

Journal Pre-proof

The COVID-19 Pandemic in 2021: Avoiding Overdiagnosis of Anaphylaxis Risk While Safely Vaccinating the World

Matthew Greenhawt, MD MBA MSc, Elissa M. Abrams, MD MPH, John Oppenheimer, MD, Timothy K. Vander Leek, MD, Douglas P. Mack, MD, MSc, Alexander G. Singer, MB BAO BCh, Marcus Shaker, MD MSc

PII: S2213-2198(21)00080-5

DOI: <https://doi.org/10.1016/j.jaip.2021.01.022>

Reference: JAIP 3399

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 2 January 2021

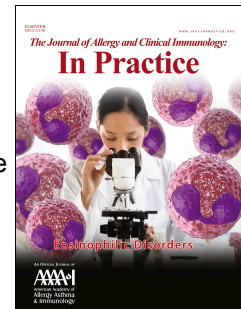
Revised Date: 21 January 2021

Accepted Date: 22 January 2021

Please cite this article as: Greenhawt M, Abrams EM, Oppenheimer J, Vander Leek TK, Mack DP, Singer AG, Shaker M, The COVID-19 Pandemic in 2021: Avoiding Overdiagnosis of Anaphylaxis Risk While Safely Vaccinating the World, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.01.022>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology



The COVID-19 Pandemic in 2021: Avoiding Overdiagnosis of Anaphylaxis Risk While Safely Vaccinating the World

Authors

Matthew Greenhawt, MD MBA MSc

Department of Pediatrics, Section of Allergy and Immunology, Children's Hospital Colorado,
University of Colorado Denver School of Medicine

Matthew.Greenhawt@childrenscolorado.org

Elissa M. Abrams, MD MPH (2021)

Department of Pediatrics, Section of Allergy and Clinical Immunology, University of Manitoba
elissa.abrams@gmail.com

John Oppenheimer, MD

Rutgers New Jersey Medical School, Newark, NJ

nallop22@gmail.com

Timothy K. Vander Leek, MD

Pediatric Allergy and Asthma, Department of Pediatrics, University of Alberta, Edmonton, AB

tim.vanderleek@ualberta.ca

Douglas P. Mack, MD, MSc

McMaster University, Hamilton, ON, Canada and Halton Pediatric Allergy, Burlington, ON,
Canada

dougpmack@gmail.com

Alexander G. Singer, MB BAO BCh

Department of Family Medicine, University of Manitoba

alexander.singer@umanitoba.ca

Marcus Shaker MD MSc

Dartmouth-Hitchcock Medical Center, Section of Allergy and Immunology, Lebanon, NH,
Geisel School of Medicine at Dartmouth, Hanover, NH

Marcus.Shaker@dartmouth.edu

word count: 3013

Corresponding Author: Matthew Greenhawt. Section of Allergy and Immunology, Children's
Hospital Colorado, University of Colorado School of Medicine 13123 E. 16th Ave. Aurora, CO
80045. 720-777-2575. Matthew.Greenhawt@childrenscolorado.org

Source of any financial support: None Trial registration: Not applicable

Key Words: COVID-19; Vaccine; Adverse Effects; Anaphylaxis; Guideline; Parameter; Graded
Challenge; Shared Decision Making

Conflict of interest:

MG has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intromune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Sanofi/Genzyme, Genentech, Nutricia, Kaleo Pharmaceutical, Nestle, Acquestive, Allergy Therapeutics, Pfizer, US World Meds, Allergenics, Aravax, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, Aimmune, DBV, Before Brands, multiple state allergy societies, the American College of Allergy Asthma and Immunology, the European Academy of Allergy and Clinical Immunology; is an associate editor for the Annals of Allergy, Asthma, and Immunology; and is a member of the Joint Taskforce on Allergy Practice Parameters. EA is on the Steering Committee of Food Allergy Canada's National Food Allergy Action Plan; is a collaborator with the Institute for Health metrics and Evaluation; and has received moderator/speaker fees from AstraZeneca, GSK and Sanofi. EA is a collaborator with the Institute for Health Metrics and Evaluation, is on the National Advisory Board for Food Allergy Canada and is on the National Food Allergy Action Plan Action Steering Team for Food Allergy Canada. JO declares the following: Research/Adjudication: AZ, GSK, Sanofi, Novartis; Consultant: GSK, AZ, Sanofi; Associate Editor: Annals of Allergy Asthma Immunology, AllergyWatch; Section Editor: Current Opinion of Allergy; Royalties: Up to Date; Board Liaison ABIM for ABAI. TVL has served on advisory boards and received honoraria from Aralez, Bausch Health, and Pfizer. DM is a member of the Board of Directors for the Canadian Society of Allergy and Clinical Immunology; serves on the Editorial Board of the Journal of Food Allergy. He has provided consultation and speaker services for Pfizer, Aimmune, Merck, Covis and Pediapharm and has been part of an advisory board for Pfizer and Bausch Health. DM is a member of the Board of Directors for the Canadian Society of Allergy and Clinical Immunology; serves on the Editorial Board of the Journal of Food Allergy; is an investigator for ALK. He has provided consultation and speaker services for Pfizer, Aimmune, Merck, Covis and Pediapharm and has been part of an advisory board for Pfizer and Bausch Health. AS has no conflicts to disclose. MS is a member of the Joint Taskforce on Allergy Practice Parameters; has a family member who is CEO of Altrix Medical; serves on the Editorial Board of the Journal of Food Allergy and the Annals of Allergy, Asthma, and Immunology.

In this issue of *In Practice*, Banerji et al outline an approach to allergic reactions from mRNA vaccines, and provide a review of an evolving situation.⁽¹⁾ As the authors emphasize, we are living and practicing in uncertain and unprecedented times. Their review serves to provide an up-to-date understanding of the challenges faced not only by the allergy community but by broader international public health efforts to combat the pandemic.

It is important to realize that as current knowledge evolves guidance will likely be conditional – and may change as our understanding of the pandemic and COVID-19 vaccines develops. Particularly in light of present uncertainties and a somewhat volatile future, a judicious approach involves decision making grounded in understanding lessons learned from prior experience with vaccine anaphylaxis. Such lessons can be applied to approaches to vaccine skin testing, management of known excipient allergy, vaccine graded challenge, and vaccine deferral during the COVID-19 pandemic. As Banerji and colleagues discuss, any approach must balance risks and benefits – both of preventing COVID-19 on patient and population levels, as well as mitigating risk for anaphylaxis. Navigating these somewhat competing priorities remains a challenge. As allergists, we must remain focused on risk assessment, cost-effectiveness, broad public health implementation, and consideration of the potential unintended consequences of screening and vaccine avoidance. In this regard, there are several important points to highlight when approaching patients who are concerned about allergy risk and COVID-19 vaccination.

First, when considering the many uncertainties in COVID-19 vaccine adverse reactions, one thing is clear – at present it is unlikely that all of the reported reactions to the mRNA vaccines are IgE mediated. This reality may fundamentally alter the necessity of allergy-based risk

stratification to some degree. (1-4) Indeed, a complete understanding of the underlying pathophysiology of the reported COVID-19 vaccine adverse reactions is yet to be determined. As noted by the authors, while an event may be reported as allergic, and a particular excipient identified as a potential culprit, when reviewing the available evidence regarding symptom presentation in these cases, many patients have reported atypical features. These features have included a number of highly subjective symptoms, which may be explained at least in part through a vasovagal or non-immune-mediated mechanism. (1, 2) While anaphylaxis is not a requirement for epinephrine use, similarly a response to epinephrine does not necessarily imply the presence of an allergic reaction as etiology. Anaphylaxis is a *clinical diagnosis* established by the *timing and nature of symptoms*.(6) As Banerji and colleagues highlight (1), the differential diagnosis of vaccine-related reactions is not limited to IgE or other immune-mediated phenomena. If such events are not definitively allergic, it raises questions about the unintended consequences of any strategy aimed at pre-emptive screening to prevent vaccine anaphylaxis (5). We need better understanding of adverse reactions to COVID-19 vaccines, and we as allergists need to be discerning in our investigation of these events, rather than simply accepting self-reported encounters or media coverage as bona fide evidence of an allergic reaction. We would urge restraint in concluding that vaccine anaphylaxis to this agent is anything more than a statistically rare event. Moreover, even assuming these reported events were indeed immune-mediated, the broader population perspective must be considered. Specifically, if we are to presume every case considered to be anaphylaxis in a recent MMWR report is correctly classified, 21 events out nearly 2 million doses remains an exceedingly low absolute risk (7). In this setting, the contrast between relative and absolute risk becomes important. While the increase from 1.3 to 11.1 cases per million is a large relative risk, the absolute risk increase is

quite low (7). In fact, this remains still much lower than the disclosed hypersensitivity rate of 0.1% stated in the EUA (1000 cases per 1 million vaccinations) for all-comer hypersensitivity. (8,9)

Second, there is speculation, but not certainty, that polyethylene glycol (PEG) is a definitive culprit allergen. While there remains no clear proof that PEG is causative at present, responses to date in the UK, Canada, and the US have restricted vaccination of individuals with a history of prior PEG reactions from parenteral medication.(3,4,10) While this is understandable in the context of evolving and rapidly changing information, it is presumptive at present and potentially unnecessary. It is also worthwhile to consider past experience with vaccine excipients constituting a risk of an allergic reaction. Indeed, there is a mixed and somewhat inglorious recent history with respect to well-intentioned risk assessment of key vaccine excipients in excipient allergic individuals, which has led to unnecessary exclusion and declaration of risk. For example, modern influenza vaccine contains egg. For years, guidance recommended caution and restricting influenza vaccination in egg allergic individuals, only to discover that this risk was unfounded for modern influenza vaccines, with no risk over baseline to the egg sensitized recipient, resulting in unnecessary avoidance of the vaccine. Furthermore, egg is a far more ubiquitous allergen than PEG, and it is worthwhile to recall this experience with egg and influenza vaccine (as well as with measles, mumps, and rubella (MMR) vaccine, which was handled similarly). (5, 6) However, particularly in the context of the MMR vaccine, it is also important not to completely disregard any potential role of excipients in triggering allergic reactions to vaccines, and gelatin content in MMR vaccine is a notable example that can be mitigated and managed by allergists to successfully achieve subsequent vaccination.(6)

Importantly, perception of risk becomes anchored with earliest available information, and is very difficult to retroactively change, in particular when professional organizations declare an excipient a culprit without firm evidence of causality, and recommend altered management for particular vaccine recipients. This is the current case with some COVID-19 vaccine recommendations, which is concerning, given the lack of clear evidence to inform practice. We can ill afford additional communication missteps during the current pandemic. The bottom line is that even in excipient-allergic persons, it is rare that the excipient concentration is of sufficient threshold to provoke an allergic reaction deeming vaccine deferral necessary, and we may very well cause more harm through preventing their vaccination than we do by preventing an allergic reaction to the vaccine (if efforts at risk-stratification even have the ability to mitigate anaphylaxis). From a risk communication perspective, it is important to anchor guidance in robust and accurate information. We must be cautious to avoid slipping backwards into “presuming danger until proven safe” as this has the possible unintended consequence of contributing to vaccine hesitancy, or in the worst case, chasing the wrong risk factor (e.g., egg and MMR/ modern influenza vaccines). We should learn from the mistakes of the past in this regard as the stakes are too high with SARS-CoV-2 to repeat the same course.

Third, even assuming PEG is the allergen, there is historical difficulty in consistently and accurately assessing anti-PEG IgE through skin testing. Again, the literature on PEG allergy is small, albeit growing, but the one commonality in all the small case reports has been that skin testing does not always produce wheal and flare in recipients with true PEG allergy. (11-14) That inconsistency speaks to poor reliability of the substance as a skin testing allergen when applied at full concentration, and decreases confidence in being able to use the results for clinical

175 decision-making. (15) Presently there is not standardized skin test material for PEG, and in the
176 most basic situation we are unable to definitively determine that a) any wheal and flare produced
177 from application is both not the result of irritation AND unequivocally indicates the presence of
178 IgE; and b) the same application, producing the absence of a wheal and flare unequivocally
179 means no IgE is present. While a basic tenet in the field of allergy, this lack of reliability is why
180 allergens must be standardized, to allow us to inform clinical decisions with confidence. As
181 simple as it is to apply a skin prick test to any agent, we have to understand what the results
182 mean – particularly if we are to create policy surrounding these test results and implement it on a
183 broad scale. This is only further complicated if the skin testing approach adds multiple
184 medicinal agents to which patients have not demonstrated an allergy but that contain PEG or
185 polysorbates – which can further confuse interpretation of which component of any given
186 mixture may be responsible for any wheal or flare identified, notwithstanding if this even
187 represents IgE recognition. This creates opportunity cost in the form of healthcare utilization and
188 resultant vaccination delay. Moreover, we do not know the population prevalence of PEG allergy
189 with high enough certainty to clearly establish predictive values, or have widespread enough
190 understanding of PEG skin testing to establish positive and negative likelihood ratios. As a result
191 of this uncertainty, our interpretation of the value offered in clinical decision making of a
192 “positive” skin test response to a non-irritating concentration of PEG differs somewhat from
193 Banerji and colleagues. The lack of proven reliability of PEG skin testing suggests clinicians
194 exercise caution if basing decisions on a “positive” or “negative” result, because there is an
195 absence of any positive predictive value for a non-standardized allergen testing agent without a
196 discernable population prevalence. In such an instance, the only thing that could be established
197 would be a positive or negative likelihood ratio, but even that is lacking for PEG skin testing.

While this situation is not unique to PEG, the lack of a clearer understanding of predictive values warrants cautious interpretation of results, particularly if recommending vaccine be withheld in skin-test positive individuals. At least at present, an approach of universal vaccine deferral in patients with positive skin tests for PEG could risk more harm than benefit. However, if testing is pursued, we do agree with Banerji and colleagues that shared-decision making is a critical component in the management of the PEG-sensitized patient. This must involve a close linkage to an opportunity for allergist-supervised graded vaccine challenge, which is key to providing safe vaccination that is consistent with individual values and preferences. Still, we would urge restraint in indiscriminate testing to PEG, given the low certainty of any evidence of benefit and significant risk that testing could be misinterpreted.

Fourth, while pre-vaccination risk-stratification medical questionnaires provide a framework to move forward with vaccination and address some stakeholder concerns, questionnaires also risk added medical complexity that could create confusion and dilute vaccination messaging. As Banerji and colleagues highlight, there is no clear evidence that past history of anaphylaxis, medication allergy, food allergy, asthma, allergic rhinitis, or family history produces an incremental risk for an adverse reaction of any kind to COVID-19 vaccination. This fact does raise questions about the value of requiring longer observation of patients with prior “potential” anaphylaxis to culprits which are not present in COVID-19 vaccines – particularly if more prolonged observation decreases implementation of broad vaccination through reduced acceptability of vaccination by patients, or reduced broad feasibility at a population level. (1) The only contraindication to COVID-19 vaccination, as currently stated in both the United States and Canada, is an allergy to the actual vaccine or excipient ingredient. Importantly, any

population screening approach for sensitization to excipients is not justified, has no validity, is not necessary prior to COVID-19 vaccination, is likely poorly feasible and sustainable on a broad scale, and has the potential to reduce vaccine acceptance and rollout. As allergists, we must guard against a tendency of ‘screening creep’ to populations without severe allergic reactions to parenteral PEG containing agents who can simply receive vaccination. Fortunately, for patients who experience an adverse reaction to any vaccination, a simple algorithm exists which can effectively allow vaccination through graded challenge, if that is felt to be necessary.(6) Graded dose challenges to COVID-19 vaccines have been endorsed under allergist supervision for patients with a suspected allergic reaction to the COVID-19 vaccine in preliminary guidance by the European Academy of Allergy and Clinical Immunology and the Canadian Society of Allergy and Clinical Immunology (16, 17). This approach is consistent with decades of experience in managing vaccine allergy; however, as for most vaccines, the safety and efficacy of this approach specifically as it relates to newly released COVID-19 vaccines is unknown or not informed by high certainty evidence.(6) It is also important for allergists to note that confidence is generally quite low in the ability of premedication with antihistamines and/or glucocorticoids to prevent anaphylaxis, and such an approach has not been recommended previously in evaluation and management of vaccine hypersensitivity.(6,18) Again, we would urge restraint in presuming that prior history of a reaction to an injectable medication is a risk for COVID-19 vaccine anaphylaxis, and strongly caution against deferring, delaying, or requiring additional supervision for vaccinating such individuals. While Banerji and colleagues highlight the fact that 17/21 cases of anaphylaxis reported by the CDC on January 6, 2021 had an imprecise history of pre-existing “allergy” (including “bee stings”, “sulfa drugs”, “cats and dogs”, “iodinated contrast media”, and “hydrocodone, nut”), we do not know the number of the

some 2 million other individuals who were successfully vaccinated without incident who may have also shared this history. (7) Here, it is important to not be deductively selective in presuming risk from a small group of individuals without considering the larger experience from the remainder of cases.

Lastly, comparative risk must be properly assessed, and our actions toward anaphylaxis risk-reduction should be consistent. Most importantly, we must keep in mind that COVID-19 had already infected 82 million individuals and cost 1.79 million lives at the close of 2020. (19) This pales the comparison of morbidity and mortality caused by anaphylaxis, and we need to be honest and open about that. The pandemic is the much larger and more pressing public health risk. Patients are seen in allergy clinics every day with an array of conditions that place them at risk for allergic reactions, anaphylaxis, and even death. However, it must be remembered that many of these conditions carry a risk of fatality much lower than risks patients take in everyday living – risks that even include driving to the doctor’s office for that very appointment, or even being struck by lightning. One example of comparative anaphylaxis risk resonates with all allergists. Every day, in nearly every allergy practice in the US, we inject persons with known allergic sensitivity to a mixture of allergens in the form of immunotherapy, bearing a known risk of reactions and even fatality.(20) We are confident in the safety of allergen immunotherapy because we (a) understand the risk context, and (b) manage this risk quite effectively. This example is imperfect as immunotherapy relates to targeted and managed immunological phenomenon. However, the point is that allergists are trained and experienced to provide needed medications and therapies to patients at risk for anaphylaxis – and it is very, very rare that we are unable to provide a critical medication (or vaccine) to a patient at risk. And whether it be through

immunotherapy, drug desensitization, or graded challenge, allergists have the tools to provide therapies in spite of (and sometimes because of) demonstrable allergen sensitization. Even assuming an at-risk population can be identified, that PEG is a culprit for reactions, and that PEG skin testing is reliable and predictive, providing an mRNA vaccine containing PEG to someone with a positive skin test to PEG may not be a larger risk than we manage routinely in our clinics. Worse, without any data to suggest, pre-emptively, that PEG allergic individuals (or individuals with some prior history of anaphylaxis to a medication) consistently and reliably do not tolerate these mRNA vaccines, we may be instilling our own values in pre-determining what is a greater risk for our patients if, at minimum, graded vaccine challenge is not offered. If we deny any vaccination opportunity flat-out, based on our own concerns, we bypass the shared decision making process and the outcome may reflect neither the medical reality of the situation or the desires of the patient.

It would be harmful to restrict vaccination beyond presently labelled contraindications during the COVID-19 pandemic without a higher burden of proof. For individuals with an a priori documented allergy to the mRNA vaccine, an approach similar to that outlined in the 2012 vaccine parameter may be appropriate.(6) If vaccine quantities are insufficient for skin testing (which is a present issue given rationed supply in the early phase roll-out of the vaccination campaign), a graded challenge may be a very reasonable approach for a patient with documented history of prior mRNA vaccine anaphylaxis, to ensure both safety and ability to receive the vaccine (6, 16, 17). Even presuming patients can wait for an alternative vaccine (also a decision where we could be instilling our values onto the patient), such as an adenovirus vector vaccine, there is no guarantee at the moment that or that it will be safer or as effective as other vaccines.

More to the point, such delay could facilitate overdiagnosis of anaphylaxis risk. Should anaphylaxis occur, effective treatment is rapidly available. We are unable to say this with the same certainty if an unvaccinated individual was to contract COVID-19.

We must be vigilant to avoid adding complexity through over-diagnosing anaphylaxis risk to a global vaccine effort which is already facing unprecedented challenges of distrust and disinformation campaigns. As allergists, we must provide a clear, evidence based, and balanced perspective on anaphylaxis risk. The world is looking to our expertise, as we rise to meet this moment. This is a virus that has killed millions worldwide, whereas only a very small number of patients have suffered from reactions following vaccination, none of which have led to a fatality. The medical community has begun to evaluate these reactions and respond. The guidance provided by Banerji and colleagues is an example for a starting approach, and we wish to supplement how the allergist-immunologist can approach this through discussing some additional contextualized issues to consider in weighing options for how to proceed. While we wait for evolving science to further inform our practice, we applaud the incorporation of shared decision-making into COVID-19 vaccination, to make sure the patient's values and preferences are at the forefront of critical efforts to immunize the world and turn the tide on a devastating pandemic.

References

- 1) Banerji A, Wickner PG, Saff R, Stone CA, Robinson LB Long AA et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Approach. J Allergy Clin Immunol Pract 2020; <https://doi.org/10.1016/j.jaip.2020.12.047>

- 2) Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 Vaccines. *N Engl J Med*. 2020 Dec 30. doi: 10.1056/NEJMr2035343. Epub ahead of print. PMID: 33378605.
- 3) Interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States - Appendix B. Atlanta, GA: United States Centers for Disease Control and Prevention; 2020 (Reviewed December 20, 2020). Available at: <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinicalconsiderations.html#Appendix-B>. Accessed December 31, 2020.
- 4) Gov.UK. Confirmation of guidance to vaccination centres on managing allergic reactions following COVID-19 vaccination with the Pfizer/BioNTech vaccine [Available from: <https://www.gov.uk/government/news/confirmation-of-guidance-to-vaccination-centres-on-managing-allergic-reactions-following-covid-19-vaccination-with-the-pfizer-biontech-vaccine>.
- 5) Greenhawt M, Turner PJ, Kelso JM. Administration of influenza vaccines to egg allergic recipients: A practice parameter update 2017. *Ann Allergy Asthma Immunol*. 2018;120:49–52.
- 6) Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol*. 2012;130(1):25-43.
- 7) CDC COVID-19 Response Team Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine – United States, December 14-23, 2020. *MMWR Morb Mortal Wkly Rep*. 2021 Jan 6; 70:1-6.
- 8) McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. *J Allergy Clin Immunol*. 2018 Feb;141(2):463-472. doi: 10.1016/j.jaci.2017.12.971. PMID: 29413255; PMCID: PMC6602527.
- 9) Pfizer-BioNTech COVID-19 vaccine (BNT162, PF-07302048) [FDA Briefing Document]. Silver Spring, MD: United States Food and Drug Administration, Vaccines and Related Biological Products Advisory Committee; 2020. Available at: <https://www.fda.gov/media/144246/download>. Accessed December 18, 2020
- 10) CSACI Statement on Pfizer/BioNTech Vaccine Anaphylaxis [Internet]. Available from: <https://csaci.ca/wp-content/uploads/2020/12/PressRelease-Pfizer-COVID-19vaccine-DEC-14.pdf>
- 11) Zhou Z-H, Stone CA, Jakubovic B, Phillips EJ, Sussman G, Park J, et al. Anti-PEG IgE in anaphylaxis associated with polyethylene glycol. *J Allergy Clin Immunol Pr* [Internet]. 2020;in press. Available from: <http://www.sciencedirect.com/science/article/pii/S2213219820312319>
- 12) Sellaturay P, Nasser S, Ewan P. Polyethylene Glycol-Induced Systemic Allergic Reactions (Anaphylaxis). *J Allergy Clin Immunol Pr*. 2020;in press.
- 13) Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. *Clin Exp Allergy*. 2016;46(7):907-22.
- 14) Stone CA, Jr., Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, et al. Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized. *J Allergy Clin Immunol Pract*. 2019;7(5):1533-40.e8.
- 15) Bernstein IL, Li JT, Bernstein DI, Hamilton R, Spector SL, Tan R, Sicherer S, Golden DB, Khan DA, Nicklas RA, Portnoy JM, Blessing-Moore J, Cox L, Lang DM,

- 361 Oppenheimer J, Randolph CC, Schuller DE, Tilles SA, Wallace DV, Levetin E, Weber
362 R; American Academy of Allergy, Asthma and Immunology; American College of
363 Allergy, Asthma and Immunology. Allergy diagnostic testing: an updated practice
364 parameter. *Ann Allergy Asthma Immunol*. 2008 Mar;100(3 Suppl 3):S1-148. doi:
365 10.1016/s1081-1206(10)60305-5. PMID: 18431959.
- 366 16) Klimek L, Jutel M, Akdis C, et al. ARIA-EAACI statement on severe allergic reactions to
367 COVID-19 vaccines – an EAACI-ARIA position paper. *Allergy*. 2020; Dec 30. Doi:
368 10.1111/all.14726.
- 369 17) Canadian Society of Allergy and Clinical Immunology. COVID-19 vaccine testing and
370 administration guidance for allergists/immunologists from the CSACI.
371 [https://csaci.ca/wp-content/uploads/2021/01/COVID-19-VaccineTesting-](https://csaci.ca/wp-content/uploads/2021/01/COVID-19-VaccineTesting-AdministrationGuidance-JAN5.pdf)
372 [AdministrationGuidance-JAN5.pdf](https://csaci.ca/wp-content/uploads/2021/01/COVID-19-VaccineTesting-AdministrationGuidance-JAN5.pdf). Accessed January 21, 2021
- 373 18) Shaker MS, Wallace DV, Golden DBK, et al. Anaphylaxis-a 2020 practice parameter
374 update, systematic review, and Grading of Recommendations, Assessment, Development
375 and Evaluation (GRADE) analysis. *J Allergy Clin Immunol* 2020;145:1082-123.
- 376 19) Johns Hopkins Coronavirus Resource Center [Internet]. Available from:
377 <https://coronavirus.jhu.edu/map.html>
- 378 20) Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, Nelson M, Weber R,
379 Bernstein DI, Blessing-Moore J, Khan DA, Lang DM, Nicklas RA, Oppenheimer J,
380 Portnoy JM, Randolph C, Schuller DE, Spector SL, Tilles S, Wallace D. Allergen
381 immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011
382 Jan;127(1 Suppl):S1-55. doi: 10.1016/j.jaci.2010.09.034. Epub 2010 Dec 3.
383