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Anaphylaxis after COVID-19 vaccination:

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Clinical Implications

COVID-19 vaccine-induced anaphylaxis comprised 12% of all records for patients with reactions reported in a US-based case registry. Anaphylaxis reports were highest with first doses and Pfizer-BioNTech vaccine; there were no reported deaths.

Vaccines remain the most promising tool in our fight against the COVID-19 pandemic. Currently, three vaccines are offered in the United States: Moderna Spikevax (Cambridge, MA) and Pfizer-BioNTech Comirnaty (New York, NY), both of which are approved by the US Food and Drug Administration, and J&J/ Janssen, which is under limited use authorization. Because multiple COVID-19 vaccine doses are needed and as booster dose eligibility continues to expand, it is imperative to understand and address vaccine hesitancy. Among the vaccine-hesitant, safety concerns are prominent.¹

The Centers for Disease Control and Prevention (CDC) reported that approximately five people per one million vaccinated against COVID-19 in the United States had anaphylaxis.² Despite the low risk, anaphylaxis estimates vary by study design,³ and current guidance requires post-vaccination observation times of 15 or 30 minutes. Moreover, treatment for anaphylaxis must be immediately available at all COVID-19 vaccination sites. Although COVID-19 vaccines have been used for over 1 year, to date, US-based anaphylaxis data have largely come from single sites or governmental sources.^{3,4}

The COVID-19 Vaccine Allergy Case Registry⁵ is an allergistled, institutional case registry that aims to characterize vaccinerelated allergic events clinically after COVID-19 vaccines. The registry is hosted on an institutional website and publicized through allergist professional society networks, including the American College of Allergy, Asthma & Immunology and the Federation of Regional, State, and Local Allergy, Asthma & Immunology Societies. Individual case forms are completed by patients or health professionals.

The COVID-19 Vaccine Allergy Case Registry was reviewed for all cases submitted by health professionals from February 13, 2021 to February 8, 2022. Possible and confirmed anaphylaxis cases were analyzed using SAS software (version 9.4, Cary, NC) and summarized with descriptive statistics and univariable tests comparing Pfizer-BioNTech and Moderna reported cases. A total of 481 unique patients receiving Moderna (64%), Pfizer-BioNTech (27%), and other or unknown (9%) vaccines from 46 US states were reported. Sixty patients (mean age, 41 years; SD, 18 years) had reactions considered possible or confirmed anaphylaxis (Table I). Seven patients presenting as experiencing possible anaphylaxis, but determined by their clinicians not to be undergoing it, were excluded (five received the diagnosis of having had stress-related events).

Anaphylaxis cases were from messenger RNA (mRNA) vaccines including Pfizer-BioNTech (n = 45; 75%) and Moderna (n = 15; 25%); 48 (80%) occurred with the first dose. Of the 60 patients, 85% were female. Cases of Pfizer-BioNTech anaphylaxis were more frequently female than were those of Moderna anaphylaxis (91% vs 67%; P = .036). Race was 82% White, 7% Black, and 3% Asian. Patients had a history of atopic disease (n = 35; 58%), including asthma (n = 25; 42%), allergic rhinitis (n = 19; 32%), contact dermatitis (n = 4; 7%), and eczema (n = 4; 7%). Many patients had a history of anaphylaxis (n =27; 45%), including a prior anaphylactic reaction to medication (n = 11; 18%), food (n = 10; 17%), and venom (n = 4; 7%), and idiopathic anaphylaxis (n = 2; 3%). Patients with Pfizer-BioNTech anaphylaxis more frequently had a history of anaphylaxis compared with those with Moderna anaphylaxis (56% vs 13%; P = .004).

When timing of onset was reported (n = 42), symptoms occurred within 15 minutes in 64% of patients (n = 27) and within 30 minutes in 90% (n = 38) (Table II). Reactions involved the respiratory tract (n = 39; 65%), skin or mucosa (n = 37; 62%), and, less commonly, the cardiovascular (n = 17;28%) and gastrointestinal (n = 4; 7%) systems. Respiratory signs and symptoms were more commonly associated with cases of Pfizer-BioNTech anaphylaxis compared with Moderna anaphylaxis (73% vs 40%; P = .019). Treatment of reactions occurred in the emergency department (n = 36; 60%) but rarely required hospitalization (n = 3; 5%), and no patients required the intensive care unit. Treatments for suspected anaphylaxis included H1 blocker (n = 48; 80%), H2 blocker (n = 7; 12%), bronchodilators (n = 6; 10%), oral corticosteroids (n = 13; 22%), intravenous corticosteroids (n = 19; 32%), intramuscular epinephrine (n = 27; 45%), and an epinephrine drip (n = 2; 3%). Of the 36 patients treated in the emergency department, two had tryptase levels and none had complement levels drawn. In total, 46 patients (77%) were evaluated by an allergist; of those, 10% (n = 6) were thought to have confirmed anaphylaxis and 67% (n = 40) were consistent with possible anaphylaxis.

The COVID-19 Vaccine Allergy Case Registry included 60 cases of suspected anaphylaxis, which comprised 12% of the 481 cases of allergic reactions reported by clinicians in the registry. There were no fatalities, and reactions were treatable without endotracheal intubation or intensive care unit—level care. As US Food and Drug Administration support grows for mRNA vaccine boosters and younger age groups, it is imperative that we understand and disseminate evidence regarding allergic reactions to elucidate true clinical risks and reduce vaccine hesitancy.

From December 14, 2020 through January 18, 2021, the CDC identified 66 case reports of anaphylaxis, 47 after Pfizer-BioNTech vaccine and 19 after Moderna vaccine.⁴

TABLE I. Demographics and medical history of patients with suspected anaphylaxis to COVID-19 vaccine

Characteristic	All (n = 60)	Moderna (n = 15)	Pfizer-BioNTech (n = 45)	P *
Reaction with first dose	48 (80)	10 (67)	38 (84)	.15
Age, y (means \pm SDs)	41 ± 18	40 ± 22	41 ± 17	.86
Female	51 (85)	10 (67)	41 (91)	.036
Race				.86
American Indian or Alaska Native	1 (2)	0	1 (2)	
Asian	2 (3)	1 (7)	1 (2)	
Black	4 (7)	1 (7)	3 (7)	
Latino	1 (2)	0	1 (2)	
Unknown	3 (5)	1 (7)	2 (4)	
White	49 (82)	12 (80)	37 (82)	
History of atopic disease	35 (58)	7 (47)	28 (62)	.29
Asthma	25 (42)	4 (27)	21 (47)	
Allergic rhinitis	19 (32)	4 (27)	15 (33)	
Contact dermatitis	4 (7)	2 (13)	2 (4)	
Eczema	4 (7)	1 (7)	3 (7)	
History of anaphylaxis	27 (45)	2 (13)	25 (56)	.004
Medication	11 (18)	0	11 (24)	
Food	10 (17)	2 (13)	8 (18)	
Venom	4 (7)	0	4 (9)	
Idiopathic	2 (3)	0	2 (4)	
History of chronic urticaria	5 (8)	0	5 (11)	.32

Data are shown as n (%) unless specified.

Italic indicates statistical significance.

 $*\chi^2$ or t test, as indicated.

Pfizer-BioNTech anaphylaxis patients were characterized by a median age of 39 years, 94% of whom were female, median symptom onset within 10 minutes, 34% of whom had a reported history of anaphylaxis. Moderna anaphylaxis patients were characterized by a median age of 41 years, 100% of whom were female, median symptom onset within 10 minutes, and 26% of whom had a reported history of anaphylaxis. There were no associated fatalities.⁴ This registry's 60 cases are demographically consistent with the CDC cases and other prior reports.^{3,4} Patients were largely young and middle-aged women. Interestingly, before COVID-19 vaccines, vaccine-induced anaphylaxis was more common in older ages, in males, and in those with a chronic medical condition.⁷ A majority of anaphylaxis patients had a history of atopic disease, which was observed previously in individuals with influenza vaccine-induced anaphylaxis.⁸

Of patients who presented to the emergency department, just two had tryptase levels evaluated and none had complement levels evaluated. Although no specific laboratory tests can definitively diagnose anaphylaxis, routine assessment of tryptase and complement including split products may assist with diagnosis and advance our understanding of immediate allergic reactions to mRNA COVID-19 vaccines. To date, some anaphylaxis patients have had elevated tryptase and some have had elevated C3a without tryptase elevation.^{3,9} Reactions appearing as potential anaphylaxis may instead be vasovagal, immunization stress-related response, or inducible laryngeal reactions,¹⁰ which highlights the importance of collecting objective data and allergist expertise.

This study had limitations. A case series does not allow for the assessment of incidence or risk factors of anaphylaxis. Although Pfizer-BioNTech was associated with more reports of anaphylaxis in this series, this may reflect the higher use of Pfizer-BioNTech in the United States. However, most cases reported into this registry overall were from the Moderna vaccine. Because this case registry was hosted on an institutional website and publicized through allergist professional society networks, there was potential selection bias, although cases came from 46 US states. These data represent adult cases, and so they may not be applicable to younger age groups. Data were not complete for all fields of interest. Although 77% of patients were assessed by allergy and immunology specialists, the criteria used by allergists to determine whether or not anaphylaxis occurred were not collected, and this lack of consistent anaphylaxis diagnosis is a significant limitation.

Sixty cases of potential anaphylaxis are described, but hospitalization was rare and no intensive care unit treatment or deaths were reported.

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TABLE II.	Features	and	management	of	anaphylaxis to	o I	COVID-19	vaccine
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Nausea 1 (2) 0 1 (2) Location of reaction treatment	Abdominal pain	2 (3)	1 (7)	1 (2)	
Location of reaction treatment	Nausea	1 (2)	0	1 (2)	
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H2 blocker 7 (12) 3 (20) 4 (9) .35 Bronchodilator 6 (10) 1 (7) 5 (11) .62 Corticosteroids (oral) 13 (22) 2 (13) 11 (24) .37 Corticosteroids (intravenous) 19 (32) 4 (27) 15 (33) .75	H1 blocker	48 (80)	11 (73)	37 (82)	.47
Bronchodilator 6 (10) 1 (7) 5 (11) .62 Corticosteroids (oral) 13 (22) 2 (13) 11 (24) .37 Corticosteroids (intravenous) 19 (32) 4 (27) 15 (33) .75	H2 blocker	7 (12)	3 (20)	4 (9)	.35
Corticosteroids (oral) 13 (22) 2 (13) 11 (24) .37 Corticosteroids (intravenous) 19 (32) 4 (27) 15 (33) .75	Bronchodilator	6 (10)	1 (7)	5 (11)	.62
Corticosteroids (intravenous) $19 (32)$ $4 (27)$ $15 (33)$.75	Corticosteroids (oral)	13 (22)	2 (13)	11 (24)	.37
	Corticosteroids (intravenous)	19 (32)	4 (27)	15 (33)	.75

(continued)

TABLE II. (Continued)

Characteristic		All	Moderna	Pfizer-BioNTech	P *
intramuscular epinephrine		27 (45)	5 (33)	22 (49)	.29
Epinephrine drip‡		2 (3) 0 2 (4)			1.00
Allergist evaluation [§]					.31
n		46	10	36	
Possible anaphylaxis		40 (67)	10 (67)	30 (67)	
Confirmed anaphy	laxis	6 (10)	0	6 (13)	
Skin testing results	Skin testing results		Skin tested		
Polyethylene glycol	Miralax (skin prick)	31		0	
	Methylprednisolone acetate (intradermal)	27		2	
Polysorbate 20	Hepatitis A vaccine or Twinrix (GlaxoSmithKline plc, London, United Kingdom)	8		1	
Polysorbate 80	Triamcinolone acetonide	6		0	
	Refresh Sterile Eye Drops (AbbVie, North Chicago, IL)	3		1¶	
	Prevnar 13 (Pfizer Inc., New York, NY)	4		0	
Vaccine		2		0	

Data are shown as n (%) unless specified. No individuals had increased use of accessory respiratory muscles, recession, cyanosis, grunting, or reduced peak expiratory flow (respiratory); localized injection site urticaria (dermatologic); low heart rate, abnormal heart rhythm, loss of consciousness, decreased level of consciousness, capillary refill time greater than 3 seconds, reduced central pulse volume, hypotonia (collapse), or incontinence (cardiovascular), or diarrhea or vomiting (gastrointestinal). Italics indicate statistical significance.

 $*\chi^2$ test.

 \dagger Timing was missing in 18 cases: six Moderna and 12 Pfizer-BioNTech. The remaining four patients had symptoms within 30 to 40 minutes (n = 2) and 45 minutes (n = 2). \ddagger These two individuals required an epinephrine drip after three doses of intramuscular epinephrine and were admitted to the hospital.

§Seven individuals submitted as potential cases of anaphylaxis were subsequently found not to have possible or confirmed anaphylaxis after allergist evaluation; five of these seven had stress responses.

Refresh Sterile Eye Drops have since been described as an irritant.⁶

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