



May polyethylene glycol be the cause of anaphylaxis to mRNA COVID-19 vaccines?

Pedro Giavina-Bianchi* and Jorge Kalil

ABSTRACT

Vaccination against coronavirus is essential to minimize the impact of the COVID-19 pandemic. Rare cases of anaphylaxis associated with the mRNA COVID-19 vaccines are being described, and the mechanisms involved in these reactions are poorly understood. A potential culprit agent of these vaccine-induced anaphylaxis events is polyethylene glycol, which has been reported as a cause of anaphylaxis. However, a cause-effect association has not been demonstrated, and the cases of anaphylaxis to mRNA COVID-19 vaccines should be further investigated. In this scenario, the recommendations are inaccurate and can lead to misinterpretation. At the moment, a more accurate recommendation would be the contraindication of mRNA COVID-19 vaccines in patients with immediate hypersensitivity reaction to polyethylene glycol or polysorbate. Patients with history of anaphylaxis to other or unknown causes should be referred to an allergist-immunologist for further orientation.

Keywords: BNT162b2 mRNA COVID-19 vaccine, Polyethylene glycol, Macrogol, Polysorbate, Anaphylaxis, Immediate hypersensitivity reaction, Immunization

To the Editor,

The COVID-19 pandemic has been plaguing the world for one year. In this period, there were about 100 million people infected and 2 million dead. The effects of the pandemic on public health, economy, and society have been devastating, and vaccination against coronavirus is essential to minimize the impact of this catastrophe. Therefore,

the clinical trials showing the efficacy and safety of the BNT162b2 mRNA COVID-19 (Pfizer/BioNTech) and the mRNA-1273 COVID-19 (Moderna) vaccines are encouraging and revolutionary.^{1,2} Several countries around the world have started vaccinating their citizens.

After two cases of anaphylaxis associated with the Pfizer/BioNTech vaccine were described, the National Health Service (NHS) of United Kingdom stated: "Any person with a history of anaphylaxis to a vaccine, medicine or food should not receive the Pfizer/BioNTech vaccine".³ We consider this statement vague and very generalist. It may cause fear and confusion, depriving patients with a history of anaphylaxis from being vaccinated. Right after the vaccination started in England, the United States started immunizing their population and also detected rare cases of anaphylaxis to both mRNA vaccines.^{4,5} The recommendations of the US Centers for Disease Control and Prevention (CDC) were that, while cases of anaphylaxis are investigated, "History of severe

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mRNA vaccine to SARS-CoV-2	Constituents	Incidence of anaphylaxis per doses administered	CDC recommendations regarding adverse reactions
BNT162b2 mRNA COVID-19 (Pfizer/BioNTech)	<ul style="list-style-type: none"> • Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 • 2 [(polyethylene glycol)-2000]-N,N-ditetradecylacetamide • 1,2-distearoyl-<i>sn</i>-glycero-3-phosphocholine • Cholesterol • (4-hydroxybutyl)azanediyl)bis (hexane-6,1-diyl)bis (2-hexyldecanoate) • Potassium chloride • Monobasic potassium phosphate • Sodium chloride • Dibasic sodium phosphate dihydrate • Sucrose 	11.1:1 million	<ul style="list-style-type: none"> • Contraindication Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG]). • Immediate allergic reaction of any severity to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG)
mRNA-1273 COVID-19 (Moderna)	<ul style="list-style-type: none"> • Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 • PEG2000-DMG: 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol • 1,2-distearoyl-<i>sn</i>-glycero-3-phosphocholine • Cholesterol • SM-102: heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate • Tromethamine • Tromethamine hydrochloride • Acetic acid • Sodium acetate • Sucrose 	2.5:1 million	<ul style="list-style-type: none"> • Precautions History of any immediate allergic reaction to other vaccines or injectables therapies

Table 1. mRNA SARS-CoV-2 vaccines, incidence of anaphylaxis and current CDC recommendations regarding adverse reactions (4-6)

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1 allergic reaction to any vaccine or any injectable
2 therapy is a precaution, but not contraindication,
3 to vaccination".⁶

4 Anaphylaxis is a serious, life-threatening imme-
5 diate systemic hypersensitivity reaction (HR)
6 induced by mast cells and basophils degranula-
7 tion. Anaphylaxis can be classified as allergic, in
8 which there is a specific immune response medi-
9 ated by IgE, or nonallergic, with direct degranu-
10 lation of mast cells/basophils induced by the
11 culprit agent. The three main causes of anaphylaxis
12 are drugs, food, and hymenoptera venom. Inci-
13 dence, prevalence and fatalities of drug-induced
14 anaphylaxis have been increasing.⁷ Risk of
15 anaphylaxis after all vaccines is estimated to be
16 1.31 (95% CI, 0.90-1.84) per million vaccine
17 doses, but it differs depending on the vaccine
18 involved and allergies to latex, gelatin, and eggs
19 should be considered.⁸ In these cases,
20 concomitant use of non-steroidal anti-inflamma-
21 tory drugs, a major cause of drug-induced
22 anaphylaxis, must also be ruled out.⁹ The mRNA
23 COVID-19 vaccines do not contain eggs or gelatin.

24 Looking at the constituents of the mRNA
25 COVID-19 vaccines, there is a possible cause of
26 these vaccine-induced anaphylaxis events: the
27 polyethylene glycol (PEG). In the vaccine, the
28 nucleoside-modified RNA encoding the SARS-
29 CoV-2 full-length spike protein is formulated into
30 lipid nanoparticles, which contain PEG. Immediate
31 HRs to PEG, also known as macrogol, are under-
32 recognized and poorly understood. PEGs consti-
33 tute a family of hydrophilic polymers of ethylene
34 oxide ($H(OCH_2CH_2)_nOH$), and these substances
35 are present in thousands of medications, cos-
36 metics, and food products. Although rare,
37 anaphylaxis to PEG has been described in the
38 literature, mainly in patients using bowel prepara-
39 tion solutions or steroid depot formulations.¹⁰
40 Recently, a case series of five patients with PEG
41 allergy was described, warning that "PEG is a
42 high-risk 'hidden' allergen, usually unsuspected,
43 and can cause frequent allergic reactions due to
44 inadvertent reexposure".¹¹ The mechanisms of
45 PEG-induced anaphylaxis are not fully under-
46 stood and may involve IgE- and non IgE-mediated
47 immediate HRs. Serum specific-IgE was detected
48 in patients with anaphylaxis to PEG, showing that at
49 least some of these immediate HRs could be
50 allergic. PEG is structurally related to polysorbate,

and cross-reactive hypersensitivity between these
52 compounds may occur.^{10,12}

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54 Recently, two case series were published
55 bringing more information on anaphylaxis to the
56 mRNA vaccines of Pfizer/BioNTech (4) and Mod-
57 erna.⁵ They were based on notifications and
58 reports of immediate HRs following mRNA
59 vaccination, which were captured in the Vaccine
60 Adverse Event Reporting System (VAERS), the
61 passive surveillance system in the United States
62 for adverse events after immunization.¹³ Table 1
63 shows the incidence of anaphylaxis to mRNA
64 SARS-CoV-2 vaccines,^{4,5} the vaccine constituents
65 and the current CDC recommendations
66 regarding adverse reactions.⁶

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68 Analyzing these case series, 87.1% and 96.8% of
69 the immediate HRs started within 30 and 60 mi-
70 nutes of vaccination, respectively. They were
71 characterized by diffuse erythematous rash;
72 generalized urticaria; wheezing; stridor; hoarse-
73 ness; difficulty swallowing; lips, eyelids, tongue,
74 and throat swelling; dry cough; hypotension;
75 decreased peripheral perfusion; and anaphylaxis.
76 Patients who had anaphylaxis to the mRNA COVID-
77 19 vaccines reported past history of immediate
78 HRs and anaphylaxis in 80.6% and 38.7% of the
79 cases, respectively (Table 2). There was an
80 association between anaphylaxis to mRNA
81 COVID-19 vaccines and past history of anaphy-
82 laxis to several etiologies, including drugs, food,
83 and *Hymenoptera* venom (Fig. 1). None of the
84 patients had history of previous immediate HR to
85 PEG. There are many questions to be answered:
86 Is PEG-anaphylaxis underdiagnosed? Are patients
87 with PEG-anaphylaxis misdiagnosed and the re-
88 action is associated with wrong causes? If PEG-
89 anaphylaxis is an allergic reaction, with a specific
90 immune response mediated by IgE, why is
91 anaphylaxis to several unrelated etiologies a risk
92 factor for PEG-anaphylaxis? If PEG-anaphylaxis is a
93 non-allergic reaction, why is anaphylaxis to several
94 unrelated etiologies a risk factor for PEG-
95 anaphylaxis?

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97 It is essential to prevent vaccination against
98 coronavirus from being harmful and, conse-
99 quently, being hampered by public opinion.
100 Hippocrates stated "Primum non nocere", which
101 ironically was published in his work "Epidemic".
102 The mRNA COVID-19 vaccines should be

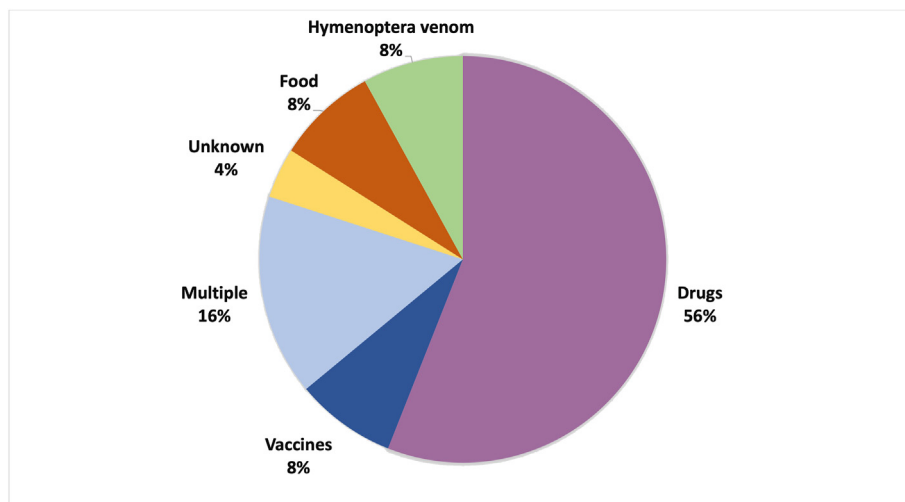


Fig. 1 Cause of previous immediate hypersensitivity reaction in patients with anaphylaxis to mRNA COVID-19 vaccines

administered in settings with an appropriate structure and with trained health professionals for the prompt treatment of any anaphylaxis event.¹⁴

At the moment, a more accurate recommendation would be the contraindication of mRNA COVID-19 vaccines in patients with immediate HR to polyethylene glycol or polysorbate. Patients with

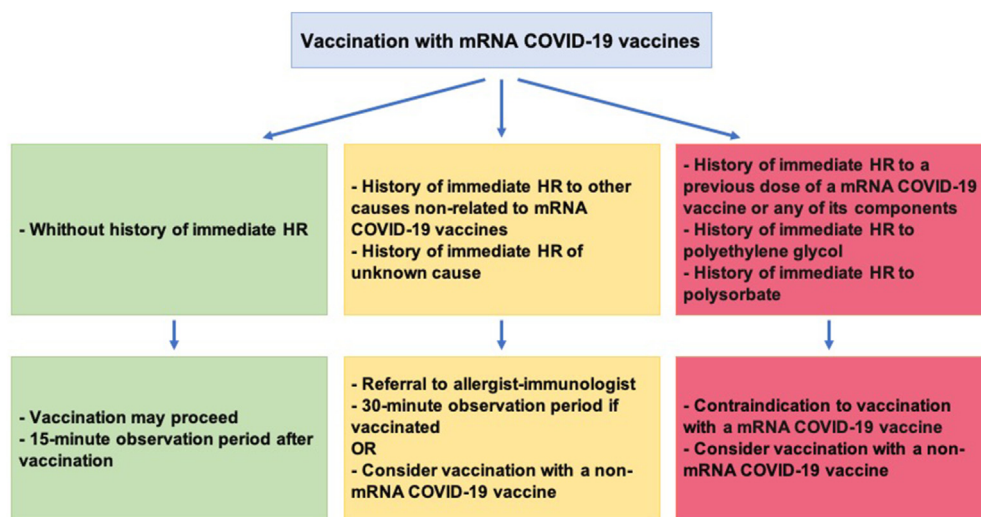


Fig. 2 Algorithm to manage individuals intending to be vaccinated with an mRNA COVID-19 vaccine. Legend: immediate HR - Immediate Hypersensitivity Reaction (anaphylactic type reaction)

mRNA SARS-CoV-2 vaccine	n patients (n women)	Mean age (range)	Past history of immediate HRs (%)	Past history of anaphylaxis (%)
BNT162b2 mRNA COVID-19 (Pfizer/BioNTech)	21 (19)	40.5 (27-60)	76.2%	33.3%
mRNA-1273 COVID-19 (Moderna)	10 (10)	46.2 (31-63)	90%	50%
Total	31 (29)	42.3 (27-63)	80.6%	38.7%

Table 2. Immediate hypersensitivity reactions following mRNA SARS-CoV-2 vaccination (4, 5)

history of immediate HR to other or unknown causes should be referred to an allergist-immunologist for further orientation. Here we suggest an algorithm to manage individuals intending to be vaccinated with an mRNA COVID-19 vaccine (Fig. 2). Evidence-based decisions are crucial to increase the confidence and adherence of the world population in vaccination for COVID-19. Further studies on anaphylaxis associated with the mRNA COVID-19 vaccines are needed.

Abbreviations

National Health Service, NHS; Center for Disease Control, CDC; hypersensitivity reaction, HSR; polyethylene glycol, PEG; Vaccine Adverse Event Reporting System, VAERS.

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Ethics

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Conflict of interest

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