

Immediate reactions following the first dose of the SARS-CoV2 mRNA vaccines do not preclude second dose administration

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Abstract:

Addressing COVID19 vaccine hesitancy and minimizing potential vaccine contraindications are critical to combat the ongoing pandemic. We describe a practical approach to immediate adverse events after the first dose of the SARS-CoV2 mRNA vaccines, focusing on allergic reactions with respect to their diagnosis and management.

Key words: vaccine allergy; graded challenge; polyethylene glycol

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Abbreviations: PEG - polyethylene glycol

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Background: True allergic reactions to the SARS-CoV2 mRNA vaccines are rare with an initial estimate of 11 events per million doses [1], but these events and the associated media coverage can beget vaccine. The Centers for Disease Control guidelines recommend against second dose administration of either the Pfizer-BioNTech or Moderna vaccine in patients with immediate allergic reactions to the first dose, but do not distinguish between levels of reaction severity [2]. However, the majority of suspected allergic reactions following vaccine administration are not immunologically-mediated – for example, there are several mimics of anaphylaxis including vasovagal syncope and vocal cord dysfunction. Patients with these symptoms may unnecessarily avoid the second dose, raising concern for incomplete immunization and decreased vaccine efficacy.

While it is speculated that polyethylene glycol (PEG) is the culprit allergen in the Pfizer and Moderna vaccines, PEG skin testing for first dose reactors has low positive and negative predictive values and therefore has poor reliability for guiding clinical decisions [3]. Recent guidelines suggest that skin testing should be restricted to settings with high probability of true anaphylaxis [4], and lower risk patients should be revaccinated with full or split dosing [5]. We describe our institutional experience with immediate reactions to the COVID-19 vaccine, and our protocol for graded- or full-dose vaccine re-administration for immediate reactors at low risk for true anaphylaxis.

Methods: We retrospectively reviewed immediate onset reactions (≤ 6 hours) to the first dose of either the Pfizer-BioNTech or Moderna COVID-19 vaccination in healthcare workers at a single institution over a two-month period (12/17/2020 and 02/16/2020). Subjects were identified through review of occupational health records that documented both management of reactions identified at the vaccine clinic, and reactions later reported by employees via telephone. Any healthcare worker who reported symptoms concerning for allergy within 6 hours of vaccine administration was included. We excluded delayed reactions with onset > 6 hours due to limited literature and unknown mechanisms of most delayed vaccine hypersensitivity, and reactions consistent with known vaccine side effects (e.g., site pain, fatigue, myalgias, fever). We also excluded subjects who had experienced isolated local reactions without systemic symptoms, based on prior reports that these are not contraindications to second dose [6].

The probability of immunological anaphylaxis was estimated using the Brighton Criteria case definition which defines the level of anaphylaxis based on the likelihood of true reactivity [7]. Brighton level 1 represents the highest level of certainty and level 3 the lowest. Reactors were classified as high (Brighton level 1), intermediate (Brighton level 2) or low (Brighton level 3) likelihood for true anaphylaxis. Following this stratification, the decision was made to proceed with skin testing followed by graded-dose vaccine challenge if negative in the highest-risk cases, graded-dose vaccine challenge without skin testing in intermediate-risk cases, and direct vaccine challenge in low-risk cases (**Figure 1**). Due to the low yield of PEG skin testing in patients deemed to have probable anaphylaxis, we transitioned to performing graded-dose challenge alone for Brighton levels 1 and 2. This was at the discretion of a trained allergist in conjunction with an infectious disease specialist, and contingent upon the reaction history and patient comfort with proceeding.

Skin testing was performed in a dedicated allergy clinic. Patients underwent skin prick tests with stock solutions of PEG-2000 and methylprednisolone acetate 20 mg/ml (which contains PEG-3350), followed by intradermal testing with 1:10 solution of methylprednisolone if prick tests were negative. Patients with negative skin tests, as well as those cleared for graded- or full-dose vaccine challenge went on to receive the second dose. Vaccine challenges were undertaken with either a single full dose or a 2-step graded dose challenge protocol (10% vaccine dose followed by the remaining 90%). The 10% challenge dose solution was mixed by pharmacists using a full vaccine

dose. Patients undergoing challenge were monitored for 30 minutes after the 10% challenge, and for 60-minutes after the 90% dose in a monitored environment with on-site emergency facilities.

Results: Out of 20,657 first doses of Pfizer and Moderna vaccines administered to healthcare workers prior to 2/16/21, a total of 138 reactions were reported (0.66%). 20 patients were excluded due to isolated local symptoms, mostly numbness at the injection site, or complaints that were unrelated to allergy. 30 patients were excluded due to delayed reactions >6 hours after dose administration. 88 of 138 (73%) patients who reported symptoms were classified as immediate reactions, with a marked female predominance (92%).

Immediate reactions were classified as Brighton category I in none of the reports, 7 as category 2, and 81 as category 3). Therefore, only 8% of episodes were categorized as likely anaphylactic (Brighton level 2). There were no Brighton level 1 cases. 39 of 86 (45%) patients had underlying medication/vaccine allergies. This data was not available for two subjects.

The most frequently reported primary symptoms among Brighton class 3 reactors were numbness/tingling (46/88), sensation of throat closure (24/88), lightheadedness (23/88), flushing (19/88), pruritus (18/88), palpitations (16/88), subjective swelling of the eyes/lips/mouth (15/88), and other respiratory symptoms (3/88). Among the seven reactors categorized as Brighton class 2, an objective rash or hives was documented in addition to lip swelling (1/7) and throat tightness (5/7). 57 (64.7%) of non-anaphylactic first dose reactions resolved without any intervention, whereas the remaining patients received a combination of antihistamines (29.5%), corticosteroids (4.5%), and short-acting β -agonists (1.1%). Epinephrine was only administered as emergency treatment in 2 cases despite its status as first line treatment of anaphylaxis. This may reflect the perceived mild nature of most reactions for which management with steroids and antihistamines were considered sufficient. Of note, acute tryptase levels were not obtained on-site due to logistical difficulties with procuring blood draws. 14/88 patients were evaluated at the ER, but tryptase was not sent due to the time elapsed between symptom onset and wait times in the ER due to a corresponding COVID case surge.

73/88 (82.9%) subjects tolerated the second dose of the vaccine, 57/88 (64.7%) through full dose vaccine challenge without precaution and 16/88 (18.2%) through graded dose challenge. Among Brighton class 2 reactors, 4/7 underwent graded dose challenge uneventfully, two declined and 1 was lost to follow-up. Five patients had recurrent immediate reactions with full dose administration that were either self-limited or resolved with antihistamines/bronchodilator use. Of the reactors who underwent allergist-supervised graded vaccine challenge, skin tests were performed in 4 of these patients (4.5%) with no positive tests to any reagents. 100% of those who underwent graded challenges tolerated both the test and 90% doses with only few reports of subjective itching. All participants were hemodynamically stable, and none required emergency treatment. 9/88 (10.2%) of reactors did not receive dose 2 and this information was not available for 6 (6.8%) patients.

Discussion: We present a narrative review of adverse events at a single institution to the COVID19 mRNA vaccines, our investigational protocol, and outcomes following rechallenge with the second dose. In our cohort of 88 immediate reactors to the first dose, revaccination was administered to ~83% of subjects. This is consistent with previous studies of graded drug challenges with overall reaction rates between 4-12%, but significantly lower true reaction rates [8]. The low reaction rate for single dose and test dose protocols indicates the comparable safety of both procedures.

Most immediate reactions following COVID-19 immunization were not suggestive of true immunological anaphylaxis akin to other studies of vaccine reactions. Despite the concern for an underlying allergic mechanism, 7 (7.9%) of episodes were diagnosed as high-risk (Brighton 2) upon

reviewing symptom presentation and reaction course. Most of these patients presented with largely subjective symptoms, that can be explained at least partly through non-immune mediated mechanisms such as a vasovagal reaction or vocal cord dysfunction. However, the fear of anaphylaxis upon re-vaccination often prompts presumptive allergy diagnosis and precautionary discontinuation of further vaccine doses pending allergist evaluation.

There is also increasing evidence that direct or split dose vaccine challenge may be a sufficiently cautious approach to reimmunization even without antecedent skin testing. In a recent pediatric study of potential IgE-mediated vaccine reactions, 71/73 direct challenges to the vaccine were negative [9]. Allergist referral for skin testing should be restricted to those patients whose reactions are compatible with true anaphylaxis, and full/split dose revaccination protocols considered for low-risk patients, as has been performed without incident in a case series of immediate reactors to the Moderna vaccine [10].

Our study was limited by its retrospective nature and protocol adaptations that resulted in some non-uniformity of the diagnostic process. Another limitation was the high percentage of subjects in whom second dose tolerance could not be confirmed due to patient refusal. It is therefore possible that we may have underestimated the number of patients confirmed as tolerant. Additional challenges with more widespread implementation of our protocol would include the necessity of trained allergists for assessment of risk, the desire to perform challenges in a more monitored environment than a typical vaccine clinic, and the need for some minimal vaccine waste to perform graded-dose challenges.

Our experience highlights the importance of evaluation of COVID vaccine adverse events to ensure that patients without a history of true anaphylaxis can proceed to the second vaccine dose. A history of mild immediate symptoms following the first vaccine dose should not preclude second dose administration, in order to maintain this vital public health intervention.

Funding: None.

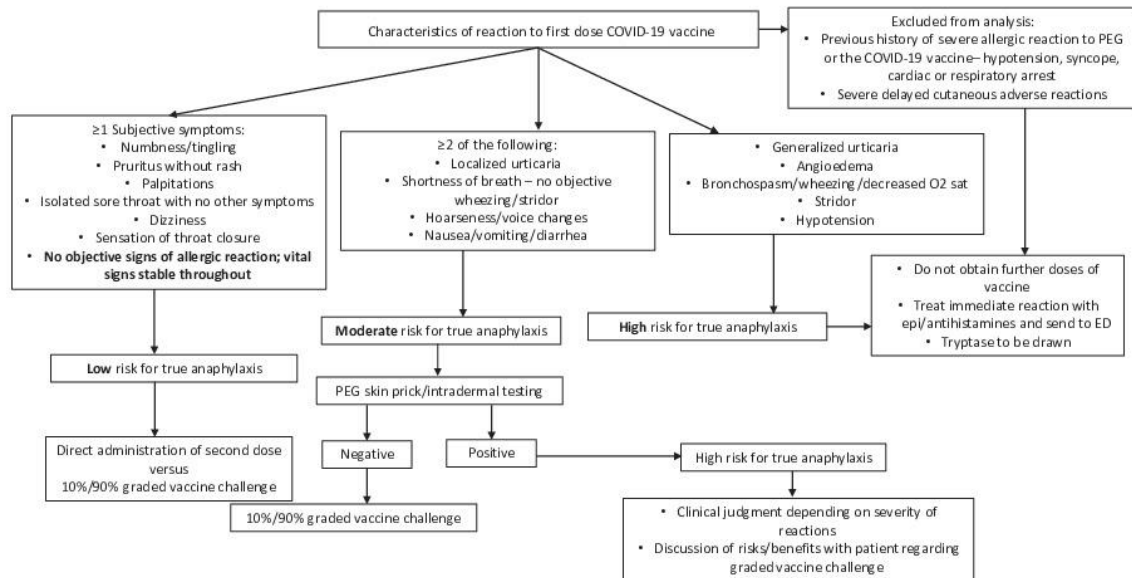
Conflicts of interest for all F. E-H. L. reports grants P01AI125180, U01AI045969, and R01AI121252; grants from NIH, Bill & Melinda Gates Foundation, and Genentech, Inc; product from Emory patent from Berkeley Lights inc.; advisory board for Astra Zeneca; SAB for Be Bio Pharma; founder of MicroB-plex, Inc.; and stock/stock options from Be Bio Pharma, outside the submitted work. J.S. is President elect of AAISG (state allergy society).

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Figure 1. Approach to immediate reactions following the first dose of SARS CoV2 mRNA vaccines.



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