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Abstract

Older adults, 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 prioritised 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.

Key words: COVID-19 vaccines, anaphylaxis, older (adults/people), adrenaline,

Introduction

Older adults (over 65 years of age), ^{1,2} especially men and/or those with diabetes, ³ hypertension ⁴ and/or obesity ⁵, are prone to severe COVID-19. Older men have more severe COVID-19 infections than women of the same age. ⁶⁻⁹Frailty is a risk factor for mortality from COVID-19 ^{10,11}. The population residing in nursing homes generally includes subjects who are both old and suffering from multimorbidity. Residential context increases social contacts in the same setting. A large number of COVID-19-related deaths have been reported in nursing homes ¹²⁻¹⁶, and recommendations to control COVID-19 in these settings have been issued. ¹⁶⁻¹⁸ Discharge from hospitals to nursing homes also puts residents at risk.

In some countries, older adults, particularly those residing in nursing homes, have been prioritised to receive COVID-19 vaccines due to high risk of death.

There are several peculiarities of the immune response to COVID-19 vaccines in older people. For example, vaccine-induced local and systemic reactogenicity - such as pain, fatigue, headache or fever - was generally lower in older recipients of mRNA-based COVID-19 than in younger ones during the clinical trial phases.

However, in very rare instances, COVID-19 vaccines can induce anaphylaxis ¹⁹⁻²¹. Anaphylaxis in older people is not uncommon and is often more severe than in younger adults ²². Vaccinations are known to cause anaphylaxis, although very rarely. ^{23,24}The benefit of the vaccination clearly outweighs the risk of severe anaphylaxis reaction to the COVID-19 vaccines, even in older people suffering from severe allergic diseases.

The staff responsible for vaccinating in nursing homes may come from different educational backgrounds and include primary care staff or geriatricians who may not have had much experience in the management of anaphylaxis. Potential rapid evaluation and differential diagnosis of symptoms are therefore important. Moreover, in many countries, the equipment is insufficient in nursing homes (e.g., lack of emergency medication, no possibility to provide IV therapy or infusion).

An ARIA-EAACI-EuGMS (Allergic Rhinitis and its Impact on Asthma, European Academy of Allergy and Clinical Immunology, European Geriatric Medicine Society) Working Group has proposed some recommendations for older adults receiving the COVID-19 vaccines.

1- Anaphylaxis to COVID-19 vaccines

Several adverse reactions are reported for the COVID-19 vaccines. They are classified into very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), 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 are 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.^{19,21} 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 January 18, 2021 reports a rate of 5 anaphylaxis per million doses administered for the BNT162b2 and 2.8 per million for the Moderna vaccine.²⁵ Polyethylene glycol (PEG) contained in PEGylated excipients has been proposed to be an allergenic component of the vaccines.²⁶ The median age of patients with anaphylaxis was 40 years (range = 27–60 years), and 90% of the reported cases occurred in women²⁷. Allergic reactions often, but not always, occurred in people with a previous history of severe allergic reactions, many of them carrying an adrenaline (epinephrine) auto-injector. Moreover, during the clinical trial phases, vaccine-induced local and systemic reactogenicity, such as pain, fatigue, headache or fever, were generally lower in older recipients of the mRNA-based COVID-19 vaccine than in younger ones. Similar reactions occurred with the Moderna vaccine albeit at a lower frequency (around 2.5 per million), but possibly more severe²⁸.

The COVID-19 vaccines will be administered to billions of individuals worldwide and there are raised concerns that severe adverse reactions - requiring continuous alertness and careful management - 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.^{21, 27, 29}

2- 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 centres specialised in allergology and/or dermatology in Austria, Bulgaria, France, Germany, Italy, Poland, Spain and Switzerland.³⁰ 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.³¹ 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 dyspnoea, 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,³² 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). Adrenaline was administered in 30% of older patients. Hospitalisation 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 hospitalisation and ICU care ³² (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.³³

Anaphylaxis is usually graded according to Ring and Messmer³² (Table 1), although there are proposals for new grading systems ^{34,35}. However, WHO and regulatory authorities recommend the use of the Brighton Collaboration Anaphylaxis Working Group for pharmacovigilance registers.²³

Classification according to the most severe symptom is mandatory.

3- Risk factors for severity of anaphylaxis in older people

a- Comorbidity

In the European Anaphylaxis Registry, older age (excluding the confounding factor of concomitant cardiovascular or other diseases) and concomitant mastocytosis³⁸ were the most important predictors for an increased risk of severe anaphylaxis. ^{30,37,39,40} 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 ischaemic cardiomyopathy. In addition, atherosclerotic lesions make coronary arteries more susceptible to

the effects of mast cell- and basophil-derived mediators,⁴¹ 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.³⁷

b- 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%).³⁹

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.³⁹ 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 diseases⁴².

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.

4- Management of anaphylaxis in older people

a. The ABCDE approach

The Airway, Breathing, Circulation, Disability, Exposure (ABCDE) algorithm is applicable in all clinical emergencies for immediate assessment and treatment⁴³ (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 are⁴³:

- 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.

b. Adrenaline in older people

Guidelines from EAACI⁴⁴ and the World Allergy Organization⁴⁵ recommend prompt intramuscular injection of adrenaline as first-line therapy for anaphylaxis. Adrenaline can counteract most severe symptoms of anaphylaxis in older people²². 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 interval²². The subcutaneous route should not be used because the vasoconstrictor effect of adrenaline injected into the subcutaneous tissue potentially delays adrenaline absorption⁴⁶. The intra-vascular route should be avoided since most cardiovascular adverse events of adrenaline appear to occur via this route⁴⁷. Intravenous continuous infusion should only be given to patients not responding to intramuscular injection under careful ECG monitoring⁴⁴.

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.⁴¹ 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 autoinjectors.⁴⁸ 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.⁴⁹

c. 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, if epinephrine is not effective, glucagon can be administered intravenously, as it has a mechanism of action independent of the β -receptors.^{50,51} Older patients may be using sedating or psychotropic drugs, and these could affect the recognition and perception of anaphylactic symptoms.⁵²

d. 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 recognise and manage an emergency situation, including anaphylaxis.

5- 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.^{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 an 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 recognise and treat anaphylaxis properly, particularly since older patients tend to have more severe anaphylactic symptoms. If a severe reaction occurs, hospitalisation 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)²⁹

Accepted Article

Table 1: Symptoms and anaphylaxis grades (from Ring and Messmer^{32,36})

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

Figure 1: Hospitalisations and intensive care units in older people (from ³⁰)

Grades of anaphylaxis according to Ring and Messner

Old age people: N=1,123, adults: N=5,768

***: p<0.001

In this study, hospitalization and ICU were differentiated between adults and old age people

Figure 2: The ABCDE approach in emergencies (from ⁴³)

Figure 3: Diagnosis and management of severe allergic reactions after COVID-19 vaccination in the vaccination center (from²⁹)

Abbreviations

ACE-inhibitors (angiotensin converting enzyme inhibitor)

Airway, Breathing, Circulation, Disability, Exposure (ABCDE)

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

Conflict of interest :

IA reports is Associate Editor Allergy and CTA.

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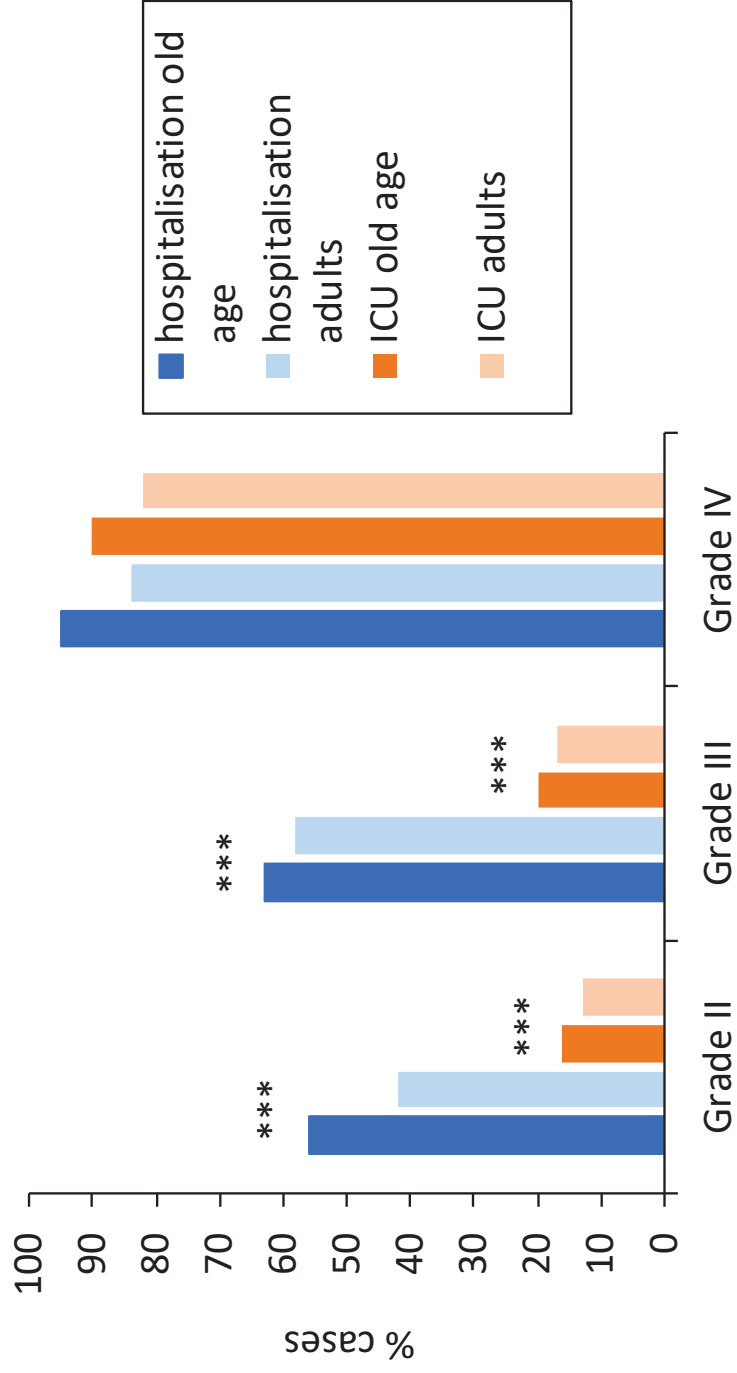
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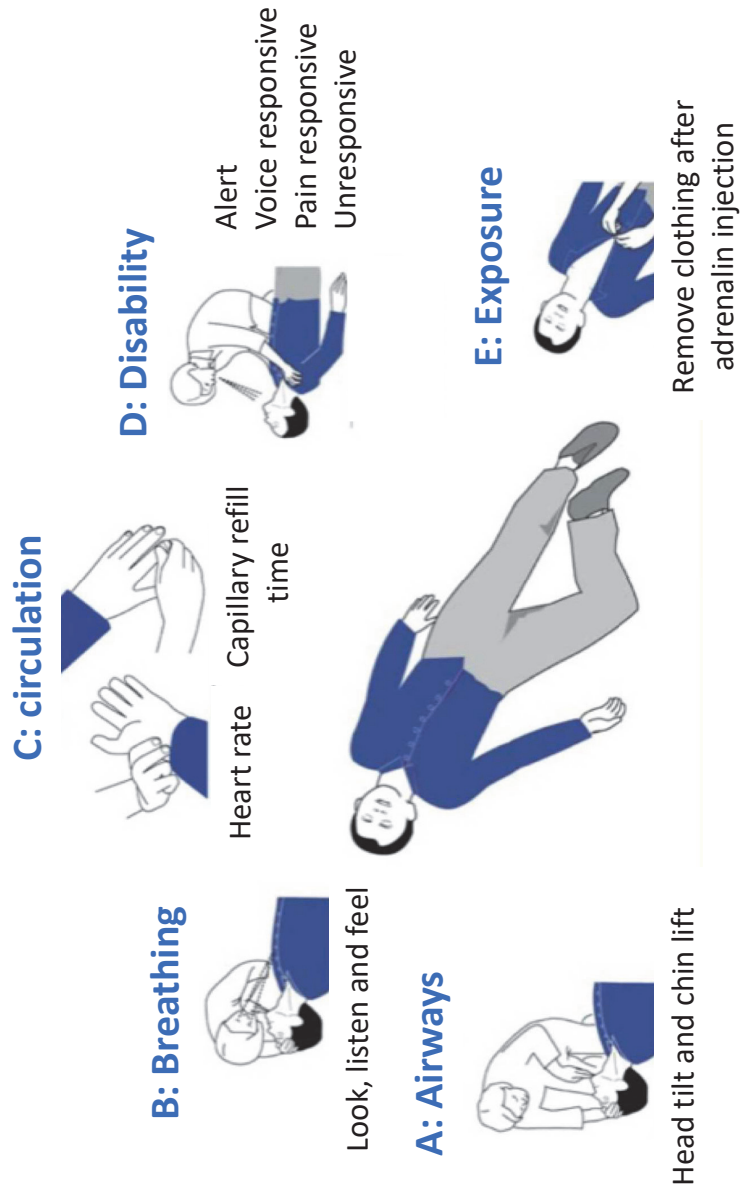


Fig. 1. Diagnosis and management of severe allergic reactions after COVID-19 vaccination in the vaccination center

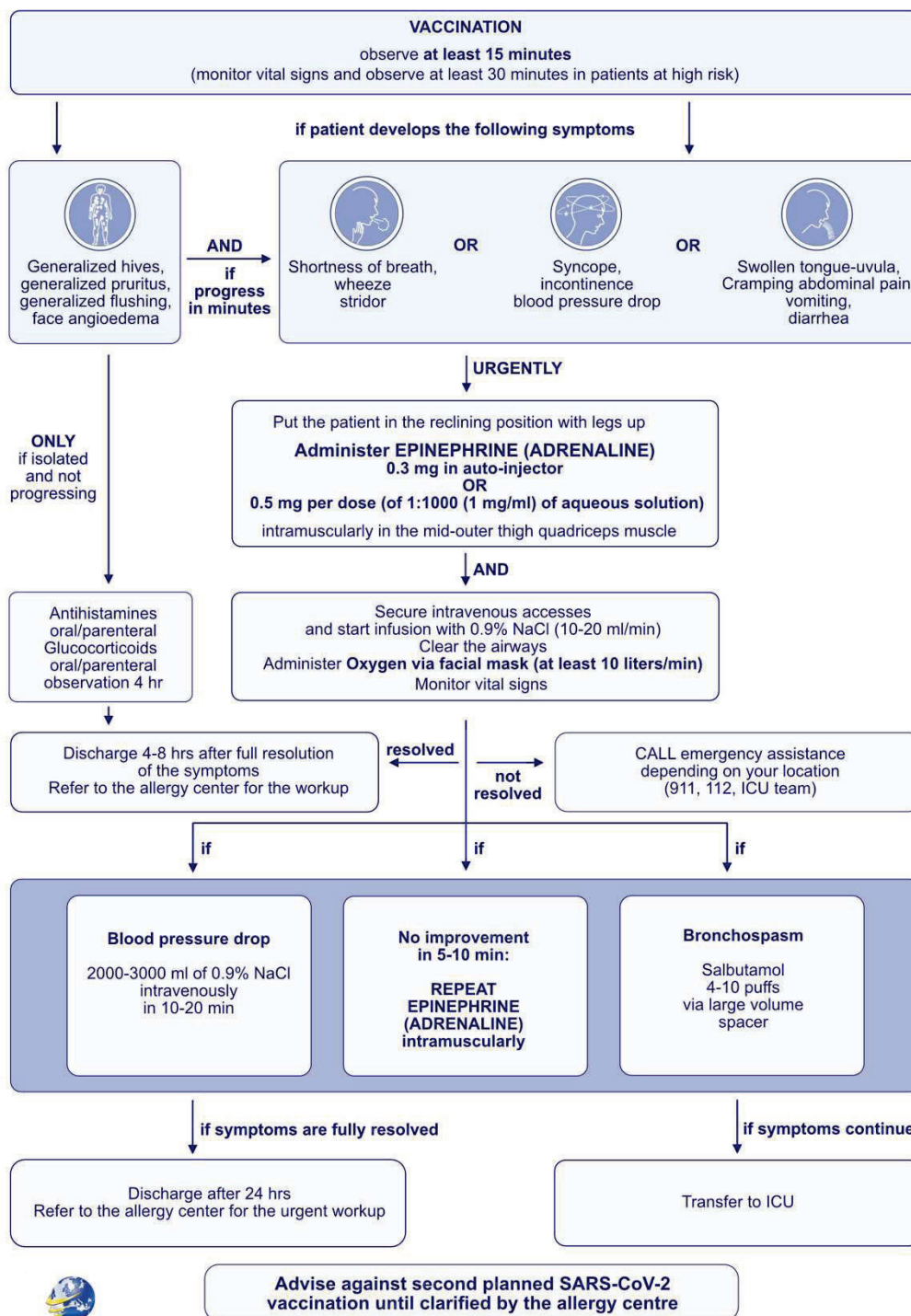


Figure 1_Sokolowska et al.