EAACI POSITION PAPER

Management of anaphylaxis due to COVID-19 vaccines in the elderly

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Abbreviations: ACE inhibitors, angiotensin converting enzyme inhibitor; ABCDE, Airway, Breathing, Circulation, Disability, Exposure; ARIA, Allergic Rhinitis and its Impact on Asthma; AT-2-antagonists, Angiotensin II receptor type 2; EAACI, European Academy of Allergy and Clinical Immunology; EuGMS, European Geriatric Medicine Society; ICU, intensive care unit; IM, intramuscular; IV, intravenous.
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1 INTRODUCTION

Older adults (over 65 years of age), especially men and/or those with diabetes, hypertension, and/or obesity, are prone to severe COVID-19. In some countries, older adults, particularly those residing in nursing homes, have been prioritized to receive COVID-19 vaccines due to high risk of death. In very rare instances, the COVID-19 vaccines can induce anaphylaxis, and the management of anaphylaxis in older people should be considered carefully. An ARIA-EAACI-EuGMS (Allergic Rhinitis and its Impact on Asthma, European Academy of Allergy and Clinical Immunology, and European Geriatric Medicine Society) Working Group has proposed some recommendations for older adults receiving the COVID-19 vaccines. Anaphylaxis to COVID-19 vaccines is extremely rare (from 1 per 100,000 to 5 per million injections). Symptoms are similar in younger and older adults but they tend to be more severe in the older patients. Adrenaline is the mainstay treatment and should be readily available. A flowchart is proposed to manage anaphylaxis in the older patients.

KEYWORDS
adrenaline, anaphylaxis, COVID-19 vaccines, older (adults/people)

2 ANAPHYLAXIS TO COVID-19 VACCINES

Several adverse reactions are reported for the COVID-19 vaccines. They are classified into very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data). Currently, due to lack of sufficient confirmed data, anaphylaxis/hypersensitivity is included under the "not known" category.

Following the approval of the COVID-19 vaccine BNT162b2 (Pfizer-BioNTech), several severe anaphylaxis cases occurred within the first few days of public vaccination. A first analysis of the data reported in the Vaccine Adverse Events Reporting System (VAERS, https://vaers.hhs.gov) of the United States showed an incidence of 11.1 cases of anaphylaxis per million doses of the COVID-19 vaccine BNT162b2. The VAERS report of 18 January 2021 reports a rate of 5 anaphylaxis cases per million doses administered for the BNT162b2 and 2.8 per million for the Moderna vaccine. Polyethylene glycol (PEG) contained in PEGylated excipients has been proposed to be an
ALLERGIC REACTIONS OF COVID-19 VACCINES IN OLDER PEOPLE

Allergic reactions of COVID-19 vaccines are less frequent in older people compared to younger adults. Severe allergic reactions such as anaphylaxis are more common in older adults. However, the severity of anaphylaxis in older people is decreased compared to younger adults. Adrenalin was administered in 30% of older patients. Hospitalization was required in 60%, and 19% of older patients were treated in an intensive care unit (ICU).

The COVID-19 vaccines will be administered to billions of individuals worldwide and there are raised concerns that severe adverse reactions might sometimes occur. With the current information, the European Academy of Allergy and Clinical Immunology (EAACI) stated its position for preliminary recommendations that are to be revised as soon as more data emerge.

**3 | SYMPTOMS OF ANAPHYLAXIS IN OLDER PEOPLE**

The European Anaphylaxis Registry includes data from 1,123 patients over 65 years of age with anaphylactic reactions. These data are provided by tertiary referral centers specialized in allergology and/or dermatology in Austria, Bulgaria, France, Germany, Italy, Poland, Spain, and Switzerland. In the registry, anaphylactic symptoms were similar in younger adults and older people, but their frequency differed: cardiovascular symptoms occurred more frequently in older people (80% compared to 75% in adults). This confirmed previous observations that in patients presenting with anaphylaxis at the Emergency Department, an age of 65 or older was associated with an increased likelihood of cardiovascular symptoms. A major cardiovascular symptom was loss of consciousness (33%), while dizziness and tachycardia were more prevalent in younger adults. Cardiac arrest occurred in 3% of older persons and in 2% of younger adults. The skin was the most frequently involved organ system. Urticaria and angioedema are two clinical manifestations of anaphylaxis and usually appear before other symptoms. The severity of anaphylactic reactions in older patients without skin symptoms was increased in comparison to younger adults. Gastrointestinal symptoms occurred in a similar proportion in both groups. The respiratory system, especially dyspnea, was less frequently affected in older persons (63% compared to 70% in younger adults). However, cyanosis, syncope, and dizziness are highly predictive of shock development in older people. Severe anaphylactic reactions, including grade III (47%) and grade IV (4%) of the anaphylaxis Ring and Messmer classification, were more prevalent in people aged 65+.

This registry indicates that symptoms are similar in younger/middle-aged adults and older people but that they are more severe in the older age group (Figure 1). Adrenalin was administered in 30% of older patients. Hospitalization was required in 60%, and 19% of older patients were treated in an intensive care unit (ICU). Significantly more older people as compared to younger and middle-aged adults with grade II and III anaphylaxis needed hospitalization and ICU care (Figure 1 and Table 1). Considering different triggers of anaphylaxis, higher age has been consistently associated with increased rates of fatal drug anaphylaxis. This may be related to an increased prevalence of drug allergy following an increased drug exposure, and/or to an increased underlying cardiovascular vulnerability.

Anaphylaxis is usually graded according to Ring and Messmer (Table 1), although there are proposals for new grading systems. However, WHO and regulatory authorities recommend the use of the Brighton Collaboration Anaphylaxis Working Group for pharmacovigilance registers.

Classification according to the most severe symptom is mandatory.

**4 | RISK FACTORS FOR SEVERITY OF ANAPHYLAXIS IN OLDER PEOPLE**

**4.1 | Comorbidity**

In the European Anaphylaxis Registry, older age (excluding the confounding factor of concomitant cardiovascular or other diseases) and concomitant mastocytosis were the most important predictors for an increased risk of severe anaphylaxis. Hereditary alpha-tryptasemia is another risk factor. Anaphylaxis is more severe and has an increased risk of death in patients with coronary artery disease because both the number of mast cells and the production of their vasoactive mediators are increased in ischemic cardiomyopathy. In addition, atherosclerotic lesions make coronary arteries more susceptible to the effects of mast cell- and basophil-derived mediators, and individuals with an underlying vascular illness less tolerant to hypoxia and hypotension during anaphylaxis.
In older people from the registry, cardiovascular diseases, thyroid diseases, and cancer were more common than in younger adults.  

4.2 Polypharmacy and medications used in older people

In the European Anaphylaxis Registry, medications associated with an increased risk of severe anaphylaxis risk cofactors—such as ACE inhibitors (angiotensin-converting enzyme inhibitor), AT-2-antagonists (Angiotensin II receptor type 2), β-blockers, acetylcholine, and proton pump inhibitors—were significantly more frequently prescribed in older people (57%) than in younger adults (18%).

Independent of the age of the patient, β-blockers and ACE inhibitors administered close to allergen immunotherapy increased the risk of developing severe anaphylaxis, while aspirin and AT-2 did not. However, a systematic review with low-quality evidence showed that β-blockers and ACE inhibitors increased the severity of anaphylaxis, due to differences in confounders, in particular, cardiovascular diseases.

It is important to highlight the significant number of older patients who are being treated with anxiolytics, antidepressants, hypnotics, and other drugs that can act on the central nervous system and alter the individual person’s recognition and perception of the symptoms and signs of anaphylaxis.

5 MANAGEMENT OF ANAPHYLAXIS IN OLDER PEOPLE

5.1 The ABCDE approach

The Airway, Breathing, Circulation, Disability, Exposure (ABCDE) algorithm is applicable in all clinical emergencies for immediate assessment and treatment (Figure 2). If anaphylaxis is suspected, every patient should receive rapid evaluation of vital functions via ABCDE, and problems should be addressed in a targeted manner.

The aims of the ABCDE approach are:

- To provide life-saving treatment.
- To break down complex clinical situations into more manageable parts.
- To serve as an assessment and treatment algorithm.
- To establish common situational awareness among all treatment providers.
- To buy time to establish a final diagnosis and treatment.

### TABLE 1 Symptoms and anaphylaxis grades (from Ring and Messmer)

| Grades | Skin          | Abdomen           | Airways            | Cardiovascular system       |
|--------|---------------|--------------------|--------------------|------------------------------|
| I      | Itch          | Nausea             | Rhinorrhea         | Tachycardia (>120/min)       |
| II     | Flush         | Cramps             | Hoarseness         | Hypotension (<90 mm Hg syst) |
|        | Urticaria     |                    | Dyspnea            | Arrhythmia                   |
|        | Angioedema    |                    |                    |                              |
| III    | Vomiting      | Laryngeal edema    | Bronchospasm       | Shock                        |
|        | Defecation    |                    | Cyanosis           |                              |
| IV     |               |                    | Respiratory arrest | Cardiac arrest               |

C: circulation

- Look, listen and feel
- Head tilt and chin lift

B: Breathing

- Heart rate
- Capillary refill time

D: Disability

- Alert
- Voice responsive
- Pain responsive
- Unresponsive

E: Exposure

- Remove clothing after adrenaline injection

FIGURE 2 The ABCDE approach in emergencies (from)
**VACCINATION**

observe at least 15 minutes
(monitor vital signs and observe at least 30 minutes in patients at high risk)

if patient develops the following symptoms

- Generalized hives, generalized pruritus, generalized flushing, face angioedema
- Shortness of breath, wheezing, stridor
- Syncope, incontinence, blood pressure drop
- Swollen tongue-uvula, Cramping abdominal-Vomiting, diarrhea

** Urgently**

Put the patient in the reclining position with legs up

**Administer EPINEPHRINE (ADRENALINE)**

0.3 mg in auto-injector
OR
0.5 mg per dose (of 1:1000 (1 mg/ml) of aqueous solution)
intramuscularly in the mid-outter thigh quadriceps muscle

**AND**

Antihistamines
oral/parenteral
Glucocorticoids
oral/parenteral
observation 4 hr

**Secure intravenous accesses**
and start infusion with 0.9% NaCl (10-20 ml/min)
Clear the airways
Administer Oxygen via facial mask (at least 10 liters/min)
Monitor vital signs

**Discharge 4-8 hrs after full resolution**
Refer to the allergy center for the workup

**Resolved**

CALL emergency assistance depending on your location (911, 112, ICU team)

**Not resolved**

**Blood pressure drop**

2000-3000 ml of 0.9% NaCl intravenously in 10-20 min

**No improvement**

in 5-10 min:

**REPEAT EPINEPHRINE (ADRENALINE)**
intramuscularly

**Bronchospasm**

Salbutamol
4-10 puffs via large volume spacer

**Advise against second planned SARS-CoV-2 vaccination until clarified by the allergy centre**
5.2 | Adrenaline in older people

Guidelines from EAACI\textsuperscript{43} and the World Allergy Organization\textsuperscript{44} recommend prompt intramuscular injection of adrenaline as first-line therapy for anaphylaxis. Adrenaline can counteract most severe symptoms of anaphylaxis in older people.\textsuperscript{22} Intramuscular administration of adrenaline, if possible using a ready-to-use preparation or auto-injector, is recommended. The initial dose is 0.3–0.5 ml of a 1:1000 dilution (1 mg/ml). The patient should then be monitored, and, if ineffective, the administration can be repeated after at least a 5-minute interval.\textsuperscript{22} The subcutaneous route should not be used because the vasoconstrictor effect of adrenaline injected into the subcutaneous tissue potentially delays adrenaline absorption.\textsuperscript{45} The intra-vascular route should be avoided since most cardiovascular adverse events of adrenaline appear to occur via this route.\textsuperscript{46} Intravenous continuous infusion should only be given to patients not responding to intramuscular injection under careful ECG monitoring.\textsuperscript{43}

During an anaphylactic reaction occurring in patients with cardiovascular disease, the benefits versus the harms of adrenaline injection should be weighed carefully. The presence of cardiovascular disease does not exclude the use of adrenaline in anaphylaxis since no other medications have life-saving effects in this medical emergency.\textsuperscript{49} There are no absolute contraindications to the prescription of self-injectable adrenaline in older patients or in those with a cardiovascular disease who are at risk of anaphylaxis. Serious adverse effects, such as ventricular arrhythmias, hypertension, or myocardial ischemia, have not been reported following the use of adrenaline auto-injectors.\textsuperscript{47} However, older patients with anaphylaxis seem to be more likely to experience a cardiac adverse event after adrenaline injection, with those older than 80 years having the highest risk.\textsuperscript{48}

5.3 | Other treatments

Regular intake of multiple medications is frequent in older patients (polypharmacy). Co-medication may modify the evolution of anaphylaxis, and also its management. The therapeutic effect of adrenaline may be blunted by β-blockers. In this situation, epinephrine is not effective, glucagon can be administered intravenously, as it has a mechanism of action independent of the β-receptors.\textsuperscript{49,50} Older patients may be using sedating or psychotropic drugs, and these could affect the recognition and perception of anaphylactic symptoms.\textsuperscript{51}

5.4 | Equipment needed to perform vaccination safely in older people

- Vaccination should always be performed in a healthcare setting, which may be a mobile unit.
- All necessary aids and rescue drugs must be available in the vaccination setting.
- All medical personnel assigned should receive training and be able to immediately recognize and manage an emergency situation, including anaphylaxis.

6 | PRACTICAL PREVENTION AND MANAGEMENT OF AN ANAPHYLACTIC REACTION

As proposed in three ARIA-EAACI Position Papers on anaphylaxis to COVID-19 vaccines, recommendations have been adapted for older patients.\textsuperscript{21,28,29}

- Patients with a history of allergic diseases should not be excluded from the vaccines as the exclusion of all these patients from vaccination may have a significant impact on reaching the goal of herd immunity. However, without any allergist advice, a previously known allergy to the substances contained in the vaccines presents a contraindication, as well as a reaction to the first dose of the COVID-19 vaccine, which presents a contraindication for administering the second dose. A previous severe anaphylactic reaction to other vaccines or drugs does not represent a contraindication. However, consultation with an allergist may be helpful to assess the individual situation.
- Healthcare practitioners vaccinating against COVID-19 are required to be sufficiently prepared to recognize and treat anaphylaxis properly, particularly since older patients tend to have more severe anaphylactic symptoms. If a severe reaction occurs, hospitalization may be considered more readily than for younger adults after first-aid action.
- After vaccine administration, a mandatory observation period of at least 15 minutes is necessary for all individuals. This should include the possibility to administer adrenaline intra-muscularly (IM) in a sufficient dose. The observation period should be extended to 30 minutes for patients deemed at putative risk for anaphylactic reaction.
- The person injecting the vaccine should be capable of managing an anaphylaxis reaction at first instance and should have all the relevant medication for management readily available.
- In the case of COVID-19 vaccines, there will be new procedures outside of the medical setting. Thus, it is imperative that the relevant emergency medication (adrenaline and saline) is readily available at the setting—particularly in nursing homes or vaccine caravans—and that training of the personnel has been accomplished.
- The EAACI recently published the practical management of anaphylaxis (Figure 3).\textsuperscript{29}
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REFERENCES

1. Esteve A, Permuyer I, Boertien D, Vaupel JW. National age and co-residence patterns shape COVID-19 vulnerability. Proc Natl Acad Sci U S A. 2020;117(28):16118-16120.
2. Giangreco G. Case fatality rate analysis of Italian COVID-19 outbreak. J Med Virol. 2020;92(7):919-923.
3. Mantovani A, Dalbeni A, Beatrice G. Coronavirus disease 2019 (COVID-19): we don’t leave women alone. Int J Public Health. 2020;65(3):235-236.
4. Iaccarino G, Grassi G, Borghi C, et al. Age and multimorbidity predict death among COVID-19 patients: results of the SARS-RAS study of the Italian Society of Hypertension. Hypertension 2020;76(2):366-372.
5. Finucane FM, Davenport C. Coronavirus and obesity; could insulin resistance mediate the severity of COVID-19 infection? Front Public Health. 2020;8:184.
6. Klein SL, Dhakal S, Ursin RL, Deshpande S, Sandberg K, Mauvais-Jarvis F. Biological sex impacts COVID-19 outcomes. PLoS Pathog. 2020;16(6):e1008570.
7. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ. 2020;11(1):29.
8. Barek MA, Aziz MA, Islam MS. Impact of age, sex, comorbidities and clinical symptoms on the severity of COVID-19 cases: a meta-analysis with 55 studies and 10014 cases. Hellyon. 2020;6(12):e05684.
9. Scortichini M, Schneider Dos Santos R, De' Donato F, et al. Excess mortality during the COVID-19 outbreak in Italy: a two-stage interrupted time-series analysis. Int J Epidemiol. 2021;49(6):1909-1917.
10. Pranata R, Henriina J, Lim MA, et al. Clinical frailty scale and mortality in COVID-19: A systematic review and dose-response meta-analysis. Arch Gerontol Geriatr. 2020;93:10432.
11. Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health. 2020;5(8):e444-e451.
12. McMichael TM, Currie DW, Clark S, et al. Epidemiology of COVID-19 in a long-term care facility in King County, Washington. N Engl J Med. 2020;382(21):2005–2011.
13. Blain H, Rolland Y, Tuillon E, et al. Efficacy of a test-retest strategy in residents and health care personnel of a nursing home facing a COVID-19 outbreak. J Am Med Dir Assoc. 2020;21(7):933-936.
14. Telford CT, Onwubiko U, Holland D, et al. Mass screening for SARS-CoV-2 infection among residents and staff in twenty-eight long-term care facilities in Fulton County, Georgia. medRxiv 2020. doi:10.1101/2020.07.01.20144162.
15. He M, Li Y, Fang F. Is there a link between nursing home reported quality and COVID-19 cases? Evidence from California skilled nursing facilities. J Am Med Dir Assoc. 2020;21(7):905-908.
16. Grabowski DC, Mor V. Nursing home care in crisis in the wake of COVID-19. JAMA 2020;324(1):23.
17. Gordon AL, Goodman C, Achterberg W, et al. Commentary: COVID in care-homes-challenges and dilemmas in healthcare delivery. Age Ageing 2020;49(5):701-705.
18. Blain H, Rolland Y, Schols J, et al. August 2020 interim EuGMS guidance to prepare European long-term care facilities for COVID-19. Eur Geriatr Med. 2020;11(6):899-913.
19. Banerji A, Wickner PG, Saff R, et al. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and approach. J Allergy Clin Immunol Pract 2021;9(4):1423-1437.
26. Cabanillas B, Akdis C, Novak N. Allergic reactions to the first COVID-19 vaccine: is polyethylene glycol (PEG) the culprit? Br J Anaesth. 2021;126(3). https://doi.org/10.1016/j.bja.2020.12.020. [Epub ahead of print].

27. Klimek L, Jutel M, Akdis CA, et al. ARIA-EAACI statement on severe allergic reactions to COVID-19 vaccines - an EAACI-ARIA position paper. Allergy. 2021;76(6):1624-1628.

28. Klimek L, Novak N, Cabanillas B, Jutel M, Bousquet J, Akdis CA. Anaphylaxis and COVID-19 vaccine safety update. Advisory Committee on Immunization Practices (ACIP) January 27, 2021. National Center for Immunization and respiratory diseases CDC https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01-06-COVID-Shimabukuro.pdf. 2021.

29. Sokolowska M, Eiwegger T, Ollert M, et al. EAACI statement on the possible involvement of polyethylene glycol and IgG-mediated complement activation. Allergy 2021; https://doi.org/10.1111/all.14794.

30. Aurich S, Dolle-Bierke S, Francuzik W, et al. Anaphylaxis in elderly patients-data from the European anaphylaxis registry. Front Immunol. 2019;10:750.

31. Campbell RL, Hagan JB, Li JT, et al. A Rapid review of advanced life support guidelines for cardiac arrest associated with anaphylaxis. Resuscitation 2021;78(8):2888-2890.

32. Rukma P. Glucagon for refractory anaphylaxis. Am J Ther. 2021;24(6):e755-e756.

33. Lieberman PL. Recognition and first-line treatment of anaphylaxis. Am J Med. 2014;127(1 Suppl):S6-11.