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Paradigms and perspectives

Management of patients with immediate reactions to COVID-19 vaccines

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Immediate reactions suggestive of an allergic reaction to either a first or subsequent mRNA coronavirus disease 2019 (COVID-19) vaccine dose are very rare. Reactive patients have tended to be overrepresented by females and persons self-reporting multiple drug allergies or intolerances, past adverse reactions to vaccines, and anxiety.^{1,2} Few such reactions meet the level 1 Brighton Collaboration Criteria (BCC), and of those meeting the level 1 to level 3 BCC, many would not meet the stringent anaphylaxis criteria established by either the National Institutes of Allergy and Infectious Diseases or the World Allergy Organization.³ In adjudication of these reports, it has become clear that multiple postvaccination symptom patterns can mimic and be interpreted as anaphylaxis.¹ The reported symptoms that can mimic anaphylaxis include flushing, erythema, dizziness, nausea, throat tightness, urticaria, wheezing, and dyspnea.^{1,2} Although there is considerable overlap, several phenotypes of immediate reactions can be recognized and used to guide management. Our field's increasing awareness of the phenotypes of "immediate adverse vaccine responses," the majority of which are nonallergic, has provided allergists with a new perspective on management of such responses. This review will detail the most important phenotypes and suggest management strategies for each (Fig 1).

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ISRR

Immunization stress-related response (ISRR) encompasses (1) acute anxiety and/or stress responses, which can cause flushing, urticaria, tachycardia, dyspnea, and globus sensation; (2) vasovagal reactions, which can manifest as hypotension, syncope, and sometimes pseudoseizures; and (3) dissociative neurologic symptom reactions, which can cause weakness, abnormal movements, and speech difficulties among others.⁴ There may be overlap in these nocebo responses to vaccination, which appear to be the leading cause of immediate adverse responses to COVID-19 vaccines.⁵ In addition, media coverage of immediate "reactions" to a new vaccine and strong debate within the community about the safety and efficacy of those vaccines can amplify these types of symptoms.⁴ Reassurance about the benign nature of these responses is key, as is establishing a relationship of trust with the patient by showing compassion and competence.⁴ Different techniques to alleviate these symptoms are described in a World Health Organization document on ISRR.⁴

VCD/ILO

Patients have also reported immediate adverse responses that include upper airway-predominant symptoms, inclusive of objective and subjective symptoms and signs. These have included the sensation of throat closure, acute dyspnea, hoarse voice, and stridor, and sometimes wheezing and tachypnea with increased respiratory effort.⁶ Vocal cord dysfunction/inducible laryngeal obstruction (VCD/ILO) can accompany urticaria/angioedema, thereby being consistent with or probable for anaphylaxis under the National Institutes of Allergy and Infectious Diseases, World Allergy Organization, and BCC criteria.⁶ Because these symptoms may be perceived as life-threatening and are often treated with epinephrine in the emergency department, it may be difficult to reassure the patient that this was not an IgE-mediated reaction, and to accept (or permit) a subsequent dose of the vaccine. Moreover, VCD/ILO has the potential to recur after revaccination.⁶ Such patients may benefit from revaccination in a particular setup under close observation and under the supervision of an allergist skilled in identifying and managing VCD/ILO and differentiating it from anaphylaxis in a setting where there is rapid access to laryngoscopy. Importantly, laryngoscopy may not demonstrate the characteristic abnormal adduction of the membranous true vocal folds, but if performed shortly after the event, it can be helpful to demonstrate the absence of laryngeal edema.⁶ Respiratory symptoms are best treated with reassurance, breathing techniques such as panting or "sniff-hiss," and if necessary, a fast-acting benzodiazepine.⁶

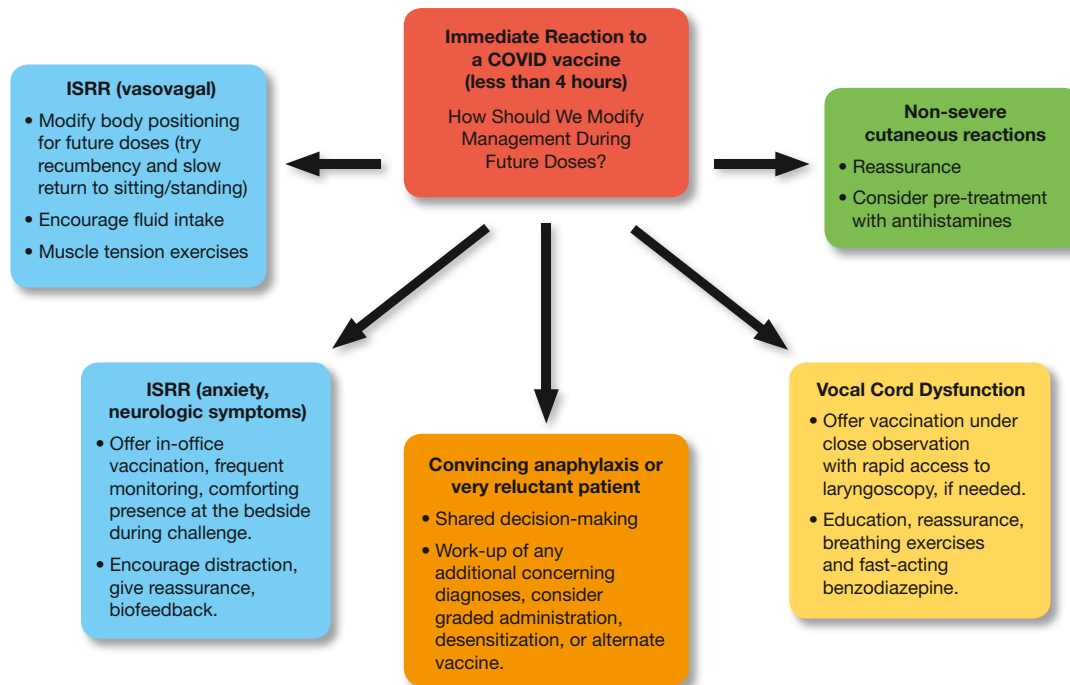


FIG 1. Strategies for management of immediate reactions to COVID-19 vaccines.

IMMEDIATE AND DELAYED CUTANEOUS REACTIONS

Within 3 days of mRNA COVID-19 vaccination, approximately 2% of patients may experience a cutaneous reaction, most commonly manifesting as non-injection site pruritis or rash, followed by urticaria and angioedema⁷ as the next most common presentation. Although onset can happen within minutes of vaccination, most such reactions occur several hours to even days later and fall outside the classification of what would be considered “immediate” (ie, <4 hours for vaccination).⁷ Importantly, many vaccine-tolerant patients exhibit a positive intradermal skin test result in response to the vaccine starting 12 hours after vaccination and persisting for 2 days, probably indicating protective T-cell immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rather than a T-cell-mediated hypersensitivity.⁸ Such sensitization does not preclude tolerance of additional doses. Antihistamines could be used prophylactically in some patients, especially in those in whom underlying spontaneous urticaria is suspected, although a meta-analysis of studies of second-dose reactions did not show a beneficial effect for the use of premedication in less differentiated patients.⁹ In about 80% of patients, these reactions do not recur following reexposure, and there is no evidence supporting the idea that these reactions are prelude to a more severe subsequent reaction.⁷ Patients should be reassured of the non-life-threatening nature of these reactions and encouraged to seek revaccination where possible.

CONVINCING HISTORY OF ANAPHYLAXIS

After more than 11 billion doses administered worldwide, there is no certain report of a patient with an IgE-mediated allergy to a COVID-19 vaccine or with fatal anaphylaxis. In a recent meta-analysis of 22 studies including a total of 1366 patients with a past

immediate reaction to a COVID-19 vaccine who were revaccinated, there were 78 individuals with a past severe reaction.⁹ Among those, only 19 experienced another reaction with revaccination, of which 4 were considered severe. Only 2 other patients in the whole cohort experienced severe symptoms following revaccination. Importantly, all patients with severe symptoms recovered rapidly. Therefore, almost all patients (including those with severe initial reactions) can tolerate, without any symptom, the same vaccine that triggered the initial reaction. In those with reactions, symptoms are usually mild, are self-limited, and resolve with antihistamines alone or no treatment.

There is no evidence that skin testing or a basophil activation test to the vaccine itself or to any of its components (eg, polyethylene glycol [PEG]) is of any value in guiding reexposure after a reaction,⁹ although some have advocated that obtaining a negative test result may help reassure a concerned patient. A meta-analysis showed poor sensitivity of PEG (3%) or provoking mRNA vaccine (19%) skin testing in predicting a reaction to revaccination (Greenhawt et al, unpublished communication, 2022). Although this meta-analysis noted that vaccine and vaccine excipient skin test specificity was high, such high specificity should not lead to the conclusion that a positive skin test result rules in vaccine allergy or indicates an IgE-mediated mechanism because an irrelevant skin test yielding few positive results would also have a high specificity.

Skin testing to PEG would be useful only in patients with a history of reaction to another PEG-containing product. Although experience is still limited, patients with PEG allergy, many of whom tolerate mRNA or adenoviral vector COVID-19 vaccines, may exhibit a false-positive skin test result in response to an mRNA vaccine.¹⁰ Overall, most patients who have been tested have negative skin test results in response to mRNA COVID-19 vaccines on immediate reading, and regardless of the skin test result, there is a very low rate of

repeat severe reaction if such patients are revaccinated.⁹ Although graded administration of the vaccine could be useful to convincing reluctant patients to accept revaccination, there is no evidence to suggest that it reduces the risk of recurrent reaction or is necessary.⁹

CONCLUSIONS

Our worldwide, collective experience with immediate adverse vaccine responses to mRNA COVID-19 vaccines has been of value to our perspective on the etiology of such responses and to their management. Patients with immediate reactions to COVID-19 vaccines can be safely revaccinated using the same vaccine, without vaccine or vaccine component skin testing, and in a single dose. In those reluctant to be revaccinated or with more worrisome symptoms (eg, throat symptoms), increased surveillance is recommended. For those with strong preferences, despite the absence of evidence, using graded administration, changing to another vaccine brand or platform, or administering antihistamine premedication could be considered in the setting of shared decision making.

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