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ADVERSE REACTIONS TO VACCINES: AN ALLERGIST'S APPROACH

Introduction

Vaccination is one of the most impactful and cost-effective interventions for improving global health.[1] Routine immunization has reduced mortality and morbidity resulting from numerous types of infectious diseases.[2]

The widespread use of any reagent is always associated with the risk of adverse reactions, including expected and common side effects, as well as those that are unexpected or idiosyncratic.[3] Mild, local injection site reactions such as redness, tenderness, swelling, or constitutional symptoms such as fever and malaise, are common after vaccination and are not contraindications to further vaccination; they are generally manifestations of the physiologic response to vaccination. Uncommon reactions can vary; they may manifest as delayed hypersensitivity to vaccine components causing injection site nodules or severe, rare anaphylactic reactions.[4] Anaphylaxis occurs at approximately one per million doses administered.[5] The extremely rare Arthus reaction, a type of local Type 3 hypersensitivity reaction, resulting in local immune complex deposition due to the presence of pre-existing IgG antibodies, is typically limited in duration and is not a contraindication to further tetanus vaccination.[6]

Allergists are often seen as stewards of information regarding many of these reactions, although most of these reactions are not allergic in nature. It can be difficult to distinguish between a true allergic reaction to a vaccine and other clinical manifestations that may occur during or acutely after vaccination, such as anxiety, vasovagal responses, and pronounced local reactions.[7] Patients who have had adverse reactions to vaccines may be unnecessarily advised to avoid subsequent immunization, which can put them at risk of morbidity or mortality.[2] The importance of making this clinical distinction has become particularly significant during the ongoing COVID-19 pandemic. The allergist plays an important role in investigating adverse reactions to vaccines and ensuring that patients who are eligible can be safely vaccinated following appropriate investigation. For those patients with true immediate-onset allergic reactions, allergists are able to provide safe revaccination following established protocols.[8]

There are very few true contraindications to vaccination, and they are reviewed in **Table 1**. When reactions are deemed to be allergic or in possible cases of anaphylaxis, patients require assessment by an allergist prior to proceeding with vaccination as some may require confirmatory testing, a more monitored environment, and possibly graded dosing.

Allergist's Approach to Adverse Reactions to Vaccines

This approach is summarized in **Figure 1**.

Allergists are typically confronted with two common scenarios:

1. The patient requires guidance on receiving additional doses of a particular vaccine and/or other related vaccines following an apparent allergic reaction to that vaccine.
2. A patient with a history of known allergy to a vaccine ingredient or component requires guidance on future vaccination containing that component.

In both scenarios, the initial question to ask is, "Were the character and timing of the previous reaction consistent with anaphylaxis or an immediate IgE-meditated allergy to the vaccine, or did the patient have an allergic reaction to a component of concern?" Features consistent with a probable anaphylactic reaction generally occur within the first four hours following vaccine administration, although in practice this is typically much shorter i.e., within the first few minutes to one hour post-vaccination. The criteria for this include typical signs or symptoms for more than one of the following systems.[8–10]

Absolute Contraindications to Specific Vaccines:
Influenza vaccine → GBS within 6 weeks of receiving an influenza vaccination Pertussis containing vaccine → History of encephalopathy soon after a pertussis containing vaccine Rotavirus vaccine → History of GI anatomical issues e.g., malrotation Live vaccines in pregnancy
Contraindications to Routine Vaccination (Require Specialty Consultation):
Live vaccines in immunodeficiency, primary or secondary or immunosuppression→ Require consultation with relevant specialist e.g., Infectious disease, Immunology, Oncology, etc. True allergy to a vaccine or component of a vaccine → Require consultation with Allergist to determine how to vaccinate e.g., one dose, graded dosing, etc.
Note: Contact dermatitis to a component of the vaccine e.g., Neomycin, Thimerosal, PEG is not a contraindication to vaccination with vaccines containing these components Note: Some primary immunodeficiencies are absolute contraindications to use of live vaccine. However, this may not be the case of some non-combined immunodeficiencies.

Table 1: *Contraindications to Vaccination; courtesy of Zainab B. Abdurrahman, MMath, MD, FRCPC, David M. Putman, MD, PhD*

If the patient's history is suggestive of a non-immediate reaction, generally no allergic workup is required.[8,11] For delayed-onset nodules, patch testing may potentially be helpful for investigation of possible contact dermatitis. However, delayed-type hypersensitivity or local formation of nodules are not contraindications to future vaccination.[3] These non-immediate reactions are not contraindications to further vaccination. Subsequent doses of vaccine can be administered following standard recommendations. Of note, certain vaccine adverse reactions are best assessed by other medical specialties, as they can better evaluate the risk of recurrence and use joint decision-making with the patient to guide future vaccination. This includes referral to cardiology for myocarditis after mRNA-based COVID-19 vaccines; neurology for encephalitis, Guillain-Barré syndrome (GBS), or encephalopathy within a few weeks of the administration of any vaccine; and hematology for significant symptomatic thrombocytopenia within a few weeks of the administration of measles, mumps and rubella-(MMR)-containing vaccines.

If there is a suspicion of anaphylaxis or immediate-type allergy, skin prick testing with vaccine, and if clinically indicated, vaccine components, can be conducted **(Figure 1)**. Allergy to the components can be ruled out on history. For example, a history of eating eggs without reaction rules out egg allergy. If there is still a suspicion for a particular component in the vaccine of concern, skin prick testing can be used for that component. It is not recommended to test for unrelated components or components the patient is tolerating on history. Specific vaccine components of concern are reviewed below.

Skin prick testing is done with a full-strength vaccine unless there is a history of severe anaphylaxis, in which case it can be initiated at a 1:10 or 1:100 dilution. Skin prick testing should be completed with both positive and negative controls. If the test is negative, one can proceed to intradermal testing with 0.02 mL of 1:100 dilution of the vaccine. A negative control intradermal test should also be performed. If skin testing is negative and further doses are required, the vaccine can be administered in the usual manner with a 30-minute observation period following vaccine administration. If additional doses of this vaccine are required and skin testing is positive, the vaccine can generally still be safely administered in graded doses in a setting prepared to treat possible anaphylaxis.[8] However, as an alternative approach, if specific IgG levels of the immunization target are already in a range considered to indicate serologic protection from infection, further boosters may be delayed until the levels start to decline.

An example of a graded dosing regimen appears below. It involves 15-minute intervals between completed steps, performed in a setting prepared to treat a systemic allergic reaction with each dose administered via the usual route of the vaccine.[8]

1. 0.05 mL of 1:10 dilution
2. 10% of the target full dose undiluted
3. 20% dose undiluted
4. 30% dose undiluted
5. 40% dose undiluted

Allergy Evaluation of Vaccines Components

Common components associated with reactions to vaccines include gelatin, egg, yeast and latex.[8,12] Egg and yeast extracts for skin prick testing are commercially available. Gelatin for skin prick testing can be prepared by dissolving 5 g of commercially available food-grade gelatin powder in 5 mL of normal saline. Commercial latex preparations for skin prick testing are available. Alternatively, although non-standardized, a latex glove in saline also solubilizes latex for skin testing. Allergen-specific, quantitative IgE in vitro testing is commercially available for latex, gelatin, egg, and yeast.

Latex

Latex is not an ingredient within actual vaccines. Certain multidose vial stoppers or general packaging may contain latex which is leached into the vaccine solution. Therefore, for patients with a history of latex allergy, we recommend avoiding products with latex packaging or stoppers.[13]

Gelatin Allergy

Gelatin is used as a stabilizer and has been identified as an antigen responsible for anaphylactic reactions to MMR, varicella and Japanese encephalitis vaccines.[14] As gelatin has been identified as the etiologic agent in some cases of anaphylaxis, its manufacturers have since changed their formulations to contain either less or no gelatin.[11] In patients with a history of gelatin allergy, the current guidelines recommend referral to an allergist to facilitate vaccination for MMR, varicella or Japanese encephalitis. If a gelatin-free alternative vaccine is available, it should be used instead.[15]

Egg Allergy

Historically, there have been concerns about patients with egg allergy receiving influenza vaccination. However, numerous clinical studies have specifically

evaluated the administration of these vaccines in patients with egg allergy, including those with severe reactions or anaphylaxis.[16,17] Therefore, the most recent guidelines state that no special precautions are required regarding the administration of influenza, MMR or rabies vaccines in patients with egg allergy[3]. Yellow fever vaccine does contain egg protein.[16,18] The current recommendation is that patients with egg allergy have allergy testing with yellow fever vaccine as described above and in **Figure 1**.

Yeast

It is recommended that patients with a history of probable immediate-onset allergic reactions to baker's or brewer's yeast be referred to an allergist prior to vaccination with hepatitis B or quadrivalent human papillomavirus vaccine (HPV4). Both of these are reported to contain residual yeast protein due to their manufacturing processes.[19] Of note, yeast allergy is extremely rare.

Milk

Small amounts of milk protein derivatives are present in the pentavalent and quadrivalent Tdap vaccines. There are rare case reports of this as an etiology for anaphylactic reaction to these vaccines in patients with severe milk allergies.[20]

Polyethylene Glycol (PEG)

In the early evaluation of possible allergic reactions to the mRNA COVID-19 vaccines, polyethylene glycol (PEG) was identified as a possible etiologic agent. However, subsequent studies have suggested that PEG skin testing is of limited to no use either clinically or in the evaluation of possible allergic reactions to mRNA-based COVID-19 vaccines.[21] If true anaphylaxis to an mRNA-based COVID-19 vaccine is suspected, a clinician may consider graded dosing or the use of an alternative platform such as a viral-vector vaccine rather than an mRNA vaccine.[22,23]

Conclusion

The allergist plays an important role in investigating and safely vaccinating patients with a history of possible allergic reactions to vaccines. Through methodical risk stratification guided by the careful collection of patient history data, and the judicious use of skin testing, we can generally safely vaccinate patients even if there is a history suggestive of anaphylaxis.

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Financial Disclosures:

None declared

References

1. *Greenwood B. The contribution of vaccination to global health: past, present and future. Philosophical Transactions of the Royal Society B: Biological Sciences. 2014 Jun 19;369(1645):20130433.*
2. *Roush, S. W. et al. Historical Comparisons of Morbidity and Mortality for Vaccine-Preventable Diseases in the United States. JAMA. 2007;298:2155–2163.*
3. *National Advisory Committee on Immunization. Canadian Immunization Guide - Canada.ca. Public Health Agency of Canada https://www.canada.ca/en/public-health/services/canadian-immunization-guide.html (2023).*
4. *Muñoz CE, MacDonald B, Pham-Huy A, Vaudry W, Pernica JM, Boucher FD, Constantinescu C, Sadarangani M, Bettinger JA, Tapiéro B, Morris SK. Revaccination and Adverse Event Recurrence in Patients with Adverse Events following Immunization. The Journal of Pediatrics. 2022 Nov 1;250:45-53.*
5. *McNeil MM, Weintraub ES, Duffy J, Sukumaran L, Jacobsen SJ, Klein NP, Hambidge SJ, Lee GM, Jackson LA, Irving SA, King JP. Risk of anaphylaxis after vaccination in children and adults. Journal of Allergy and Clinical Immunology. 2016 Mar 1;137(3):868-78.*
6. *Liang JL, Tiwari T, Moro P, Messonnier NE, Reingold A, Sawyer M, Clark TA. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations and Reports. 2018 Apr 4;67(2):1.*
7. *Kelso JM. Misdiagnosis of systemic allergic reactions to mRNA COVID-19 vaccines. Annals of Allergy, Asthma & Immunology. 2021 Jul 1;127(1):133-4.*
8. *Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, Cox L, Khan D, Lang DM, Oppenheimer J, Portnoy JM. Adverse reactions to vaccines practice parameter 2012 update. Journal of Allergy and Clinical Immunology. 2012 Jul 1;130(1):25-43.*
9. *Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Rivas MF, Fineman S, Geller M, Gonzalez-Estrada A, Greenberger PA, Borges MS, Senna G. World allergy organization anaphylaxis guidance 2020. World Allergy Organization Journal. 2020 Oct 1;13(10):100472.*
10. *Government of Canada. Anaphylaxis and other Acute Reactions following Vaccination: Canadian Immunization Guide. 1–23 https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-2-vaccine-safety/page-4-early-vaccine-reactions-including-anaphylaxis.html (2021).*
11. *Dreskin SC, Halsey NA, Kelso JM, Wood RA, Hummell DS, Edwards KM, Caubet JC, Engler RJ, Gold MS, Ponvert C, Demoly P. International Consensus (ICON): allergic reactions to vaccines. World Allergy Organization Journal. 2016 Jan 1;9:32.*
12. *Nilsson L, Brockow K, Alm J, Cardona V, Caubet JC, Gomes E, Jenmalm MC, Lau S, Netterlid E, Schwarze J, Sheikh A. Vaccination and allergy: EAACI position paper, practical aspects. Pediatric Allergy and Immunology. 2017 Nov;28(7):628-40.*
13. *Chu DK, Abdurrahman Z. Vaccine allergy. CMAJ. 2019 Apr 8;191(14):E395.*
14. *Sakaguchi M, Nakayama T, Inouye S. Food allergy to gelatin in children with systemic immediate-type reactions, including anaphylaxis, to vaccines. Journal of Allergy and Clinical Immunology. 1996 Dec 1;98(6):1058-61.*
15. *Kelso JM. The adverse reactions to vaccines practice parameter 10 years on-what have we learned?. Annals of Allergy, Asthma & Immunology. 2022 Jan 31.*
16. *Gerhardt CM, Castro AP, Pastorino AC, de Barros Dorna M, de Jesus Nunes-Santos C, Aquilante BP, Miyaji KT, Lopes MH. Safety of yellow fever vaccine administration in confirmed egg-allergic patients. Vaccine. 2020 Sep 29;38(42):6539-44.*
17. *Greenhawt M, Turner PJ, Kelso JM. Administration of influenza vaccines to egg allergic recipients: a practice parameter update 2017. Annals of Allergy, Asthma & Immunology. 2018 Jan 1;120(1):49-52.*
18. *Cancado B, Aranda C, Mallozi M, Weckx L, Sole D. Yellow fever vaccine and egg allergy. The Lancet Infectious Diseases. 2019 Aug 1;19(8):812.*
19. *DiMiceli L, Pool V, Kelso JM, Shadomy SV, Iskander J, VAERS Team. Vaccination of yeast sensitive individuals: review of safety data in the US vaccine adverse event reporting system (VAERS). Vaccine. 2006 Feb 6;24(6):703-7.*
20. *Scheffler SA, Vakaljan SL, Wu V, Ohayon JA. Disguised Dairy: Anaphylaxis to "Hidden" Allergens in Routine Vaccinations in Child with Severe Cow's Milk Allergy. Journal of Allergy and Clinical Immunology. 2019 Feb 1;143(2):AB57.*
21. *Wolfson AR, Robinson LB, Li L, McMahon AE, Cogan AS, Fu X, Wickner P, Samarakoon U, Saff RR, Blumenthal KG, Banerji A. First-dose mRNA COVID-19 vaccine allergic reactions: limited role for excipient skin testing. The Journal of Allergy and Clinical Immunology: In Practice. 2021 Sep 1;9(9):3308-20.*
22. *Krantz MS, Kwah JH, Stone CA, Phillips EJ, Ortega G, Banerji A, Blumenthal KG. Safety evaluation of the second dose of messenger RNA COVID-19 vaccines in patients with immediate reactions to the first dose. JAMA Internal Medicine. 2021 Nov 1;181(11):1530-3.*
23. *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 Apr 1;9(4):1438-41.*

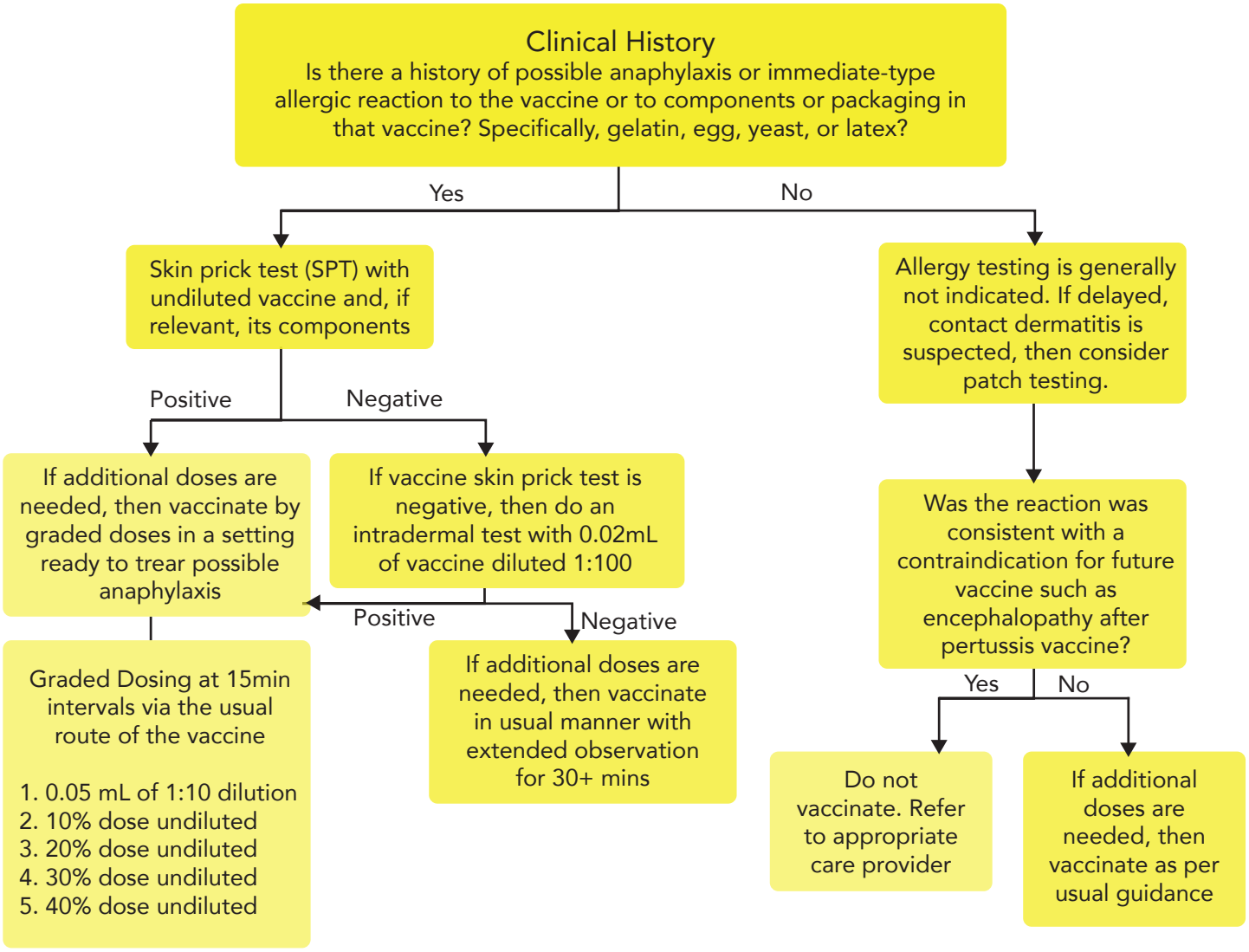

Figure 1: *Allergist's approach to adverse reactions to vaccine or vaccine components; adapted from AAAAI practice parameters (Kelso et al., 2012) and ICON guidelines (Dreskin et al., 2016).*