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COVID-19 Vaccine-associated Anaphylaxis and Allergic Reactions: Consensus Statements of the KAAACI Urticaria/Angioedema/Anaphylaxis Working Group

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ABSTRACT

In the era of novel coronavirus epidemics, vaccines against coronavirus disease 2019 (COVID-19) have been recognized as the most effective public health interventions to control the pandemic. An adverse event following immunization (AEFI) is defined as any untoward occurrence following immunization, and the majority of AEFIs are caused by protective immune responses stimulated by vaccines. Most of the reported AEFIs are not serious, and many are not immunologically mediated or even reproducible on re-exposure. However, uncommon severe allergic adverse reactions, such as anaphylaxis or other allergic reactions, can occur after vaccinations. Confirmed allergic reactions to vaccines may be caused by residual non-human protein, preservatives, or stabilizers in the vaccine formulation (also known as excipients). There are 2 main potential allergenic/immunogenic excipients in COVID-19 vaccines, polyethylene glycol (PEG) and polysorbate 80. PEG, also known as

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macrogol, is an ingredient in various laxatives and injectable formulations, such as depot steroids. Polysorbate 80 is present in various medical products, creams, ointments, lotions, and medication tablets. Contraindications to the administration of COVID-19 vaccines include a previous history of severe allergic reactions to the first dose of COVID-19 vaccine or proven hypersensitivity to a vaccine component, such as PEG or polysorbate 80. Anaphylaxis or other allergic reactions following immunization can cause fear and loss of confidence in the safety of vaccines among the public. A better understanding of these events is thought to help alleviate concerns about the current COVID-19 vaccines and provide reassurance to the general population by analyzing the exact incidence of anaphylaxis and potential risk factors. COVID-19 vaccine-associated anaphylaxis could be prevented and managed by risk stratification based on our local and global experience.

Keywords: COVID-19; vaccine; anaphylaxis; pandemics; public health; immunization; immunity; hypersensitivity; preservatives

INTRODUCTION

Vaccines against coronavirus disease 2019 (COVID-19) have been recognized as one of the most effective public health interventions to control the pandemic.[1] Vaccines are intended to produce active immunity to specific antigens.

Adverse events following immunization (AEFIs), including any untoward medical occurrences, does not necessarily have a causal relationship with the vaccine. AEFIs may be related not only to the vaccine itself, but also to the vaccination procedure (vaccine quality defects, immunization errors or anxiety) and coincidental events (not linked to the vaccine). Most of the reported AEFIs are not serious and are mediated by non-immunological mechanisms.[2] However, these events can cause fear and loss of confidence in the safety of vaccines among the public. A good understanding of AEFIs will help alleviate fears about the current COVID-19 vaccines.

Currently, 2 COVID-19 vaccines manufactured by Oxford-AstraZeneca and Pfizer-BioNTech have been used in Korea, and 3 additional vaccines manufactured by Moderna, Johnson & Johnson and Novavax are expected to receive regulatory approval (**Table 1**). The Oxford-AstraZeneca ChAdOx1 and Johnson & Johnson (Janssen) Ad26.COV2.S vaccines have recombinant adenovirus vector platforms,[3,4] the Pfizer-BioNTech BNT162b2 and Moderna

Table 1. Summary of coronavirus disease 2019 vaccines and their excipients introduced or considered for introduction in South Korea

Vaccine name (manufacturer)	Platform	Dose and interval	Storage	Excipients
ChAdOx1 (AstraZeneca Korea Covid-19 Vaccine®) (Oxford-AstraZeneca)	Adenovirus vector	2 doses, 8–12 weeks (permission: 4–12 weeks) apart	2°C–8°C	L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, ***polysorbate 80***, ethanol, sucrose, sodium chloride, disodium edetate dehydrate
Ad26.COV2.S (Johnson & Johnson)	Adenovirus vector	1 dose	−20°C	Sodium chloride, citric acid monohydrate, ***polysorbate 80***, 2 hydroxypropyl-B-cyclodextrin (HBCD), ethanol, sodium hydroxide
BNT162b2 (Comirnaty®) (Pfizer-BioNTech)	mRNA-based vaccine	2 doses, 21 days apart	−90°C to −60°C	Lipids ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), **[(*polyethylene glycol2000*)**-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, cholesterol, potassium chloride and monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate dihydrate, sucrose
mRNA-1273 (Moderna)	mRNA-based vaccine	2 doses, 28 days apart	−20°C	Lipids (SM-102; 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 **[*PEG 2000*-DMG]**; cholesterol; and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, hydrochloride, acetic acid, sodium acetate, sucrose
NVX-COV2373 (Novavax)	Protein subunit	2 doses, 21 days apart	2°C–8°C	Full-length spike protein formulated in ***polysorbate 80*** detergent and Matrix M1 adjuvant

mRNA-1273 vaccines are mRNA-based vaccines using lipid nanoparticles to facilitate the transport of mRNA into cells,[5,6] and the Novavax NVX-COV2373 vaccine contains SARS-CoV-2 recombinant spike protein nanoparticles with Matrix-M1 adjuvant.[7] To date, the specific mechanism of allergy and the inciting antigen have not been identified. Although local reactions may commonly be associated with the active antigen in the vaccine, confirmed allergic reactions to vaccines may be caused by residual non-human protein, or preservatives and stabilizers in the vaccine formulation, also known as excipients.[8] Excipients are necessary and added to a vaccine for specific purposes, such as stimulating a stronger immune response, preventing contamination by bacteria, or stabilizing the potency of the vaccine during transportation and storage (**Table 1**).

POTENTIAL ALLERGENIC/IMMUNOGENIC COMPONENTS OF COVID-19 VACCINES

An excipients present in both Pfizer-BioNTech and Moderna vaccines, polyethylene glycol (PEG), is a known potential allergen, but is widely used due to its stabilizing properties.[9] The Moderna vaccine also contains trometamol as an excipient.[10] The Oxford-AstraZeneca, Johnson & Johnson, and Novavax vaccines all contain PEG derivatives such as polysorbate 80.[11]

PEG is an ingredient in many laxatives present in approximately 30% of the tablets and it is used as a surfactant in many injectable formulations, such as depot steroids where a prolonged effect is needed. PEG is also used as an excipient in other medicinal products, including everyday products, such as moisturizers, toothpaste, cosmetics, shampoo, and hair dye, as well as some biologics.[12] Although PEG is considered safe and biologically inert, a recent study in the general population showed that 5%–9% of the 1721 tested serum samples were positive for anti-PEG IgG, 3%–6% of the 948 were positive for anti-PEG IgM, and 2 of 2,091 (0.1%) were positive for anti-PEG immunoglobulin E (IgE).[13] The molecular weight (MW) of the different PEG excipients varies from 300 to over 10,000 g/mol, and hypersensitivity reactions may occur to PEG of any MW, with higher rates of reaction to MWs between 3,350 and 6,000 g/mol.[14] The exact threshold of reactivity based on the MW of PEG has not been clarified, but tolerance to PEG with lower MW (≤400 g/mol) has been described in patients with documented anaphylaxis to PEG 3350.[15] A recent study reported that those who lose reactivity to low-MW PEG over time may still remain sensitized to very high-MW PEG.[16] Therefore, many allergists have hypothesized that cases of anaphylaxis during the rollout of the Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines containing PEG 2000 could potentially be due to preexisting PEG allergy.[10,11,17]

The Moderna vaccine contains trometamol, also known as tromethamine (molecular formula: $C_4H_{11}NO_3$), an organic amine, that is widely used in several medications for topical, enteral, or parenteral administration. Trometamol is also used in cosmetic products as an emulsifier, and contact sensitization and allergy to this compound have been reported.[18] Recently, trometamol has been reported to cause anaphylaxis in a patient receiving gadolinium-based contrast agent.[19]

Polysorbate is also an excipient in various medical products (*e.g.*, vaccines, vitamins, biologics, steroids, and chemotherapeutics), creams, ointments, lotions, and medication tablets. At least 70% of the injectable biological agents and monoclonal antibody treatments (Xolair®, Dupixent®, Prevenar®, Lantus®, *etc.*) contain polysorbate (usually polysorbate 80).[20] Polysorbate is a derivative of PEG, but tends to have lower MW (*e.g.*, polysorbate 80 has a MW

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of 1,310 g/mol).[1] Some cases of polysorbate 80-induced anaphylaxis have been reported in Korea.[21,22] A case of anaphylaxis was reported after the third administration of quadrivalent human papillomavirus vaccine (Gardasil®), which contains polysorbate 80.[23] First-dose reactions to vaccines containing polysorbates may have occurred because of previous sensitization to polysorbate 80.[15]

AEFI AGAINST COVID-19: NON-ALLERGIC AEFI

Local injection site reactions (swelling, redness, and/or soreness) and systemic symptoms, especially fever, are common after administration of most vaccines and are usually non-allergic reactions.[24] Clinical trial data indicated that in the case of the Pfizer-BioNTech vaccine, the most frequent AEFIs were pain at the injection site, fatigue, headache, myalgia, chill, arthralgia, and fever, each of which was reported in more than 1 in 10 recipients.[6] Clinical trials of the Oxford-AstraZeneca vaccine in more than 23,000 participants showed that the AEFIs frequently reported in more than 1 in 10 people were injection site tenderness and pain, headache, fatigue, myalgia, malaise, fever, chill, arthralgia, and nausea.[25]

In the UK, the first country to begin administering COVID-19 vaccines, both the Oxford-AstraZeneca and Pfizer-BioNTech vaccines have been authorized for supply by the Medicines and Healthcare products Regulatory Agency (MHRA). According to the MHRA report through the Yellow Card reporting system, the majority of reports on AEFIs are injection site reactions, such as sore arm, and generalized symptoms, such as flu-like symptoms, headache, chill, fatigue, nausea, fever, dizziness, weakness, aching muscle, and rapid heartbeat.[26] These reactions seem to reflect the body's normal immune response to vaccines. They are typically seen with most vaccines and tend to resolve within a few days. These types of AEFI associated with COVID-19 vaccines are broadly similar across age groups, although they may be slightly more frequent in younger adults.[27]

Some non-allergic systemic reactions may be complicated by the onset of syncope (vasovagal or vasodepressor reaction),[27] which can occur after many types of vaccination and is most common among adolescents and young adults. In particular, the Vaccine Adverse Event Reporting System (VAERS) in the US has detected a trend toward increasing syncope reports linked to three shots specifically for adolescents with different ingredients: human papillomavirus vaccine, meningococcal conjugate vaccine, and Tdap (tetanus, diphtheria, and pertussis).[26,27] According to the Centers for Disease Control and Prevention (CDC), 80% of the reported syncope episodes occur within 15 minutes of vaccine administration.[27] A vasovagal syncope episode is usually triggered by pain and anxiety, but not by the vaccine itself, causing sudden drops in heart rate and blood pressure. Many experts have concluded that syncope may result from the temporary pain of vaccination rather than the COVID-19 vaccine itself. Syncope itself is generally not serious, but syncope-related falls or other accidents can cause injury.[25,26] Although syncope itself may or may not be preventable, it is important to prevent injuries when people faint. An interesting study estimated the baseline incidences of several AEFIs, including syncope. The mean predicted monthly incidence of vasovagal syncope was 23.89 (19.81-27.98) cases per 100,000 in 2021, suggesting that it is possible that cases could develop at COVID-19 vaccination sites, so thorough preparations are required.[28] To date, frequent non-allergic AEFIs associated with COVID-19 vaccines generally appear to be the same as those associated with other existing vaccines. There is also a safety issue regarding thrombosis, which has yet to be resolved.

AEFI AGAINST COVID-19: ALLERGIC AEFI

Confirmed allergic reactions to vaccines are not frequently attributed to active ingredients, but rather to inactive ingredients or excipients, such as egg protein, gelatin, formaldehyde, thimerosal, and neomycin.[29] PEG from the mRNA-based vaccines and polysorbate 80 from the viral vector vaccines have been recognized as major allergenic excipients.[1] Although allergic reactions to vaccination are a common concern, the rates of vaccine-associated allergic reactions are not high, and most are not serious. In fact, the risk of anaphylaxis (1 per 1,000,000 doses) is very low for many vaccines.[30] However, anaphylactic reactions are potentially life-threatening and can occur immediately, usually within minutes, after exposure to a vaccine. Even mild allergic reactions can still lead to serious complications, and therefore prompt attention, prevention, and treatment are required.

Vaccine-associated allergic reactions can affect any part of the body, including cutaneous, respiratory, cardiovascular and gastrointestinal systems.[1] Mild-to-moderate allergic reactions are usually local and non-anaphylactic reactions such as flush, pruritus, local or generalized urticaria, angioedema, facial edema, tachycardia, dizziness, sneezing, itchy nose, wheezing, chest tightness, laryngeal edema, nausea, vomiting, abdominal pain, and diarrhea.[29] The severity grade of the reported systemic events increased after the second dose of the Moderna vaccine,[5] while less severe side effects were noted after the lower and second doses of the Oxford-AstraZeneca vaccine.[23] It is important to note that if these allergic reactions involve multiple organ systems simultaneously and occur immediately, these symptoms and signs are considered anaphylactic reactions according to the Brighton Collaboration case definition.[31]

However, a careful clinical phenotyping of AEFIs is important to prevent avoidance of the COVID-19 vaccine due to fear in the population. In the CDC report analyzing allergic AEFI associated with the Pfizer-BioNTech vaccine, 175 possible allergic reactions were demonstrated after case reviews to include 86 (49%) non-anaphylactic allergic reactions and 61 (35%) non-allergic reactions.[32] At the same time, of the 108 possible allergic reactions to the Moderna vaccine, 43 (40%) were classified as non-anaphylactic allergic reactions and 47 (44%) were non-allergic adverse events.[33]

INCIDENCE OF ANAPHYLAXIS TO COVID-19 VACCINES

As of May 8, 2021, the total number of cumulative administered COVID-19 vaccine doses per 100 people has reached 16.45 worldwide (*e.g.*, 121.24 in Israel, 76.95 in the USA, 77.19 in the UK, 38.43 in the EU, 37.84 in Singapore, 22.06 in China, 14.80 in Russia, 12.14 in India, 3.32 in Japan, and 8.15 in Korea).[34] In the USA, the number of cumulative administered doses has been reported as 137.22 million doses of Pfizer-BioNTech, 111.09 million doses of Moderna, and 2.98 million doses of Johnson & Johnson until May 8, 2021.[34] In the UK, as of April 28, 2021, an estimated 11.4 million first doses of the Pfizer-BioNTech and 22.6 million first doses of the Oxford-AstraZeneca vaccines, and 0.1 million first doses of Moderna had been administered.[26]

Within the first day after initiating mass vaccination with the Pfizer-BioNTech vaccine, there were reports of anaphylaxis in both the UK and the US.[1] The World Allergy Organization (WAO) estimated the incidence of anaphylaxis as close to 0.5:100,000 doses (0.0005%) for the Pfizer-BioNTech vaccine.[1] The initial estimated rates of anaphylaxis associated with mRNA COVID-19 vaccination in the US was estimated to range from 0.25 to 1.11 cases per

100,000 doses.[35] Subsequently, the CDC reported a total of 66 cases of anaphylaxis among 17,524,676 doses administered between December 14, 2020 and January 18, 2021 (0.37 cases per 100,000 doses).[35] The occurrence of anaphylaxis after COVID-19 vaccination is in the range reported after inactivated influenza vaccine (0.14 per 100,000 doses), pneumococcal polysaccharide vaccine (0.25 per 100,000 doses), and live attenuated herpes zoster vaccine (0.96 per 100,000 doses).[31,36,37] In addition, a total of 640 (9.2%) serious adverse events and 113 deaths following COVID-19 vaccinations were also reported to the VAERS, including 78 deaths among long-term care facility residents.[36,38] Causality assessments between COVID-19 vaccination and death have not yet been completed.

In the US, a report distinguished the incidence of anaphylaxis from the above data. In the prospective cohort of health care employees of Mass General Brigham in Boston who received their first dose of an mRNA COVID-19 vaccine between December 16, 2020 and February 12, 2021, a total of 64,900 employees had received their first dose of a COVID-19 vaccine (25,929 with the Pfizer-BioNTech vaccine and 38,971 with the Moderna vaccine).[36] Among them, 52,805 completed an electronic symptom survey and acute allergic reactions were reported in 1,365 employees (2.10%). Anaphylaxis was confirmed in 16 employees (7 cases with the Pfizer-BioNTech vaccine and 9 cases with the Moderna vaccine). The incidence of anaphylaxis was estimated to be 24.7 cases per 100,000 doses (27.0 cases per 100,000 doses of Pfizer-BioNTech vaccine and 23.1 cases per 100,000 doses of Moderna vaccine). All recovered from anaphylaxis except one employee who was admitted to the intensive care unit (ICU).[36] The difference in the incidence of anaphylaxis would be explained by the fact that the CDC data were collected from a passive voluntary reporting system in the general population, while healthcare employees used a more approachable reporting method in addition to having more knowledge about medicine.[34,35,38] It is also possible that healthcare workers have been exposed more frequently to PEG-like components in their occupational environment than the general population, which may result in the increased sensitization rate.

In the UK, the Yellow Card reporting scheme collected spontaneous public and health professional safety update reports of adverse reactions following immunization with both vaccines, and the overall reporting rate was approximately 3-6 Yellow Cards per 1,000 doses.[26] Up to April 28, 2021, the Yellow Card spontaneous reports of adverse reactions associated with anaphylaxis or suspected reactions were reported as 283 cases associated with Pfizer-BioNTech vaccine and 590 associated with Oxford-AstraZeneca vaccine. A total of 1,152 deaths were reported shortly after vaccination with the above 2 vaccines (364 deaths with the Pfizer-BioNTech vaccine, 772 deaths with the Oxford-AstraZeneca vaccine, 2 deaths with Moderna, and 14 deaths from unspecified vaccines), most of which were in elderly people with underlying illnesses.[26] However, as this was a passive spontaneous reporting system and several deaths and newly reported serious events, including thrombotic thrombocytopenia, are still under extensive causality assessment review, the precise incidence rate cannot be estimated from the data.[26] One prospective UK study regarding 627,383 individuals vaccinated with Pfizer-BioNTech and Oxford-AstraZeneca vaccines (282,103 and 345,280, respectively) reported that systemic and local side-effects after vaccinations with above 2 vaccines occur at frequencies lower than previously reported in phase 3 trials.[37]

The Japanese Ministry of Health, Labor, and Welfare issued a public/press release indicating that a total of 2,718,090 subjects, mainly healthcare workers, had been vaccinated with the Pfizer-BioNTech vaccine until April 25, 2021.[39] Among them, a total of 94 suspected cases of anaphylaxis (about 3.46 in 100,000 cases) were reported.

Table 2. Incidences of adverse events, including anaphylaxis, after coronavirus disease 2019 vaccinations in Korea (updated from February 28 to May 8, 2021)

Classification	Vaccinated cases (cumulative)	AEFI				
		Total	General*	Anaphylaxis suspected†	Severe suspected‡	Deaths§
All	4,176,221	19,631	18,917	187	432	95
Incidence, %		0.47	0.45	0.0045	0.0103	0.0023
ChAdOx1 (Oxford-AstraZeneca)	2,014,746	16,387	15,915	149	272	51
Incidence, %		0.81	0.79	0.0074	0.0135	0.0025
BNT162b2 (Pfizer-BioNTech)	2,161,475	3,244	3,002	38	160	44
Incidence, %		0.15	0.14	0.0018	0.0074	0.0020

Modified from the Press Release by the Korea Disease Control and Prevention Agency (KDCA) (available from: https://ncov.mohw.go.kr; accessed on May 9, 2021).[40]
AEFI, adverse events following immunization.
*Cases with general (common) AEFI: mild cases such as redness/pain/swelling of injection site, myalgia, fever, headache, chilling, nausea, vomiting, *etc.*
†Cases reported by healthcare institutions due to suspected anaphylaxis reactions, including suspected symptoms of anaphylaxis, such as shortness of breath, rashes, *etc.*, within 2 hours of vaccination differing from typical anaphylaxis, and anaphylactic shock.
‡Cases with severe (major serious) AEFI: adverse event special interest (*e.g.*, neurologic symptoms/convulsions, thrombotic thrombocytopenia, *etc.*), intensive care unit admission, life threatening event, and permanent disability/sequelae.
§Cases reported as suspected cases of AFEI; causal association not yet determined; investigation for assessment of causal association to take place for deaths or anaphylaxis cases.

In Korea, a total 4,176,221 doses of COVID-19 vaccination were completed (2,014,746 doses of Oxford-AstraZeneca vaccine and 2,161,475 doses of Pfizer-BioNTech vaccine) by May 8, 2021.[40] The Korea Disease Control and Prevention Agency (KDCA) has been updating detailed adverse events data on a daily basis, including suspected anaphylaxis following COVID-19 vaccination in Korea (**Table 2**). A total 19,631 cases of adverse reactions have been reported after COVID-19 vaccination, among which 187 were self-reported as anaphylaxis-like adverse events and further investigations are currently underway.[40] A total of 432 suspected serious cases with severe adverse events, including convulsions, thrombotic thrombocytopenia and ICU admission, and 95 deaths have also been reported and are currently under further investigation.[40] By March 8, 2021, the estimated incidence rate of adverse reactions to COVID-19 vaccination was 0.47% for the 2 vaccines, and the anaphylaxis incidence rate was estimated at 4.5 cases per 100,000 doses (7.4 cases for the Oxford-AstraZeneca vaccine and 1.8 cases for the Pfizer-BioNTech vaccine per 100,000 doses) (**Table 2**).[40] The above estimated rates were only analyzed based on early limited data and further causality assessments are still underway in Korea.[40] Recently, 3 academic Korean hospitals have reported 2 prospective and 1 retrospective studies with healthcare workers (7,625, 1,483, and 1,503 subjects, respectively) who received COVID-19 vaccines (Pfizer-BioNTech or Oxford-AstraZeneca) via survey or mobile adverse event reporting systems.[41-43] These studies suggested that adverse reactions to COVID-19 vaccination with the above 2 vaccines were mostly mild to moderate, and more frequently reported in female, younger age, and Oxford-AstraZeneca vaccinated groups. The drug permission requirement labels endorsed by the Korean Ministry of Food and Drug Safety state that the anaphylaxis risk of the 2 vaccines is unknown (non-assessable).[44] Therefore, continuous monitoring of adverse reactions, including anaphylaxis, is required.

DEFINING ANAPHYLAXIS AS AN AEFI BASED ON THE BRIGHTON COLLABORATION CRITERIA

Several different definitions have been used in various committees to define anaphylaxis. According to the World Health Organization (WHO) International Classification of Diseases, 11th Revision (ICD-11), 2019, anaphylaxis is defined as a severe, life-threatening systemic hypersensitivity reaction characterized by rapid onset with airway, breathing, or circulatory problems, and is usually (although not always) associated with skin and mucosal

changes.[45] According to the WAO Anaphylaxis Guidance 2020, anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in airway, breathing, and/or circulation, and may occur without typical skin features or circulatory shocks being present. A diagnosis of anaphylaxis is made when acute onset of skin or mucosal symptoms (generalized urticaria, pruritus or flushing, and swollen lips-tongue-uvula) occurred with respiratory, circulatory or gastrointestinal (GI) symptoms, or when acute onset hypotension or bronchospasm or laryngeal involvement occurred after exposure to a known or highly probable allergen for that patient.[45]

Common shared concepts of anaphylaxis are (1) acute onset, (2) rapid progression, and (3) severe, life-threatening generalized or systemic hypersensitivity reaction mediated by immunological or non-immunological mechanisms. When reporting anaphylaxis as an AEFI, clinical assessment is made according to the validated criteria published in the Brighton Collaboration Anaphylaxis Working Group guidelines for "Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data."[30] The updated case definition was released on March 5, 2021.[31] According to these guidelines, there are 5 levels of diagnostic certainty. For all levels of diagnostic certainty, anaphylaxis should fulfill 3 clinical characteristics: sudden onset; rapid progression; and involvement of multiple (≥2) organ systems. To assess organ system involvement, a RAPID assessment form is used, which includes a checklist with all of the major/minor criteria for anaphylaxis: Rash and mucosa, Airway and respiratory, Pulse and cardiovascular, Investigation, and Diarrhea and GI tract.

Criteria for defining anaphylaxis are presented in **Supplementary Table S1** and logic for determining the level of diagnostic certainty is presented in **Supplementary Fig. S1**. Briefly, the course of illness must be "sudden onset" with "rapid progression." The term "sudden onset" indicates an event that occurs unexpectedly and without warning, leading to a marked change in a subject's previously stable condition, while "rapid progression" is not defined arbitrarily. The level of diagnostic certainty is determined according to the involved organs, such as skin, respiratory, cardiovascular, and GI systems. The symptoms of skin, respiratory, and cardiovascular systems could be major or minor according to severity. For example, generalized urticaria and/or erythema are major criteria, while localized injection site urticaria is a minor criterion. All GI symptoms, such as nausea, vomiting, abdominal pain, and diarrhea, are defined as minor criteria. Similarly, an elevated tryptase level (>upper normal limit for laboratory tests) is a minor criterion. Next, we determine the level of diagnostic certainty of anaphylaxis using logic. Level 1 indicates the highest diagnostic certainty and diagnostic certainty is decreased with increasing level. The highest diagnostic certainty does not indicate the most severe disease, *i.e.*, diagnostic certainty is not equivalent to disease severity. Level 1 involves major skin symptoms with major respiratory or cardiac symptoms/signs. Level 2 includes major skin symptoms with minor respiratory or cardiac symptoms/signs. Major respiratory and cardiac symptoms/signs are also defined as level 2. In addition, major respiratory or cardiac symptoms/signs with other minor symptoms from a different system are defined as level 2. Level 3 is defined according to the presence of minor respiratory or cardiac symptoms/signs with other minor symptoms from 2 different systems. Level 4 is anaphylaxis reported with insufficient evidence to meet any of the levels of diagnostic certainty, and level 5 is not a case of anaphylaxis.

CONTRAINDICATIONS TO COVID-19 VACCINES IN THE GENERAL POPULATION

Healthcare workers must follow local authorizations and policies in terms of indications for and contraindications to COVID-19 vaccines, which will be continuously updated. In principle, COVID-19 vaccination includes all subjects without contraindications.[43,46] It is recommended to exclude and delay vaccination if subjects have a current COVID-19 infection or fever ≥ 37.5°C. People who are pregnant or ≤18 years old are also excluded from the vaccination because of a lack of safety and efficacy data. Special considerations during vaccination are needed in patients with chronic illness or immunocompromised conditions and in breast-feeding mothers. In patients with a past history of COVID-19 infection, vaccination at least 4 weeks after recovery is recommended. In asymptomatic cases, vaccination after 4 weeks of first positive polymerase chain reaction test is needed. If a patient has been using systemic steroids for more than 2 weeks for the treatment of COVID-19 infection or other diseases, it is generally recommended that vaccination be done at least 4 weeks after stopping systemic steroids. However, in patients who cannot stop taking steroids due to underlying diseases, it is better to vaccinate based on the risk-to-benefit ratio. There is no evidence regarding the safety and efficacy of the vaccine in subjects treated with monoclonal antibodies or therapeutic plasma exchange for COVID-19 infection, but it is recommended that vaccination be deferred for at least 90 days to avoid the potential interference of immune responses. In patients with inherited coagulopathy, factor replacement on the day of vaccination is necessary.[47] A summary of contraindications is shown in **Figure**.

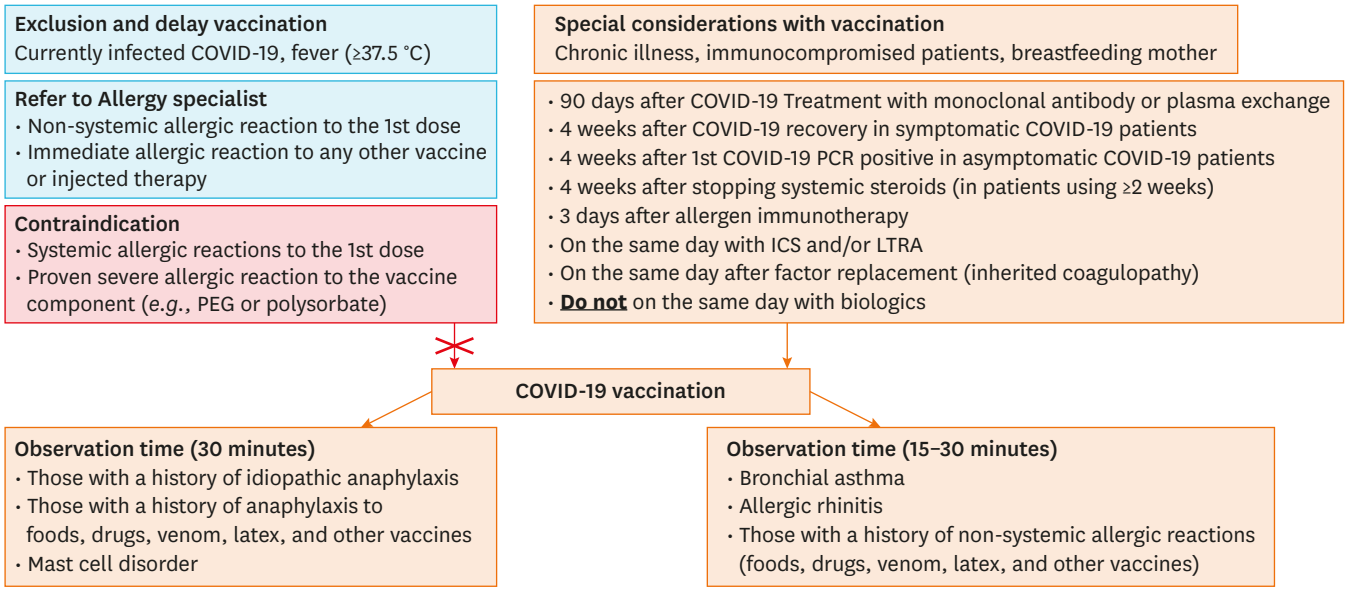

Figure. Summary of contraindication and recommended observation time by medical history.
A consensus recommendation from the KAAACI Urticaria/Angioedema/Anaphylaxis Working Group based on the KDCA guideline which is subjected to be updated. Contraindication, exclusion, and special considerations are based on the KDCA.
COVID-19, coronavirus disease 2019; KDCA, Korea Disease Control and Prevention Agency; ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; PCR, polymerase chain reaction; PEG, polyethylene glycol.

CONTRAINDICATIONS TO COVID-19 VACCINES IN PATIENTS WITH ALLERGIC DISEASES

In general, there are no contraindications to administering COVID-19 vaccines in populations with allergic diseases except in patients with a previous history of severe allergic reactions to the first dose of COVID-19 vaccine or a proven hypersensitivity to a vaccine component, such as PEG or polysorbate 80. Allergies to drugs, foods, inhalant allergens, insect venoms, and latex are not contraindications to COVID-19 vaccine.[46,48]

The CDC recommends that individuals with a history of anaphylaxis to PEG, PEG derivatives, or polysorbate avoid both of the mRNA COVID-19 vaccines.[49] The European Medicines Agency (EMA) recommends that people who have an allergy to one of the vaccine components not receive the vaccine.[50,51] EMA also recommends that advice of a relevant specialist be sought for those with a history of an immediate allergic reaction to any other vaccine or injection therapy. Administering COVID-19 mRNA vaccines requires advice of a relevant specialist in patients with a history of allergy to polysorbate 80 due to the possibility of cross-reactivity with PEG.

Leukotriene receptor blockers and/or inhaled corticosteroids for bronchial asthma have no impact on immunogenicity of the COVID-19 vaccines, and therefore routine medications can be given on the same day receiving the vaccine.[52] There are no known drug interactions for patients receiving allergen immunotherapy, but a minimum of 3 days between individual shots is recommended to check for adverse reactions. Administration of the vaccine with injection of biologics has not been studied. However, it is recommended not to receive COVID-19 vaccine on the same day as the injection of biologics.[52,53]

OTHER SUGGESTED RISK FACTORS FOR ANAPHYLAXIS AND RECOMMENDED OBSERVATION TIME

Importantly, allergic reactions, including anaphylaxis, can occur in anyone. Therefore, vaccination must be administered under close medical supervision and all subjects should be observed for at least 15 minutes after vaccination.[46] Some medications and situations are known cofactors for worsening anaphylactic reactions, such as beta-blocker, exercise, alcohol, and menstruation. Medical practitioners need to inform patients of anaphylaxis cofactors on the day of injection and to advise patients to avoid these agents.

The American Academy of Allergy and Clinical Immunology (AAAAI) has stated that individuals with a history of food, pet, venom, environmental, and latex allergy are able to proceed with vaccination with a standard 15-minute observation period. Patients with a history of anaphylaxis should use caution when receiving the vaccine and follow a 30-minute observation period.[54,55] People with allergic histories to drugs, foods, inhalants, insects, and latex are probably no more likely than the general population to have an allergic reaction to the mRNA COVID-19 vaccines.[55,56] The American College of Allergy, Asthma, and Immunology (ACAAI) identified previous anaphylaxis episodes due to injectable drugs, independent of their composition, as a specific risk factor, while the Italian Healthcare Council identified severe asthma as a risk factor for vaccination-related adverse events.[56] The European Academy of Allergy Clinical Immunology (EAACI) identified patients at risk only when they had a previous allergic reaction to the same vaccine or to its preservatives. In addition, risk factors of COVID-19 vaccine-associated adverse reactions were suggested

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to included previous documented hypersensitivity reactions to vaccines, mastocytosis with previous repeated episodes of anaphylaxis, and severe asthma.[55,57] However, another recently updated report has indicated that mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis accompanied by mast cell activation symptoms and anaphylaxis.[58] A summary of recommended observation time is presented in **Figure**.

SECOND DOSE PLANS FOR PATIENTS WITH ALLERGIC REACTIONS TO THE FIRST DOSE OF COVID-19 VACCINE

Individuals who develop anaphylaxis to a COVID-19 vaccine should not receive a second dose of that vaccine or other vaccines with similar excipients.[1,9,49] However, for patients with allergic reactions that do not meet the criteria for anaphylaxis after their first dose, such as urticaria or angioedema, there is disagreement among experts and the public health advice of different countries.[1,9,49,59] As the COVID-19 vaccines have been developed with a novel platform in a short time and distributed quickly to the public, limited safety information is available. Nonetheless, leading international allergy committees and the public health departments of various countries have published guidelines with slightly different perspectives for evaluating and managing allergic reactions to COVID-19 vaccines (**Table 3**).

The Allergic Rhinitis and its Impact on Asthma (ARIA) and EAACI recommend that the allergenic components of each vaccine need to be identified *in vitro*, such as by basophil activation test or *in vivo* by skin testing, before administration of the vaccine.[60] Similarly, the AAAAI, the WAO, and Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) recommend that patients be followed up by an allergist who can review the

Table 3. Summary of evaluation and management of patients with allergic reactions (not anaphylaxis) to the first dose of COVID-19 vaccine according to allergy organizations

Organization	Skin testing	Premedication with antihistamines	Graded challenge
WAO[1]	Consider skin test	May mask initial symptoms of a reaction	No description
ARIA-EAACI[60]	Consider skin test	No description	No description: desensitization protocols with individual vaccine components can be envisaged (4)
APAAACI[61]	Consider skin test	No description	No description
AAAAI[9]	Consider skin test	May mask initial symptoms, however, fexofenadine or cetirizine can be considered in individuals with mild symptoms (pruritis or urticaria only)	No description in the positional paper (5); allergist supervised graded vaccine challenge can be considered, however, the safety and efficacy of this approach is unknown (6)
BASCI[59]	No description (refer to allergy specialists)	May benefit from pretreatment with antihistamine, however, this may mask initial symptoms of a reaction	No description
CSACI[62]	Allergy test is not required for patients with a suspected or confirmed severe allergic reaction to a COVID-19 vaccine or any of its components	No description	Graded administration of these vaccines in someone with a suspected or confirmed allergy to the vaccine or one of its components can be considered if further doses are required
KAAACI*	Refer to allergy specialists Consider skin testing	May benefit from pretreatment with antihistamine; however, this may mask initial symptoms of a reaction	No description

COVID-19, coronavirus disease 2019; WAO, the World Allergy Organization; ARIA-EAACI, Allergic Rhinitis and its Impact on Asthma - European Academy of Allergy and Clinical Immunology; APAAACI, Asia-Pacific Association of Allergy, Asthma, and Clinical Immunology; AAAAI, American Academy of Allergy, Asthma & Immunology; BASCI, British Society for Allergy and Clinical Immunology; CSACI, Canadian Society of Allergy and Clinical Immunology; KAAACI, the Korean Academy of Asthma, Allergy and Clinical Immunology.
*This is the consensus statements of the Urticaria/Angioedema/Anaphylaxis Working Group of KAAACI.

clinical history and that PEG or polysorbate skin testing be considered if an IgE-mediated reaction is suspected for risk stratification before a second COVID-19 vaccine dose.[1,9,61] However, the British Society for Allergy & Clinical Immunology (BSACI) advises that individuals who develop only a localized urticarial skin reaction (without systemic symptoms) to the first dose of a COVID-19 vaccine can receive the second dose using the same vaccine, in a setting with full resuscitation facilities, with a 30-minute observation period.[59] The Canadian Society of Allergy and Clinical Immunology (CSACI) does not recommend skin testing, as such testing has not been standardized and its validity is not well established; nonetheless, a recent publication has suggested a possible role of allergy testing for PEG within the context of evaluation of allergy to these vaccines.[15,62] A recent editorial paper also stated that clinicians should be cautious in making their decision based on skin testing results due to the lack of proven reliability of skin testing with PEG.[63]

The latest CDC summary describes the interchangeability of COVID-19 vaccine products; in exceptional situations where a patient received the first dose of an mRNA COVID-19 vaccine but is unable to complete the series with either the same or different mRNA COVID-19 vaccine due to contraindications (*e.g.*, anaphylaxis to the first dose), a single dose of adenoviral vector-based Janssen COVID-19 vaccine can be considered at a minimum interval of 28 days after the mRNA COVID-19 vaccine dose. In addition, the CDC suggests that patients with contraindications for adenoviral vector-based Janssen COVID-19 vaccines (*e.g.*, polysorbate allergy) can be considered for mRNA COVID-19 vaccine with caution due to the possibility of cross-reactivity between PEG and polysorbate.[49] Further information about the safety and efficacy of changing or mixed vaccination in these exceptional cases is needed.

Graded dose challenges to the COVID-19 vaccine should be considered under allergist supervision for patients with a suspected allergic reaction to the COVID-19 vaccine according to the guidelines of the EAACI and CSACI.[60,62] Graded challenging has been used as a reliable approach in managing vaccine allergy for many decades. However, the safety and efficacy of this approach for newly released COVID-19 vaccines are still unknown.

Regarding the usefulness of premedication with antihistamine and/or corticosteroids, there is no evidence that premedication reduces the risk of subsequent allergic reactions.[64] Instead, premedication can mask cutaneous symptoms and lead to a delay in detection and management of severe allergic reactions. However, pretreatment with second-generation antihistamines before the second dose of COVID-19 vaccination may be considered in individuals with mild allergic symptoms.[9,59]

Taken together, we recommend that patients with anaphylaxis or potential allergic reactions after the first dose be referred to an allergy specialist. Definite anaphylaxis after the first dose is a contraindication to receiving a second dose of the same vaccine. If the patient's symptoms suggest IgE-mediated allergic reactions (not meeting the criteria for anaphylaxis), skin testing with potential culprit reagents can be considered for further vaccination. Based on the results of skin testing and the clinical context of an individual's health, shared decision-making with patients would be preferred in the current situation. The advice could be revised based on a collection of further scientific information regarding the pathogenesis of allergic reactions and pharmacovigilance data regarding the COVID-19 vaccines.

SKIN TEST FOR PEG OR POLYSORBATE

In patients with a history of possible reactivity to PEG or polysorbate, an allergist may perform a skin prick test using PEG or polysorbate 80; however, the skin prick test has not yet been standardized and its predictive value is not known.[15] In cases of doubt based on clinical history, performing the skin prick test or/and intradermal test using drugs or solutions containing powdered PEG 3350 or polysorbate 80 should be considered.[65-67] However, skin test can be associated with systemic reactions and it is still not known if an allergy to PEG or polysorbate 80 is the only cause of allergic reactivity to the COVID-19 vaccine. Therefore, routine testing is not necessary, but could still potentially clear a patient for the vaccine who may have a reaction. The method involves the use of histamine as a positive control and normal saline solution as a negative control, with skin prick testing using a solution of PEG or polysorbate (dissolved in phosphate buffered saline in the case of powder) at a concentration of 100 mg/mL and an intradermal test at a concentration of 1 mg/mL.[9,68] A mean diameter of wheals to test solution/histamine ≥ 1 is most likely positive and is compared with medical history. If necessary, diagnosis is confirmed by provocation test.[68]

GENERAL ACUTE MANAGEMENT OF ANAPHYLAXIS

Anaphylaxis can progress within minutes from the skin/oral mucosa to multiorgan involvement, such as dyspnea, wheezing, abdominal cramps, vomiting, and circulatory collapse.[45] Therefore, upon first signs of anaphylaxis, it is necessary to immediately administer intramuscular epinephrine while assessing and maintaining the airway, breathing, circulation, and mental status. The recommended epinephrine dose is 0.01 mg/kg of body weight, up to a maximum total dose of 0.5 mg for adults (0.3 mg for prepubertal children), administered intramuscularly and can be repeated every 5-15 minutes if symptoms are refractory to treatment. Once epinephrine has been administered, the patient should be placed in the supine position with a high-flow oxygen supplement via a face mask. Intravenous access and volume replacement with normal saline should be administrated in cases with cardiovascular instability. Parenteral glucagon administration may be used in patients with anaphylaxis with no optimal response to epinephrine, especially in patients taking beta-blockers. Second-line medications, such as antihistamines and glucocorticoids, can be used to control reactions isolated to the skin or mucosa. Most anaphylaxis cases have symptom onset within 30 minutes of vaccination. However, it is suggested that if patients develop signs or symptoms of an allergic reaction after their observation time ends and they have left the vaccination location, they should be instructed to seek immediate medical care.

MONITORING AND DISCHARGE PLANS AFTER INITIAL MANAGEMENT

Patients presenting with respiratory symptoms should be closely monitored for at least 6-8 hours, and those presenting with hypotension require close monitoring for at least 12-24 hours. Before discharge, patients should be provided with a discharge sheet to manage late anaphylactic reactions and a prescription for an epinephrine autoinjector, antihistamines, or inhaled β_2 agonists based on individual symptoms.[45] All patients with anaphylaxis or suspected allergic reactions should be referred to an allergists for detailed assessment. Patients should not receive the second dose of the vaccine unless allergy specialists confirm that the vaccine did not induce an allergic reaction.

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SPECIAL CONSIDERATIONS IN ANAPHYLAXIS: COFACTORS AND BIPHASIC RESPONSE

In general, the severity of anaphylaxis can be increased by endogenous factors (sex, age, cardiovascular disease, mastocytosis, atopic disease, elevated tryptase, and ongoing infection) and exogenous factors (medications, including beta-blockers, angiotensin converting enzyme inhibitors, and non-steroidal anti-inflammatory drugs, physical activity, psychological burden, certain elicitors, and sleep deprivation).[45] Outcome and severity of anaphylactic reactions depend not only on the elicitor itself and its dose, but also on the presence of cofactors.[45] Recurrent anaphylaxis within 1 to 72 hours after resolution of an initial anaphylactic episode is called biphasic anaphylaxis.[64] The estimated incidence of biphasic anaphylaxis has been reported from <1% to 20%.[64,69] Risk factors for biphasic anaphylactic reactions include severe anaphylaxis and/or the need for more than 1 dose of epinephrine injection. Additional risk factors for biphasic anaphylaxis have been reported to be wide pulse pressures, unknown anaphylaxis trigger, cutaneous signs and symptoms, and drug trigger in children.[64] Although antihistamines and glucocorticoids have traditionally been used to prevent biphasic anaphylaxis, evidence for the benefits of these additional approaches is of very low certainty and did not offer clear support for this practice. Therefore, supplemental treatment for anaphylaxis, such as glucocorticoids and antihistamines, should never delay administration of epinephrine.[64] Cases of biphasic anaphylaxis after exposure to agents containing PEGs have been reported.[70] Therefore, the risk factors mentioned above and treatment issues of biphasic anaphylaxis must be considered in selection and management for COVID-19 vaccination. Further investigations of relevant risk identification and management approaches are required.

CONCLUSION

The novel coronavirus pandemic has led to widespread COVID-19 vaccination with monitoring of adverse events simultaneously all over the world. Although the majority of AEFIs are caused by protective immune responses stimulated by vaccines, uncommon severe allergic reactions, such as anaphylaxis, can also occur. Although the incidence of anaphylaxis is low, it is highly encouraged to report COVID-19 vaccination-associated anaphylaxis cases to national surveillance systems. This could be very helpful in providing reassurance to the general population by analyzing the exact incidence of anaphylaxis and potential risk factors. Knowledge on COVID-19 vaccination-related AEFIs, including anaphylaxis, is rapidly evolving and future recommendations will be updated with the acquisition of additional data. Our hope is that COVID-19 vaccine-associated anaphylaxis could be prevented and managed by risk stratification based on our local and global experiences.

SUPPLEMENTARY MATERIALS

Supplementary Table S1

Criteria for meeting Brighton case definition of anaphylaxis.[31]

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Supplementary Fig. S1

Logic to determine the level of diagnostic certainty according to body systems involved. Modified from the Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: Case definition companion guide: Brighton Collaboration; 2021 March 5. (Available from: https://brightoncollaboration.us/anaphylaxis-case-definition-companion-guide/; Accessed: May 9, 2021).

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Supplementary Fig. S1. Logic to determine the level of diagnostic certainty according to body systems involved. Modified from the Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: Case definition companion guide: Brighton Collaboration; 2021 March 5. (Available from: https://brightoncollaboration.us/anaphylaxis-case-definition-companion-guide/; Accessed: May 9, 2021).

Level 1	≥1 Skin (Major) and [≥1 RESP (Major) and/or ≥1 CV (Major)]
Level 2	≥1 Skin (Major) and [≥1 RESP (Minor) and/or ≥1 CV (Minor) ≥1 RESP (Major) and ≥1 CV (Major) ≥1 RESP (Major) and ≥1 minor (Skin, CV, GI, Lab) ≥1 CV (Major) and ≥1 minor (Skin, RESP, GI, Lab)
Level 3	≥1 RESP (Minor) and ≥minor from 2 different systems (Skin, CV, GI, Lab) ≥1 CV (Minor) and ≥minor from 2 different systems (Skin, RESP, GI, Lab)
Level 4	Reported anaphylaxis with insufficient evidence to meet any of levels of diagnostic certainty
Level 5	Not a case of anaphylaxis

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