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Adverse Events and Safety of SARS-CoV-2 Vaccines: What's New and What's Next



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Just over 1 year following rollout of the first vaccines for coronavirus disease 2019, 572 million doses have been administered in the United States. Compared with the number of vaccines administered, adverse effects such as anaphylaxis have been rare, and seemingly, the more serious the effect, the rarer the occurrence. Despite these adverse effects, there are few, if any, true contraindications to coronavirus disease 2019 vaccination and most individuals recover without further sequelae. This review provides guidance for the allergist/immunologist regarding appropriate next steps based on patient's known allergy history or adverse reaction after receipt of coronavirus disease 2019 vaccine to assist in safe global immunization. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2254-66)

Key words: COVID-19; vaccines; anaphylaxis; allergic reaction; adverse effects

CASE DESCRIPTION

A 31-year-old White woman with a history of chronic idiopathic urticaria on antihistamines was evaluated in our outpatient drug allergy clinic after experiencing an immediate reaction to her first dose of the Pfizer-BioNTech messenger RNA (mRNA)-based

coronavirus disease 2019 (COVID-19) vaccine. Forty-five minutes after the vaccination, she developed generalized urticaria, nausea, and lightheadedness. She was seen at the local emergency department, treated with diphenhydramine with symptomatic improvement, and discharged home. Serum tryptase level drawn 7 hours after the reaction onset was 2.2 µg/L. After her initial reaction, she was evaluated in our outpatient drug allergy clinic. At this evaluation, the patient was not aware of previous intolerances to polyethylene glycol (PEG)-containing products. She had negative prick and intradermal skin testing results to standard doses of PEG and polysorbates. This was followed by an oral challenge with PEG3350 in the form of Miralax, in which the patient had no symptoms during 1.5 hours of observation. A week later, she received the second dose of the Pfizer-BioNTech COVID-19 vaccine with the recommended 0.3-mL injection as a single dose intramuscularly following premedication with cetirizine 10 mg twice a day and tolerated the vaccine well.

We describe this case to highlight the tolerance of a second dose of an mRNA vaccine despite a first-dose reaction. The following review further summarizes the important immune-mediated and additional adverse reactions associated with COVID-19 vaccines (Table I and Figure 1), potential mechanisms, and the steps forward in light of these adverse effects.

BACKGROUND

In the midst of the COVID-19 pandemic, there has been a rapid global vaccination deployment and response, with more than 11.5 billion doses administered worldwide as of April 25, 2022.¹ The mRNA vaccines were developed with unprecedented speed and safety, with both the Pfizer-BioNTech and Moderna vaccines receiving emergency use authorization by December 2020. In the United States, this was soon followed by a single-dose adenoviral vector vaccine developed by Johnson and Johnson (J&J, Janssen). Contrary to general beliefs, the technology surrounding mRNA vaccines and therapeutics was not new, and several decades had already been spent developing such technology, with vaccines in early-phase clinical trials for diseases of global importance such as HIV and Zika viruses,^{2,3} promising new vaccines for cancer,⁴ as well as therapeutics independent of vaccines.⁵ Despite this, the population was unfamiliar with mRNA vaccine technology, because this was the first time mRNA vaccines had been used in a mass vaccination strategy. Impressively, 2 mRNA vaccines were approved and deployed for emergency use within less than 12 months of the arrival of COVID-19 to the United States. In Europe and the United States, within the initial 2 weeks of rollout of the mRNA vaccines, several cases of suspected anaphylaxis were reported; however, current information supports that the vaccines have been overwhelmingly safe, with comparatively few adverse events to the large scale of vaccines administered.⁶ In addition to the 2

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The case described in this review is a representative patient based on experiences in our outpatient clinic and does not correspond to an actual patient.

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Abbreviations used

CDC- Centers for Disease Control and Prevention
COVID-19- coronavirus disease 2019
LAD- lymphadenopathy
mRNA- messenger RNA
PEG- polyethylene glycol
SARS-CoV-2- severe acute respiratory syndrome coronavirus 2
VITT- vaccine-induced immune-mediated thrombosis and thrombocytopenia
VZV- varicella zoster virus

mRNA vaccines (Pfizer-BioNTech and Moderna) and the 3 adenoviral vector vaccines (J&J, Astra Zeneca, and Sputnik) (Table II), inactivated vaccines have been deployed in China and other parts of Asia.⁷⁻¹³ Thromboembolic events and thrombosis with thrombocytopenia, though rare, have been associated with the administration of the Astra Zeneca (ChAdOx1 nCoV-19/AZD1222) and J&J (Ad26.COV2.S) adenoviral vector vaccines and are described further in the latter portion of the text. To date this has not been a signal with other viral vector vaccines such as the Sputnik V (Gam-COVID-Vac).¹⁴ At the time of this review, more than 572 million doses of COVID-19 vaccines have been administered in the United States.^{1,15}

SPECTRUM OF REACTIONS AND DIFFERENTIAL DIAGNOSIS

Immediate systemic reactions

Immediate systemic reactions are those that can be described by acute onset (within 4 hours of vaccination) of generalized symptoms such as rash, flushing, swelling, or difficulty breathing, among others; these may also be referred to as immediate hypersensitivity reactions or immediate allergic-like reactions. Since the emergency approval of the mRNA vaccines, immediate hypersensitivity reactions were initially described at rates of 2.5 to 11.1 per 1 million vaccine doses administered.¹⁶ Obtaining a true number of immediate systemic reactions has been difficult due to the variation in reports, lack of physician confirmation and a standard definition of “anaphylaxis,” and ability for self-reporting, but the real-world data seem to suggest rates that are slightly higher than the historical rates across all vaccines (about 1.3 per 1 million doses).^{17,18} The Centers for Disease Control and Prevention (CDC) suggests rates between 2 and 5 per 1 million,¹⁹ a large population-based study suggests a rate of 4.8 per 1 million,²⁰ and a recent meta-analysis describes a rate of 7.91 per 1 million vaccine doses administered.²¹ Although the mechanism behind the high rate of immediate reactions currently remains elusive, evidence to date supports a non-IgE mechanism, because we can be reassured that, across various studies, most individuals with first-dose immediate reactions to an mRNA vaccine have either tolerated subsequent doses without symptoms or had very mild symptoms not indicative of an IgE mechanism.²²⁻²⁸ Further support comes from a meta-analysis encompassing more than 1300 individuals with first-dose reactions that demonstrated that, of these individuals, only 13% went on to develop reactions at second dose, with less than 0.5% being categorized as severe reactions.²⁹ Many conceivable mechanisms have been proposed including direct mast cell activation, whether IgE- or non-IgE-mediated, complement activation, and contact system activation by nucleic acids.³⁰ It is

important to note that much of the data currently available lack the laboratory studies needed to discern mechanism of the reaction, and randomized double-blind studies are ongoing in an attempt to elucidate the mechanism of immediate reactions associated with mRNA vaccines.^{17,22,30-32} The construct or antigen that might be driving these immediate reactions, regardless of the mechanism, could be an inactive component of the vaccine such as PEG2000 used to stabilize the lipid nanoparticle, an active component of the vaccine such as the mRNA, or immune response to the translated spike protein itself.

Individuals experiencing immediate reactions commonly reported symptoms of pruritus, flushing, rash, difficulty breathing, and the sensation of throat tightness with onset minutes after immunization; some experienced disorientation and dizziness.³³ Although IgE-mediated allergy and clinical anaphylaxis are the most serious considerations given these symptoms, as mentioned, tolerance of the second dose in most individuals is not consistent with this. Therefore, although the mechanism is unclear, the tolerance of the second dose makes an IgE mechanism much less likely in most patients, and other etiologies including complement activation, paradoxical vocal cord motion or laryngospasm, anxiety or panic attacks, and vasovagal responses need to be considered.^{33,34}

Although likely very rare, true IgE-mediated allergic reaction to mRNA-based COVID vaccines is possible, though seemingly unlikely on the basis of the information we have gained in the last year. Previously, it was proposed that the mechanism surounded sensitization toward PEG present in the carrier of the mRNA in these vaccines.^{30,35,36} Initially a significant unknown, the implications for individuals with true IgE-mediated reactions to PEG—such as PEG3350 in steroids or bowel preparations—is becoming clearer with the accumulation of information. At minimum—even with polysorbate 80 cross-reactivity—adenoviral vector vaccines may be safe for PEG-allergic individuals,^{35,37,38} though this alternative has not been directly compared with risk with mRNA vaccination and leaves unanswered questions of efficacy.²¹ Data suggest that patients with immediate reactions to pegylated compounds such as PEG-asparaginase are tolerant of mRNA vaccines.^{39,40} Patients in these reports had largely tolerated PEG3350 laxatives following their immediate reactions to PEG-asparaginase. Evolving evidence suggests that mRNA vaccination may even be safe for those with a confirmed or highly suspected IgE-mediated PEG allergy, as demonstrated in a small case series of individuals with PEG allergy who tolerated mRNA vaccination and in a small study in which individuals with PEG allergy unknowingly received mRNA vaccination.^{38,41} In the case of hesitancy or anxiety of the patient or provider, an alternative to full vaccination may include graded vaccine dosing, which has been successfully implemented with administration of the vaccine in increasing doses given every 10 to 15 minutes depending on the protocol.^{42,43} However, it should be noted that the efficacy of these protocols has not been compared with full vaccination, and it is not known whether graded administration decreases the risk for immediate reactions.

Complement activation can mimic immediate hypersensitivity in the form of complement activation—related pseudoallergy, and PEG and liposomes can be implicated in this pathway.^{30,44} Historically, these reactions have occurred with intravenous preparations, and complement activation—related pseudoallergy reactions due to intramuscular medications or vaccines would be

TABLE I. Summary of rates, selected clinical features, and proposed actions for adverse events highlighted in [Figure 1](#)

Adverse event	Vaccine(s) implicated	Estimated rate of effect	Average time to onset	Average duration of symptoms	Actions/considerations
Immediate systemic reactions	All, but most prominent with mRNA vaccines	Estimates vary but anywhere between 2 and 5 per 1 million and 7.9 per 1 million	5-60 min after vaccination	24 h, typically less	<ul style="list-style-type: none"> Recent evidence suggests that these individuals have safely tolerated subsequent vaccination with the same COVID-19 vaccine formulation May consider alternate formulation or administration in divided doses Proceed to indicated subsequent vaccination Oral antihistamines used by some providers
Acute urticaria	mRNA vaccines	20,000 per 1 million	>24 h after vaccination	Variable, often within 2 wk of onset but possibly longer	<ul style="list-style-type: none"> Treatment of acute symptoms with H₁ ± H₂ blockade Safe for subsequent doses if indicated
Delayed cutaneous reactions	mRNA vaccines		7 d after vaccination	3-5 d, shorter if occurring with second dose	<ul style="list-style-type: none"> Symptoms often resolve without intervention Safe for subsequent doses unless associated with SJS/TEN or AGEP, which should be considered on a case-by-case basis More likely to experience similar, benign symptoms with subsequent vaccination
Myocarditis	mRNA vaccines	40.6 per million (males 12-29 y); 4.2 per million (females 12-29 y); 2.4 per million (males >30 y); 1 per million (females >30 y)	3-4 d after vaccination, typically with the second (or subsequent) dose but can occur after first dose	Acute symptoms for 3-5 d, then complete resolution over days to weeks	<ul style="list-style-type: none"> Consider therapy with NSAIDs or corticosteroids Highest risk for adolescent/young adult males Activity restriction until complete recovery Consider involvement of cardiologist if not done at the time of diagnosis Risk recurrence with subsequent doses unknown
Thrombosis with thrombocytopenia syndrome/VITT	Adenovirus vector vaccines	3.8 per million; mortality of up to 40% of individuals with diagnosis	Usually within 1-2 wk but up to 42 d after vaccination	Variable, sequelae can be long lasting	<ul style="list-style-type: none"> Treatment in acute care setting and close monitoring for sequelae Safe for mRNA vaccine administration after recovery Further receipt of viral vector-based COVID-19 vaccine should be avoided

AGEP, Acute generalized exanthematous pustulosis; NSAID, nonsteroidal anti-inflammatory drug; SJS/TEN, Stevens-Johnson syndrome or toxic epidermal necrolysis.

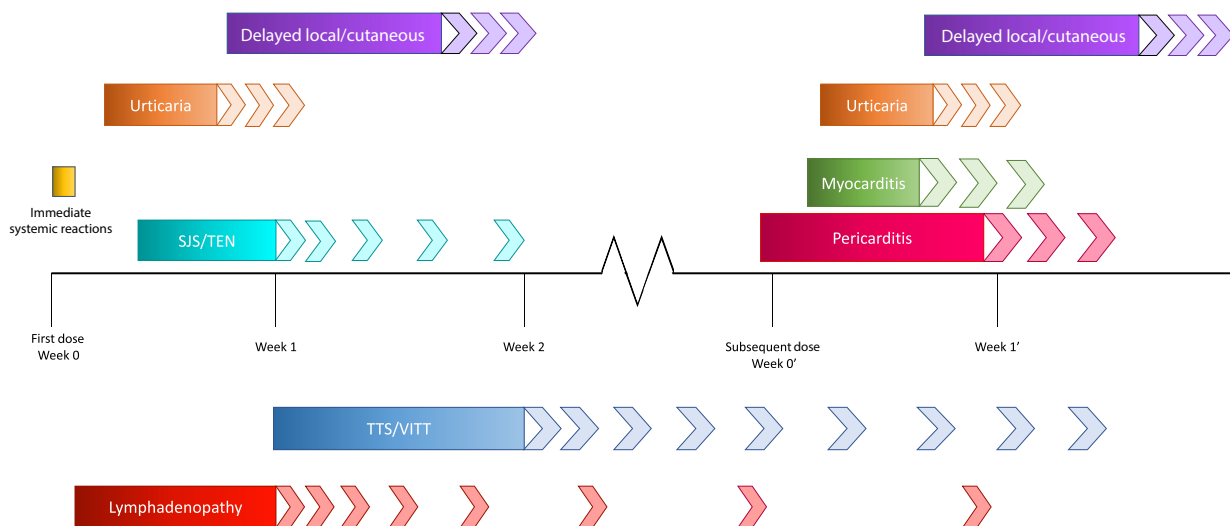


FIGURE 1. Timeline of adverse reactions. The chart displays the time frame in which an individual is at highest risk of experiencing symptoms, with each of the adverse reactions discussed. It is important to note that TTS/VITT typically occurs within 1 to 2 weeks of vaccination, but the diagnostic criteria state that this may be considered for diagnosis up to 42 days after receipt of immunization. In addition, myocarditis and pericarditis may occur after first dose. *SJS/TEN*, Stevens-Johnson syndrome or toxic epidermal necrolysis; *TTS*, thrombosis with thrombocytopenia syndrome.

a novel, though possible, finding. Patients may develop symptoms of anaphylaxis including angioedema, wheezing, urticaria, and syncope, among many other symptoms, which can be confused with an immediate IgE-mediated reaction.⁴⁵ In the acute setting, it is difficult to differentiate between potential diagnoses. Obtaining a serum tryptase level between 30 and 90 minutes of symptom onset along with screening terminal (C5-C9) complement levels can be helpful in determining an IgE- or complement-mediated etiology, respectively.³⁴ Both of these laboratory evaluations are available commercially; however, total complement may be an acceptable—but less sensitive—alternative when terminal complement cannot be obtained. With isolated cutaneous reactions, adjuncts including oral, non-sedating antihistamines may prove helpful in providing symptomatic relief while the patient remains under close observation. However, systemic steroids are generally not recommended because of their relative lack of efficacy in treatment and potential to blunt the immune response to vaccination.²¹

With initial reports of immediate systemic reactions to mRNA vaccines and the concern for PEG as a possible inciting agent, it was recommended that high-risk individuals have prevaccination screening with or without skin testing to PEG and polysorbate excipients.³⁴ As evidence has evolved, it has become clear that the role of skin testing is more limited than originally thought, with emphasis on history as an important guide for vaccination, especially in individuals with first-dose reaction history.^{21,28} Studies have highlighted the inability of skin testing to reliably predict clinical allergy to PEG and related excipients due to high rates of false positives and the increasing idea that a non-IgE-mediated mechanism is responsible for clinical reaction.^{25,28} There exist infrequent cases when skin testing may be helpful in guiding further vaccine administration. For example, individuals with significant vaccine hesitancy who would otherwise forfeit initial or subsequent vaccination may benefit from limited skin testing to PEG products with protocols outlined in the

literature.^{34,46} However, an individualized approach and shared decision making, along with counseling and discussion, should be implemented given the knowledge that most individuals with a history of immediate reactions after the first dose of mRNA vaccine have tolerated subsequent vaccination,^{23,24,26,28,29} that PEG-allergic individuals have tolerated mRNA vaccination,^{38,41} and the potential for false positives with skin testing that may further complicate vaccination.²¹ In the overwhelming majority of cases, skin testing is unlikely to provide benefit in facilitating vaccination.

When to investigate immediate systemic reactions to the COVID-19 vaccines?

In the first few months following the reports of anaphylaxis, there was an abundance of caution in terms of management of patients because it was not known whether these were IgE-mediated or whether reactions could worsen on subsequent doses. Currently, we know that most patients will tolerate subsequent doses, which strongly suggests that most immediate vaccine reactions are not IgE-mediated. In addition, many of the patients who reacted on first dose have gone on to receive booster vaccination at least 6 months later, which suggests that original thoughts of an IgE mechanism with refractory period of mast cell degranulation between first and second doses is unlikely. Several articles have now been published supporting the safety of subsequent doses even in the setting of anaphylaxis with the first dose.^{23,24,26,29} In addition, current guidelines support the idea that excipient testing does not contribute to vaccine safety and could, in theory, delay vaccination in individuals with a history of allergic-like reactions.²¹ False positives have been described with specific PEG and polysorbate reagents particularly in the setting of intradermal testing.²⁸ Moreover, the most recent evidence suggests that known small samples of PEG-allergic individuals can tolerate mRNA-based vaccines.^{38,41} For this reason, it should be a shared patient decision to investigate a systemic allergic

TABLE II. Summary of currently approved vaccines in the United States and the United Kingdom

Characteristics/administration	mRNA vaccines		Inactive viral vector vaccines	
History	<ul style="list-style-type: none"> • Studied since the 1990s for indications such as immunizations and protein replacement • Barriers to approval due to instability of mRNA • Development of lipid nanoparticle carriers allow for increased stability of mRNA and clinical use • Low cost, low incidence of side effects, rapid production • Robust antibody- and cell-mediated immunity induced 		<ul style="list-style-type: none"> • Studied since the 1970s and implemented for viruses such as Zika and Ebola • Uses known viruses (of low virulence or with virulence factors removed) to deliver a unique genetic sequence to host cells • No adjuvant required; induces strong antibody- and cell-mediated immunity 	
	Pfizer-BioNTech	Moderna	Johnson & Johnson (J&J, Janssen)	Oxford/AstraZeneca
Also known As	BNT162b2 Comirnaty	mRNA-1273 Spikevax	Ad26.COV2.S	ChAdOx1 nCoV-19/ AZD1222 Covishield; Vaxzervia
Composition	PEG2000 nanoparticle formulated nucleoside-modified mRNA encoding the spike protein of SARS-CoV-2	Single strand of mRNA encoding the spike protein of SARS-CoV-2 encapsulated in a PEG2000 lipid nanoparticle carrier	Recombinant, replication-deficient human adenovirus type 26 vector encoding SARS-CoV-2 spike protein	Replication-deficient chimpanzee adenovirus vector that is modified to encode the spike protein of SARS-CoV-2
Recommended administration	Two 0.3-mL (adult) or 0.2-mL (child) IM doses separated by at least 21 d	Two 0.5-mL IM doses separated by at least 28 d	Single 0.5-mL IM dose	Two 0.5-mL IM doses separated by 8-12 wk
Booster administration	0.3-mL IM dose at least 5 mo after primary series for those ≥12 y; no booster for children	0.25-mL IM dose at least 5 mo after primary series	Vaccination with either Pfizer (0.3 mL) or Moderna (0.25 mL) vaccines encouraged at least 2 mo after initial J&J vaccine	In the UK, vaccination with either Pfizer (0.3 mL) or Moderna (0.25 mL) vaccine at least 3 mo after primary series

IM, Intramuscular.

reaction, and vaccination should not be withheld or delayed in favor of excipient skin testing and allergist evaluation except in rare circumstances.²¹

Delayed hypersensitivity reactions

As with most vaccines, the COVID-19 mRNA vaccines have been associated with many different clinical phenotypes of delayed drug rashes. A retrospective study of 414 patients with cutaneous reactions after mRNA COVID-19 vaccination revealed that most patients experienced cutaneous symptoms after the second dose (63%) compared with the first dose (21%) and with both doses (16%).⁴⁷ After the Moderna vaccine, delayed large local reactions were most common, and with Pfizer, urticaria was the most common cutaneous finding.⁴⁷ A more recent schema has supported that delayed reactions to COVID-19 vaccines be classified as papulosquamous, papulovesicular, and pityriasis rosea-like.⁴⁸ Consistent with other reports, these typically occur more than 4 hours after vaccination and none of the 414 patients experienced severe sequelae; less than half of the individuals who experienced symptoms after the first dose had similar symptoms following the subsequent dose in series.⁴⁷ In a similar study of more than 40,000 employees of a large hospital system, 4% of individuals reported cutaneous symptoms, with rash and pruritus being the most common.⁴⁹ In all cases, symptoms were self-limited and more than 80% of individuals who had cutaneous symptoms after the first tolerated the second dose without a similar reaction.⁴⁹ These studies support the idea

that cutaneous reactions are self-limited and, in general, are not a contraindication to repeat vaccination.

Delayed rashes. Diffuse, delayed morbilliform eruptions have been described in few individuals receiving the mRNA-based COVID-19 vaccines.^{47,50,51} These reported cases typically have occurred within 48 hours following first-dose vaccination, resolve over 1 week without sequelae, and most tolerate dose 2.^{47,51} According to 2 studies, morbilliform eruptions were more common in individuals receiving the Pfizer vaccine.^{47,51} These rashes are generally not cause for concern and likely do not represent an allergic reaction, but rather, an effect of host immune response to the vaccine.⁴⁷

Rare reports of severe cutaneous adverse reactions have been associated with both COVID-19 infection and COVID-19 vaccination. Given the background rate of these reactions in the community and the background rate of COVID-19 disease, it would be difficult to prove causality. A past history of a severe cutaneous adverse reaction—such as Stevens-Johnson syndrome or toxic epidermal necrolysis, acute generalized exanthematous pustulosis, or drug reaction with eosinophilia and systemic symptoms—related to another drug or vaccine is not a contraindication to receiving a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine and is likely much safer than the risk of natural infection sequelae with COVID-19. Although erythema multiforme has been more prevalently described, SJS-like illness has been rarely reported, with

symptom onset 3 to 5 days following first- or second-dose vaccination, resolution over 10 to 14 days, and apparent response to cyclosporine or prednisone.^{52,53} In these cases, it has not clearly been delineated whether this could have been due to underlying COVID-19 infection, which has been associated with erythema multiforme major. Acute generalized exanthematous pustulosis has been reported after viral vector^{54,55} and mRNA vaccines.⁵⁶ The described cutaneous eruptions had the classic pustular appearance involving the intertriginous areas and spreading thereafter, desquamated after several days, and resolved without event.⁵⁴⁻⁵⁶ Consideration for future COVID-19 vaccination after a severe cutaneous adverse reaction should be on a case-by-case basis, because causality is often difficult to assess.

Delayed local reactions. Many individuals receiving COVID-19 mRNA-based vaccines have reported delayed, large local reactions, which have come to be known as “COVID Arm.” These delayed reactions are characterized by any combination of erythema, induration, or tenderness occurring approximately 7 days after first mRNA vaccine, lasting an average of 4 to 5 days; there is lesser time to occurrence (2 days) and resolution (3 days) when occurring after second-dose vaccination in both the Moderna and Pfizer vaccines.^{47,57,58} The incidence of COVID Arm is unclear at this time, but 1 case series, done exclusively in the Pfizer vaccine, revealed delayed local reactions in 2.1% of individuals.⁵⁹ Recurrence of delayed, large local reactions is variable, with reports of anywhere from 32% to 75% of individuals who reported symptoms with the first dose.⁵⁷⁻⁵⁹

Delayed injection-site reactions after immunizations are not new. Previously, there have been reports of delayed-type hypersensitivity reactions to vaccines containing adjuvants such as alum.^{47,60} The large, local reactions associated with mRNA vaccines have a histopathology and immunohistochemistry pattern in keeping with delayed-type hypersensitivity on limited samples, though it is unclear whether this is the true pathology.⁵⁷ Skin biopsies for delayed reactions associated with COVID-19 vaccination are not necessary and are reserved for atypical or refractory cases. Similarly, skin testing is not indicated and does not predict those individuals who may have a delayed local reaction; in fact, evidence has shown that individuals who previously tolerated vaccination or were previously unexposed to vaccination all developed local edema and erythema at the site of intradermal testing, possibly reflecting protective immune response to the vaccine rather than a pathologic immune response.⁶¹ Many patients may appear as though they have a superinfection of the injection site and are treated with oral antibiotics for bacterial cellulitis; however, antibiotics have not been shown necessary for resolution.^{47,57,58} As has been concluded with additional cutaneous reactions, the development of COVID Arm after vaccination is self-limited and does not exclude the individual from further immunization with mRNA COVID-19 vaccinations.

Delayed urticaria/angioedema. Specific analysis of vaccine-related urticaria revealed that it is most often experienced in a delayed fashion (>24 hours after vaccination) and is more likely to occur with the Moderna vaccine than with the Pfizer vaccine.^{47,49} Studies have revealed an estimated incidence of urticaria of 1% and of angioedema of 0.7%, occurring more often with the first dose of the vaccine.⁴⁹ In patients who experienced urticaria or angioedema with the first dose, less than

5% went on to develop recurrent symptoms on repeat vaccination.⁴⁹ It is thought that delayed urticaria and angioedema symptoms after mRNA vaccination represent host immune response to vaccination rather than an allergic type of reaction to the vaccine or an excipient component.⁴⁷ Delayed urticaria and/or angioedema should implore the provider to investigate any additional history that might suggest preexisting chronic urticaria, and evaluation may include complement studies to investigate delayed complement activation. Delayed urticaria is established to be associated with immune stimulation and mast cell activation independent of IgE, as is the case with infectious processes (often viral) and some immunizations.¹⁸ In cases of histamine-mediated urticaria and/or angioedema, individuals respond well to oral histamine receptor (H)₁ and H₂ blockers for symptom control while the urticaria self-resolves within weeks. In individuals who are predisposed to development of urticaria and/or angioedema, it may be beneficial to recommend premedication with oral antihistamines in the 48 to 72 hours preceding vaccination with mRNA vaccines to mitigate this uncomfortable immune response. As has been supported by clinical studies, isolated urticaria/angioedema should not be a contraindication to further immunization with mRNA vaccines.^{47,49}

Miscellaneous cutaneous reactions

SARS-CoV-2 mRNA and viral vector vaccination, as well as natural infection, has been proposed to be associated with additional cutaneous findings. Specifically, varicella zoster virus (VZV) reactivation has occurred a median of 5 days following vaccination in some individuals, though rates are inconsistent, and other, larger analyses have suggested a lack of clear evidence of reactivation after vaccination.⁶² Of the case reports supporting reactivation, the ages and medical conditions of the individuals varied, though 2 individuals had a remote history of immunosuppression that was not prescribed or relevant at the time of VZV diagnosis.^{63,64} Onset of painful, vesicular skin lesions was within 1 week of immunization and was not accompanied by any additional symptoms^{63,64}; 1 patient did have postherpetic neuralgia for about 1 month after initial symptoms that later resolved.⁶⁵ It is thought that some degree of immunomodulation by the vaccine is contributing to the reactivation of virus⁶⁴⁻⁶⁷; in addition, there have been reports of VZV reactivation in those with COVID-19 infection that is thought to be due to transient T-cell lymphopenia caused by the virus, though it is not clear that this mechanism holds true for vaccination-related VZV.⁶⁴ A large study of real-world adverse effects revealed that VZV reactivation was 1 of 3 adverse effects that was higher in those vaccinated versus the unvaccinated (risk difference, 15.8 events per 100,000).⁶ The additional adverse events greater in the vaccinated are myocarditis (risk difference, 2.7 events per 100,000) and lymphadenopathy (risk difference, 78.4 events per 100,000), both of which are discussed in further detail later.⁶ On the contrary, a retrospective cohort study with historical and contemporary controls found no difference in the risk ratio of herpes zoster between vaccinated and unvaccinated individuals (0.91 for historical and 0.98 for contemporary).⁶² Interestingly, patients who have received dermal fillers are at risk for worsening of swelling at the site of the filler injection with both mRNA COVID-19 vaccination and natural infection with COVID-19. The mechanism of edema is thought to be activation of a local

TABLE III. Summary of thrombosis with thrombocytopenia syndrome

Associated vaccines	Incidence	Presenting features	Evaluation	Diagnostic criteria	Associated risk factors	Potential therapeutics
J&J/Janssen and AstraZeneca	3.8 per million vaccine doses administered	<ul style="list-style-type: none"> Onset of symptoms between 4 and 42 d after vaccination but typically within 1-2 wk Superficial ecchymoses and/or petechial rash Pain at/around site of thrombosis, including: <ul style="list-style-type: none"> Headache, vision disturbance, vomiting Chest pain, shortness of breath Abdominal or back pain 	Based on presenting symptoms— may include extremity ultrasound, CT venogram, MRV; notably, thrombi are in unique locations including splanchnic and cerebral veins and even arteries	Receipt of adenovirus vaccine in previous 42 d	Obesity	High-dose corticosteroids
			CBC, fibrinogen level, D-dimer, anti-PF4 IgG	Thrombosis and thrombocytopenia Elevated D-dimer Anti-PF4 antibodies	Exogenous estrogen replacement Women between the ages 18 and 50 y	IVIg 1 g/kg for 2 d Anticoagulation (avoidance of heparin if VITT suspected) Platelet transfusion should be avoided

CBC, Complete blood cell count; CT, computed tomography; MRV, magnetic resonance venography; PF4, platelet factor 4.

immune response and is not a reason to withhold or delay subsequent vaccination.⁶⁸

Myocarditis/pericarditis

Reports of myocarditis and pericarditis have been some of the more concerning events that have occurred at rates higher than what would be expected in the general population, particularly in young males in whom the baseline rates of myocarditis were already higher.⁶ The rates of myocarditis vary on the basis of age group and sex; a large study of Vaccine Adverse Event Reporting System reports in the United States highlights the difference in reporting between age groups and sex, with younger individuals having reporting rates between 50 and 100 per 1 million for males and between 6 and 10 per 1 million in females.⁶⁹ Reports from the CDC have highlighted the association between COVID-19 infection and myocarditis, citing that individuals with true COVID infection have 16 times the risk of associated myocarditis when compared with myocarditis in those without COVID-19 infection.⁷⁰ A large real-world study highlights that true SARS-CoV-2 infection is associated with a higher rate of myocarditis than in vaccination, with a risk difference of 11 per 100,000 in those with COVID-19 infection,⁶ and it is important to consider that infection-associated cases tend to be more severe in nature. Another comparison in the same study supports that myocarditis seems to be higher in the vaccinated versus the unvaccinated general population, with a risk difference of 2.7 events per 100,000.⁶ Synthesis of this information together supports that infection-associated myocarditis is more common than vaccine-associated myocarditis but that vaccine-associated myocarditis does occur. It is also important to note the age and sex preference for vaccine-associated myocarditis cases in the adolescent and young adult male population,⁶⁹ the mild nature of cases, and the relatively rapid resolution without intervention⁷¹⁻⁷³ compared with the cases of myocarditis that have occurred with COVID-19 infection.

The reported myocarditis cases indicate that young, generally healthy males seem to be at the greatest risk for myocarditis, with a single case series reporting events in adolescents as young as age 15 years.^{72,74} Presenting symptoms include severe chest pain that can be associated with fever that occurs, on average, 4 days after immunization and more commonly after the second or subsequent doses of mRNA vaccines⁷⁴; events may be associated more with the Moderna vaccine over the Pfizer vaccine, with one study reporting hazard ratios of 3.92 and 1.34, respectively,⁷⁵ and another study showing reporting rates for Moderna vaccine 5.1 times higher than for the Pfizer vaccine.⁷⁶ Patients are noted to have electrocardiogram abnormalities and troponin elevation along with cardiac magnetic resonance imaging findings of inflammation, and there were no additional plausible causative agents identified.^{71,72,74} Although the reason remains unclear, there does seem to be an association between COVID-19 mRNA vaccines and increased risk for myocarditis, but clinical studies and further evaluation have supported safe and effective vaccination, especially in adolescents and children in the general population, given the comparatively low risk of side effects.⁷⁷ Recurrent myocarditis is very rare in the general population. Currently, there are no known cases of recurrent vaccine-associated myocarditis following an initial episode of vaccine-induced myocarditis; however, there are some case reports of vaccine-associated

TABLE IV. Knowns and unknowns—Examples of questions that have been answered and those that remain unanswered at this phase of the pandemic and vaccine rollout

Adverse reaction	What we don't know	What we do know
Immediate systemic reactions	<ul style="list-style-type: none"> • What is the mechanism? • Can these be prevented with premedication? • Are these rare IgE-mediated and, if yes, what is the antigen? 	<ul style="list-style-type: none"> • Low incidence of recurrence on repeat vaccination, suggesting mechanism other than IgE • Most individuals with negative skin testing results to excipients, so unlikely to be the antigen • Small numbers of PEG-allergic individuals have tolerated mRNA vaccination • Important to consider diagnoses other than anaphylaxis
Delayed cutaneous and other hypersensitivity reactions	<ul style="list-style-type: none"> • What is the mechanism? • Can these be prevented with premedication? • Are there risk factors for recurrence? 	<ul style="list-style-type: none"> • In the absence of SCAR, not a barrier to repeat vaccination with same vaccine formulation • Resolves without intervention in most cases • Likely to be due to immune response generated by immunization
Myocarditis/pericarditis	<ul style="list-style-type: none"> • What is the mechanism and risk related to that mechanism? • What is the most appropriate management? • What is the risk of recurrence with subsequent vaccination and how should these be managed? • What are the long-term outcomes? • What is the incidence of subclinical myocarditis/pericarditis and how might this affect future vaccine doses? 	<ul style="list-style-type: none"> • Most cases mild in nature with no or brief hospitalization • Limited follow-up data—available data suggest that return to baseline cardiac function is expected • Higher index of suspicion for diagnosis in adolescent and young adult males
Thrombosis with thrombocytopenia syndrome	<ul style="list-style-type: none"> • New insights into mechanisms and risk (specifically regarding the mechanism with specific adenoviral vectors vaccines)? • What is the risk of recurrence with subsequent vaccination even the same vaccine construct with a different virus? 	<ul style="list-style-type: none"> • Incidence of thrombotic events higher in individuals who contract true COVID-19 infection • Contraindication to further viral vector–based COVID vaccine • Low incidence but high mortality, especially when not recognized early

SCAR, Severe cutaneous adverse reaction.

per 1 million J&J vaccine doses administered in the United States (14,080,087 total J&J doses administered).⁸³ The incidence does increase with age up until women have reached menopause, and women in the fifth decade of life have a rate of 9.0 per 1 million J&J vaccine doses (of 1,108,495 total J&J doses in this age group).⁸³ Although the pathogenesis of the disease is not clear, it is thought to be similar to heparin-induced thrombocytopenia, because patients have similar clinical characteristics and the presence of anti–platelet factor 4 antibodies, which are pathognomonic for heparin-induced thrombocytopenia^{84–86}; however, the exogenous trigger of heparin has been absent in all these patients, suggesting a yet-to-be-determined antigen complex as a trigger and the categorization of VITT similar to autoimmune heparin-induced thrombocytopenia.^{84,87} Table III summarizes the features, diagnosis, and therapeutics of VITT.^{85,88–90} Although the incidence seems to be quite rare, the diagnosis is of particular concern due to associated mortality rates, as high as 40%, secondary to complications from thrombosis; in CDC reports, this has equated to a fatality rate of 0.6 per 1 million J&J vaccines administered (of >14 million total J&J doses).⁸³

The administration of adenovirus vector–based vaccines was briefly paused in both Europe and the United States when there were increasing reports of VITT.⁹¹ After thorough evaluation, the administration of these vaccines was deemed safe; however, there now exists a warning, not a contraindication, for females between the ages of 18 and 50 years for the slightly increased risk for the development of VITT.⁹² However, a contraindication does exist for further viral vector COVID vaccines in those who

have had VITT secondary to viral vector COVID-19 vaccination.⁹³ In addition, because of the wide availability and superior efficacy of mRNA vaccines combined with the high mortality of this event, the CDC has recommended the use of Moderna or Pfizer vaccine over the J&J vaccine.⁹⁴ In individuals who have experienced VITT, further administration of viral vector COVID-19 vaccines is contraindicated,⁹⁵ and, in the setting of universal boosters, these individuals may receive mRNA vaccines as an acceptable alternative. It is important to note that VITT is a diagnosis of exclusion, because the existence of anti–platelet factor 4 antibodies occurs in other circumstances (eg, after cardiovascular surgery) and does not confirm the diagnosis of VITT.⁸⁷ It is important to have a high index of suspicion, because this diagnosis is associated with high morbidity and mortality—between 30% and 40%.

Lymphadenopathy

Regional lymphadenopathy (LAD) was reported as an adverse effect in the original trials of both the Moderna and Pfizer vaccines at rates higher than the placebo group: 1.1% (vs 0.6%) and 0.3% (vs <0.1%) in clinical trials, respectively.^{9,10} Real-world studies have replicated findings of LAD after COVID-19 mRNA vaccination, demonstrating that this finding was more significant in individuals receiving the vaccine than in unvaccinated individuals with a risk difference of 78 events per 100,000.⁶ Thankfully, this side effect is physically harmless, albeit possibly uncomfortable for the patient, and is thought to represent the individual's protective immune response to vaccination.^{10,96} Most LAD is unilateral axillary LAD (ipsilateral to

the vaccination), but reports of supraclavicular and lateral neck LAD have been prominent as well.⁹⁷ Because of these unconventional locations, in some cases, the presence of LAD has placed a psychological and financial burden on patients, because individuals seek further evaluation, especially in patients with previous diagnoses of malignancy.^{96,97} In most cases, LAD resolved within 4 weeks of either first or subsequent doses of vaccination.⁹⁷ Although previous recommendations from the Society of Breast Imaging favored receipt of COVID-19 vaccine either before or at least 4 to 6 weeks after mammogram, recent evidence has shifted these recommendations, and in otherwise healthy, low-risk individuals, the Society of Breast Imaging does not recommend delay in mammography screening.⁹⁸ These recommendations were, in part, modified because of recent study that showed the potential for LAD to persist for several months and the low proportion of individuals who went on to biopsy (8% of 537 individuals) after imaging.⁹⁹ In general, individuals with LAD should be followed clinically to resolution with further evaluation in the absence of resolution after 5 weeks, unless additional history would suggest a high-risk situation.^{96,97}

MOVING FORWARD TO BOOSTER DOSES AND BEYOND

Fortunately, the COVID-19 vaccines have been overwhelmingly safe and there are few reasons to exempt first or subsequent doses of the COVID-19 vaccines (Figure 2). Even with an immediate systemic reaction to the first dose, increasing evidence supports either tolerance of the same vaccine or tolerance of an alternate vaccine. With increasing experience, we know that most immediate reactions are unlikely to be IgE-mediated, and the vast majority of individuals have gone on to safely tolerate subsequent doses. Largely, the response to the adverse outcomes described above has been the question of how to safely move forward with widespread immunization. In an interim analysis of mRNA COVID-19 vaccines, the incidence of specific serious outcomes was not higher 1 to 21 days postvaccination compared with 22 to 42 days postvaccination.²⁰ In addition, fortunately, and contrary to much anxiety in the general population about serious vaccine adverse events appearing years later, past experience has told us that vaccine-related adverse reactions are unlikely to occur more than 2 months following initial vaccination.^{6,22,100} Reassuringly, the reactions described—all of which have occurred in the first few weeks following vaccination—are overall rare (Table I). Thankfully, current data and the availability of different types of COVID-19 vaccines have reassured us that it would be an exceptionally rare circumstance that an adverse reaction to one COVID-19 vaccine precludes administration of any other, or even the same, COVID-19 vaccine with allergist guidance. Our knowledge of this concept is increasing, which is extremely important not only for the COVID-19 vaccines but also for many other pathogens and diseases of global importance to follow that will benefit from mRNA therapeutics. Individuals with an existing IgE-mediated PEG allergy were previously advised against receiving mRNA vaccines due to the PEG2000 lipid nanoparticle carrier; however, we now know that this may be tolerated as in patients with PEG-asparaginase hypersensitivity,^{39,40} and, more recently, known PEG allergy.^{38,41} As discussed, most of the individuals with documented first-dose immediate reactions went on to tolerate the second dose without difficulty. These individuals did not

have elevated tryptase when measured, and most had no reactions after the second dose.^{23,24} As we learn more about immediate reactions to COVID-19 vaccines, the evidence suggests that allergist evaluation is likely to further guide receipt of routine vaccination in observed, low-acuity settings, without the need for skin testing, in the large majority of cases.

CDC recommendations as of April 2022 for individuals experiencing mRNA-associated myocarditis/pericarditis include a precaution to avoid subsequent doses of any COVID-19 vaccine without an absolute contraindication.⁹³ If a patient reports an episode of thrombosis with thrombocytopenia syndrome, the CDC currently advises that further adenovirus-based COVID-19 vaccines are contraindicated, especially in light of the efficacy and availability of mRNA vaccines, which are safe for these individuals.⁹³ Many patients report a history of non-IgE-mediated reactions after receipt of previous vaccines. Nonspecific, delayed symptoms are unlikely to be related to IgE toward vaccine components and is not predictive of future reactions to vaccines, so these individuals may proceed to routine vaccination without allergy consultation needed. With more than 1 year of data, there is now a better idea of the rates of COVID-19-associated infection and mortality among those vaccinated versus those who are unvaccinated. The CDC reports the average weekly incidence rate of COVID-19 infection from July to November 2021 for those unvaccinated to be 3.1 times higher than for those vaccinated (with any vaccine) for COVID-19; during the same time period, the average weekly incidence rate of COVID-19-associated deaths was 16.3 times higher in those unvaccinated when compared with those vaccinated.¹⁰¹ The protection, especially against death from COVID-19 infection, afforded by vaccination outweighs the potential conferred risks for most, if not all, candidates.

As preventive efforts for COVID-19 infection have evolved, additional oral and injectable medications have been approved for emergency use authorization by the Food and Drug Administration. Specifically, Evusheld (tixagevimab copackaged with cilgavimab), a long-acting, combination mAb against the SARS-CoV-2 spike protein that is active against the Omicron variant, is approved for preexposure prophylaxis of COVID-19 in individuals with an underlying immunocompromised state or who may be unable to receive any of the COVID-19 vaccines.^{102,103} With initial approval, there have been concerns about the supply of these antibodies and availability especially in resource-poor settings. In light of the growing body of information supporting routine vaccination, including in those with immediate or delayed hypersensitivity history, it is likely that the pool of individuals with histories of suspected COVID-19 vaccine hypersensitivity reactions who may require Evusheld will be minimal.

CONCLUSIONS

If we come back to our case, we appreciate the example of an individual who had an immediate reaction to the first dose of an mRNA vaccine and subsequently tolerated the second dose safely. As highlighted in this review, although initially thought to be insightful, we now know that skin testing is not necessary in such a patient moving forward. This vaccine tolerance of the second dose points away from an IgE-mediated mechanism of her reaction. Recent case series have demonstrated tolerance of mRNA vaccines in patients with a confirmed or highly suspected

history of PEG allergy. These examples are reassuring and suggest that, as we accumulate more data, the initial abundance of caution that led us to risk stratify patients on the basis of knowledge of a previous reaction to a “component of the mRNA vaccines” continues to shift toward the vast majority of all patients being either outright eligible for vaccination or referred to the allergist for “vaccine allergy delabeling.”

In this mature phase of the pandemic, we can be reassured that the growing body of data supports the continued safe and efficacious administration of COVID-19 vaccines, though there still exist many unanswered questions (Table IV). It is important for providers to become familiar with the presenting features of the major vaccine reactions and take the appropriate steps for further evaluation and treatment in the rare circumstances when it is needed. Immediate and cutaneous reactions, along with myopericarditis, have no long-term sequelae that have been identified. Individuals with immediate and benign, delayed cutaneous reactions have additionally gone on to safely tolerate further doses in the vaccine series after recovering from the acute adverse events, oftentimes without the side effects experienced after the first dose. VITT/thrombosis with thrombocytopenia syndrome is rarer than these events but is associated with increased morbidity and mortality when compared with immediate, cutaneous, and myocardial side effects, and the age and medical history of the individual seeking vaccination should be taken into consideration. It is evident, with current data, that COVID-19 vaccination poses a much lower risk of adverse events than infection with SARS-CoV-2. In addition, even in the face of continued emergence of variants, completion of COVID-19 vaccination, including booster doses, provides the maximum protection against severe illness and hospitalization, which is particularly important for those with medical comorbidities and other high-risk individuals, because implementation of immunization on widespread levels globally has been life-saving for these individuals.

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