Practical recommendations for the allergological risk assessment of the COVID-19 vaccination – a harmonized statement of allergy centers in Germany

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Introduction

Vaccination is a very efficient method to prevent pathogen-related diseases. Smallpox vaccination, for example, has helped to completely eradicate this potentially life-threatening disease. In Germany, the current vaccination recommendations for the population are issued by the Standing Commission on Vaccination (StiKo) and are updated regularly [1]. Severe allergic vaccination reactions are very rare and can be caused by the vaccine itself (very rare) or the ingredients (adjuvants, antibiotics, hen’s egg, carriers, preservatives)

Abstract. Severe allergic reactions to vaccines are very rare. Single severe reactions have occurred worldwide after vaccination with the new mRNA-based COVID-19 vaccines. PEG2000 is discussed as a possible trigger. We provide guidance on risk assessment regarding COVID-19 vaccination in patients with allergic diseases and suggest a standardized, resource-oriented diagnostic and therapeutic procedure. Reports of severe allergic reactions in the context of COVID-19 vaccination can be made via www.anaphylaxie.net using an online questionnaire.
Practical recommendations for COVID-19 vaccination

The incidence of severe immediate allergic reactions after vaccination varies from 1:100,000 to 1:1 million depending on the vaccine and the population studied [2]. Since the outbreak of the COVID-19 pandemic, several vaccines have been developed worldwide, with two mRNA-based products licensed in Europe to date. An additional adenovirus-based vaccine is currently in use in the United Kingdom (Table 1).

Since the approval of the mRNA-based vaccines, several case series have been published from the United Kingdom and the United States regarding individuals who have experienced severe general reactions in the setting of COVID-19 vaccination [3]. From December 14 – 23, 2020, surveillance by the Vaccine Adverse Event Reporting System identified 21 cases of anaphylaxis after administration of 1,893,360 first doses of Pfizer-BioNTech COVID-19 vaccine (11.1 cases per million doses). In Germany, the Paul Ehrlich Institute (PEI) has received reports of 17 anaphylactic reactions as of January 10, 2021 [4]. All individuals reported to date with adverse events related to COVID-19 vaccination due to suspected allergy or intolerance have survived the reaction without harm.

Polyethylene glycol (PEG) is discussed as the trigger of the reactions [5]. It is bound to a liposomal matrix, which is a nanoparticle that coats the viral mRNA of the COVID-19 vaccine. The PEG with a molecular weight of 2,000 (PEG2000) serves as a stabilizer to prevent premature degradation of the nanoparticles by the mononuclear phagocytosis system, also as a solubilizer during the transition of the particles into the intracellular cytosol due to its hygroscopic properties, and as an adjuvant due to its immunogenic potential [6]. PEGs are produced via polymerization of ethylene oxide. Another name for PEG is macrogol. Possible cross-reactions to polysorbate 80 (polyoxyethylene-20-sorbitan monooleate, low molecular weight PEG, 1,310 Dalton, CAS 9005-65-6, Tween 80 and E-433), which has recently been identified primarily as an anaphylaxis inducer after administration of biologicals, must be considered [7, 8, 9].

Hypersensitivity to PEG is very rare, especially considering its widespread use in numerous everyday products (cosmetics, medications, laxatives, lozenges) [10, 11, 12, 13]. Various allergic manifestations such as late reactions like allergic contact dermatitis, but also contact urticaria and anaphylaxis as immediate reactions have been described. In the anaphylaxis registry, 6 PEG cases and 1 polysorbate case have been registered so far, resulting in a percentage for PEG and polysorbate of 0.3% (7/2,350) for drug-induced anaphylaxis [14].

Practical recommendations

After the British authority issued a warning regarding the use of the vaccine in patients with severe allergies following the occurrence of 2 severe allergic reactions after vaccination, there were critical statements from the allergy societies and subsequently more concrete assessments from the Euro-

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Table 1. Ingredients of the vaccines discussed in the text.

| AstraZeneca AZD1222 | BioNTech BNT162b2 | Moderna mRNA-1273 |
|---------------------|-------------------|------------------|
| L-Histidine         | (-(4-hydroxybutyl)azanediyd) bis (hexane-6,1-diyl)(bis(2-hexyldecanoate) (ALC-0315) | SM-102, 1,2-dimyrtoylrac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG) |
| L-Histidine hydrochloride monohydrate | 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159) | -Cholesterol |
| Magnesium chloride hexahydrate   | 1,2-Distearyl-sn-glycero-3-phosphocholine (DSPC) | 1,2-distearyl-sn-glycero-3-phosphocholine (DSPC) |
| Polysorbate 80   | Cholesterol | Tromethamine (-HCl) |
| Ethanol            | Potassium chloride | Acetic acid |
| Sucrose            | Potassium dihydrogen phosphate | Sodium acetate |
| Sodium chloride   | Sodium chloride | Sucrose |
| Disodium edetate dihydrate | Disodium phosphate dihydrate | Water for injections |
| Water for injections | Water for injections | SM-102, 1,2-dimyrtoylrac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG) |
| - ((4-hydroxybutyl)azanediyd) bis (hexane-6,1-diyl)(bis(2-hexyldecanoate) (ALC-0315) | -Cholesterol | -Sodium acetate |
| - 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159) | -Potassium dihydrogen phosphate | -Sucrose |
| - 1,2-Distearyl-sn-glycero-3-phosphocholine (DSPC) | -Sodium chloride | -Water for injections |
| - Cholesterol | -Disodium phosphate dihydrate | -Water for injections |
| - Potassium chloride | -Sodium chloride | -Water for injections |
| - Sodium chloride | -Disodium phosphate dihydrate | -Water for injections |
| - Disodium edetate dihydrate | -Sodium chloride | -Water for injections |
| - Water for injections | -Disodium phosphate dihydrate | -Water for injections |
| - Water for injections | -Sodium chloride | -Disodium phosphate dihydrate |
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| - Water for injections | -Sodium chloride | -Disodium phosphate dihydrate |
The allergological diagnostic work-up (Figure 1) includes, after a thorough history, the determination of basal tryptase, total IgE, and sIgE (depending on the history e.g. of latex, ethylene oxide, α-Gal or gelatine, CCD). Certified test methods for the determination of IgE antibodies against PEG2000 (or IgM antibodies), which are thought to play a role in triggering complement-mediated hypersensitivity reactions to PEG [16], are currently not available. A basophil activation test can be considered, but again, no certified and validated test systems are currently available.

Individual testing of a given patient may be considered for skin testing, which should be performed in a facility familiar with the management of severe allergic reactions. Since there are no approved test substances, a prick test can be performed with the respective vaccine solution (pure, if available – e.g., residual vaccine) as well...
as with PEG2000 and polysorbate 80 (titrated 10% and 1%). However, it is not yet known whether a negative prick test actually has sufficient positive or negative predictive power for a given vaccine to determine the risk of a severe systemic general reaction. Intracutaneous testing beyond this, and only if the prick tests are negative, can be considered after critically weighing the benefits and risks, with substances that can be used for this purpose. In the literature, severe, and in individual cases fatal, allergic reactions have been reported during the course of intracutaneous testing [10].

The systemic immediate reactions reported so far in the context of COVID-19 vaccination may be caused by different pathomechanisms. Besides IgE-mediated reactions, non-IgE-mediated mechanisms via the MAS-related G protein-coupled receptor-X2 (MRGPRX2) or complement-dependent activation pathways (complement activation-related pseudoallergy = CARPA) may play a role which cannot necessarily be detected by means of a prick test. The indication for intracutaneous testing should therefore be made strictly as described above, since firstly severe allergic reactions can occur during testing and secondly the potential risk of inducing a sensitization. Currently, a possible extended skin testing protocol is being developed in the certified allergy centers of the DGAKI (CAC) in cooperation with allergology focus centers.

If all tests are negative, a short-term vaccination may be necessary (e.g., personnel in COVID-19 intensive care units) from an allergological point of view, taking appropriate precautions (emergency medication and trained personnel available, monitoring for at least 30 minutes after vaccination). If a positive result, e.g., for PEG, is found in the skin test, another vaccine can be considered for vaccination, provided that the vaccine is available (within a reasonable time). It should be noted that polysorbate 80, which is commonly found in influenza vaccines, for example, and is also present in Astra Zeneca’s non-mRNA-based vaccine (less than 100 μg/dose), is potentially cross-reactive to PEGs [7] and may also cause anaphylactic reactions [8, 9]. In the United Kingdom, it has been recommended that patients with PEG allergy can receive Astra-Zeneca’s vaccine under 30 minutes of observation [17], whereas in the United States, the CDC most recently classified a previous reaction to polysorbate 80 as a contraindication to an mRNA-based vaccine [18].

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**Conflict of interest**

None.
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