allergic reactions to the COVID-19 vaccines, the epidemiology, and the management of patients reporting vaccine allergic reactions.

Recent Findings Although initial reports emphasized a high risk of anaphylaxis to the COVID-19 vaccines, more recent data demonstrate similar rates of anaphylaxis to the COVID-19 vaccines as to other vaccines. Alternative explanations for increased rates of apparent allergic reactions are discussed, including the role for stress-related and nocebo responses.

Summary COVID-19 vaccines and mRNA vaccine technology are overwhelmingly safe and well-tolerated by most patients. Careful history and case review will enable the discerning physician to safely vaccinate most patients. Rare patients with objective signs and symptoms of anaphylaxis may be candidates for alternatives to vaccination including monoclonal antibodies.

Keywords Vaccine allergy · Drug allergy · Anaphylaxis · mRNA vaccine · COVID-19 vaccine

Abbreviations

COVID-19	Coronavirus disease 2019
CDC	Centers for Disease Control and Prevention
NIAID	National Institute of Allergy and Infectious Diseases
WAO	World Allergy Organization
PEG	Polyethylene glycol

COVID-19 Vaccine, Background, and Importance

The novel coronavirus disease 2019 (COVID-19) not only changed our lives over the past years, but also changed our approach to vaccination and infectious disease. The overwhelming morbidity and mortality of COVID-19 have been unprecedented; as of the writing of this article, 1.03 million people have died from COVID-19 in the USA alone [1]. One of the great successes of modern science was the rapid development followed by distribution of COVID-19 vaccines. The mRNA vaccines developed by Pfizer-BioNTech and Moderna have remained an important defense in our fight against this infectious disease. Real-world data from October to November 2021 demonstrates the importance of these vaccines: unvaccinated people had 13.9 times the risk for infection and 53.2 times the risk for COVID-19-associated death compared to fully vaccinated (including boosters) people [2].

Unfortunately, there have been a number of barriers to vaccination in the USA, including politicization of the vaccine; false narratives including anti-vaccination campaigns; and concerns regarding the safety and side effect profile of the vaccines [3, 4]. For allergists, we have been at the forefront of the latter category: as soon as these exciting, new vaccines were ready for administration, reports of allergic reactions and anaphylaxis began [5]. The concern for allergic reactions to the vaccines has been a major portion of the Centers for Disease Control and Prevention's (CDC) guidelines regarding safety of vaccination. Initially, any patient with a history of any allergic reaction was counseled

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regarding safety; now, the CDC guidelines advise caution only for those with an allergy to ingredients in the vaccine or the vaccines themselves [6]. The initial broad language regarding concern for history of anaphylaxis has impacted our patients' perceptions regarding the vaccine. A Facebook survey of over 5 million people conducted in January to May 2021 reported 73,362 people who self-identified as hesitant to receive the vaccine, almost a quarter of which identified concerns regarding allergic reactions to the vaccines as a contributing factor to their hesitancy [7].

That patients experience anaphylaxis and allergic reactions to the COVID-19 vaccines was somewhat of a surprise to the medical community: historically, vaccine anaphylaxis has been characterized as rare and vaccines safe, generally well-tolerated [8]. For example, from January 2009 to December 2011, the rate of anaphylaxis was 1.31 per million vaccine doses [9]. Indeed, more recent data does reflect that the rate of anaphylaxis due to all types of COVID-19 vaccines is similar to the rate of anaphylaxis due to other vaccines [10], but this fact is not widely understood by our patients [7]. Due to the importance of these mRNA COVID-19 vaccines combined with the initial high reported rates of allergic reactions [11], allergists have worked diligently to characterize the epidemiology and risk factors leading to mRNA COVID-19 vaccine anaphylaxis and to develop an approach to patients reporting history of a reaction [12••, 13••].

Epidemiology of Allergic Reactions

The incidence of anaphylaxis to the mRNA COVID-19 vaccines has changed over time, with the highest rates initially reported in December 2020 and lower rates more recently. Initially, in December 2020, estimated rates of anaphylaxis were reported as 11.1 per million doses administered of the Pfizer-BioNTech vaccine [14] but by January 2021, the reported rate of anaphylaxis to Pfizer-BioNTech had decreased to 4.7 per million doses administered and 2.5 cases per million doses administered of the Moderna vaccine [11]. In 2021, among all COVID-19 vaccine types, the incidence was 7.91 per million vaccines administered [15]. Most recently, the rates of anaphylaxis have been reported as 5 cases per one million doses of vaccine administered [16]. Characterizing the incidence of anaphylaxis and allergic reactions has not been a straightforward endeavor; a major impact on the calculated rates of anaphylaxis has been differences in anaphylaxis criteria utilized [17]. In the paper by Hourihane et al., reassessment of cases reported as anaphylaxis using Brighton Collaboration Criteria [18] and then using other widely used criteria (National Institute of Allergy and Infectious Diseases (NIAID) 2005 [19] and World Allergy Organization (WAO) 2020 [20]) resulted in 71% of cases initially reported as anaphylaxis being reclassified as not meeting anaphylaxis criteria [17]. Hourihane et al. argue that over-estimation of vaccine-related anaphylaxis can increase vaccine hesitancy [17]. While the Brighton Collaboration Criteria has merits of its own [21] which are being debated [22], the authors stress the important point that classification and identification of anaphylaxis are difficult and require that discerning clinicians have attention to detail.

Our understanding of COVID-19 vaccine anaphylaxis was also impacted by the administration of second doses of mRNA COVID-19 vaccines only weeks after the first dose. Chu et al. published a meta-analysis of 1366 people who experienced first dose COVID-19 vaccine reactions, of which following their second vaccine, only 6 (0.4%) developed severe reactions and 232 (17%) developed mild symptoms [23••]. The finding that patients with symptoms concerning for anaphylaxis may tolerate the second dose of the vaccine led to a discussion of the mechanism of apparent anaphylaxis to the vaccine [24]. Our classic understanding of IgE-mediated reactions would not allow for tolerance within a short period [25], but non-IgE-mediated pathways can result in variable activation of mast cells and basophils to cause symptoms clinically consistent with anaphylaxis reactions [26, 27]. Another diagnostic cause to be considered in the differential diagnosis of our patients' symptoms is the possibility of anxiety related to the administration of the vaccine, deemed immunization stress–related response [28]. Partially due to the media frenzy regarding allergic reactions and the stress of the COVID-19 pandemic at large, patients may have experienced clinical symptoms due to physiological stress which were mistaken for allergic reactions, such as palpitations, dyspnea, flushing, tingling [28], or vocal cord dysfunction [29].

Risk Factors for Allergic Reactions

Certain patient characteristics are associated with an increased risk of mRNA COVID-19 vaccine anaphylaxis, but there is no absolute risk factor associated with reactions [13••]. Macy et al. published a review of over 391,000 individuals who received at least one dose of COVID-19 vaccine; 130 (0.033%) were treated for acute hypersensitivity reaction after either the first or second vaccine dose. These 130 patients were more likely to be younger and female, and with multiple drug intolerance syndrome and a history of prior vaccine-associated adverse reaction [30]. Similarly, in a cohort of 429 highly allergic patients, 9 (1.2%) had reactions following the first dose of the vaccine; 218 proceeded to second dose, of which 4 (1.8%) of these patients had reactions. The characteristics of these 13 patients were similarly more likely to be female, with a history of multiple drug allergies and prior anaphylaxis [31]. The association of adverse reaction to the vaccine with a prior history of multiple drug intolerance syndrome could be indicative of a possible role for the nocebo effect [32].

The nocebo effect is unpleasant reactions which occur following the administration of an indifferent substance [33]. Vaccines and medications are both associated with nocebo effects, and this has been true for the COVID-19 vaccines as well. In a meta-analysis review of 45,380 adverse events from trials of COVID-19 vaccines (22,578 placebo recipients; 22,802 vaccine recipients), following the first dose, 35.2% of placebo recipients reported systemic adverse events (most commonly headache and fatigue). Similarly, after the second dose, 31.8% of placebo recipients reported systemic adverse events (notably, the report of systemic adverse events was statistically significantly higher in the group receiving the vaccine). Although the focus in this meta-analysis was not on allergic effects, the important influence of the nocebo effect on our patients is demonstrated with these findings [34]. The authors of this meta-analysis also emphasize that pamphlets and information provided to patients around the time of vaccination can increase (e.g., by emphasizing the risk of the vaccine) [35] or decrease (e.g., by providing reassurance regarding the low likelihood of this risk) [36] the nocebo effect. This is important for our patients who have previously received information about the high risks of allergic reactions to mRNA COVID-19 vaccines, as they may benefit from a review of the most recent data demonstrating lower rates of reactions [16].

Evaluation of Reported Allergic Reactions

Although most patients will tolerate COVID-19 vaccines without allergic reactions, as allergists, we must be prepared to help patients with concern for vaccine reactions. The first portion of evaluating a patient with a report of an allergic reaction following the COVID-19 mRNA vaccine is to obtain a thorough history, including review of available notes, vital signs, physical exam documentation, and laboratory evaluation [8, 37]. The history will enable the physician to differentiate between a true anaphylactic reaction, a mild allergic reaction, and subjective symptoms possibly attributable to anxiety [38]. For the low-risk patient with subjective symptoms such as tachycardia and self-limited flushing, the authors would provide reassurance to this patient. A conversation encompassing the overall safety and importance of the vaccine including a review of the data discussed herein may be helpful. For a patient with a moderate-risk history, such as symptoms consistent with an apparent IgE-mediated allergy occurring less than 4 h after vaccine administration but not meeting criteria for anaphylaxis, the authors use a shared decision-making approach [12]. The authors would have a similar conversation as with the low-risk patient but would add for the moderate-risk patient consideration of pre- and post-treatment with oral antihistamines such as cetirizine 10 mg or fexofenadine 180 mg, as well as 30 min of post-vaccine observation [12••].

For the patient with a history concerning for anaphylaxis, the authors would offer skin testing to the vaccine itself. The authors use dilutions based on previously published vaccine skin testing protocols: skin prick testing with undiluted vaccine, and, if negative, intradermal testing with a 1:100 dilution [8]. Skin testing to the COVID-19 vaccine is considered to be of low utility based on data, but the authors find that patients often request this procedure. Pitlick et al. published their findings in which 55 patients with a history of first dose reactions were skin tested to the vaccine; 4 (7%) were skin test positive, of these, 3 received the vaccine and 2 tolerated the vaccine. On the other hand, among the 51 (93%) patients with negative skin tests, 40 received the vaccine and 6 had symptoms with the next dose. Similarly, 74 patients with no prior vaccine dose were skin tested; 8 (11%) were skin test positive and 3 of these received and tolerated the vaccine. In the skin test negative group, 55 (83%) received their first dose and 4 of these patients had symptoms with the vaccine [39•]. This demonstrates that both in patients with concern for vaccine reaction and reported symptoms after their first dose, vaccine skin testing was of low predictive utility in predicting tolerance. Nonetheless, the authors do offer vaccine skin testing to patients with a history of acute, severe allergic reaction following the vaccine as it does help with shared decision-making [12••, 13••]. Graded vaccine challenges [40] and observed vaccine administration in the office are both options for patients with high-risk histories [13••].

Initially, the excipient polyethylene glycol (PEG) was identified as a possible allergen in the mRNA COVID-19 vaccines [41]. Although these concerns are now largely diminished given findings of patients with known PEG allergy tolerating the vaccine [42], CDC guidelines still encourage patients with known PEG allergy to seek consultation with an allergist [6]. The first step is again to obtain a thorough clinical history, and if the patient's presentation is consistent with PEG allergy, shared decision-making would occur. The first option, given we have data demonstrating the tolerance of mRNA COVID-19 vaccine among patients with PEG allergy [42], is the patient could proceed to vaccination without further testing but with 30 minutes of observation [12••]. The second option is to perform an evaluation for PEG allergy, which is separate from the evaluation for the allergy to the mRNA COVID-19 vaccine. Negative skin testing to PEG is not predictive of vaccine tolerance [43]; it may be useful in a patient with a high-risk history of PEG allergy [44]. A patient with negative COVID-19 vaccine skin testing but positive PEG skin testing could receive the vaccine but should still avoid PEG; if the COVID-19 vaccine skin testing is positive, again shared decision-making should occur [12]. The authors do not perform PEG skin testing in the evaluation of COVID-19 vaccine allergy without compelling evidence of allergy to PEG itself. Given the possible role for tixagevimab co-packaged with cilgavimab (Evusheld)

[45] and the possibility of receiving non-mRNA COVID-19 vaccines [46], the rare patient with a history concerning for severe mRNA COVID-19 vaccine anaphylaxis may opt to not receive an mRNA COVID-19 vaccine. As allergists and immunologists, we can aid eligible patients in receiving tixagevimab/cilgavimab so they can obtain protection against COVID-19 [45], but the vast majority of patients should be reassured that they can safely receive COVID-19 vaccines.

Conclusion

The COVID-19 mRNA vaccines have served as the crux point in returning some degree of normalcy following the high morbidity and mortality associated with COVID-19. However, early reports regarding the high risk of allergic reactions associated with these vaccines may have been over-classifications due to criteria grading systems, misinterpretations of anxiety, and nocebo reactions. The rates of allergic reactions to these vaccines now seem to be similar to the rates seen with other vaccines; thus, as with vaccine allergy in general, allergists are equipped to guide patients. We are empowered to discuss the low risk and high safety of these vaccines with our patients in order to engage in shared decision-making. We can provide vaccine (and, rarely, excipient [47, 48]) skin testing when clinically appropriate, and we can advise use of antihistamines preceding vaccination in select clinical scenarios. We must be capable of managing the rare patient who does have a true anaphylactic reaction to an mRNA COVID-19 vaccine, and this patient may be a candidate for pre-exposure prophylaxis with tixagevimab/cilgavimab or possibly non-mRNA COVID-19 vaccines. As we have since December 2020 when the COVID-19 vaccines were first released, allergists remain ready and willing to help our patients safely receive these effective vaccines.

Compliance with Ethical Standards

Conflict of Interest Dr. Jaggers has nothing to declare. Dr. Wolfson has nothing to declare.

Human and Animal Rights and Informed Consent All procedures performed in studies involving human participants by the authors were in accordance with the ethical standards of the institutional research committee (Mass General Brigham Institutional Review Board protocol number 2020P004068) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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