

Egg allergy and influenza vaccination

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ABSTRACT

Many egg-allergic patients are unnecessarily restricted from receiving the influenza vaccine. Patients with suspected egg allergy who require seasonal or H1N1 influenza vaccination can pose a significant challenge and should be appropriately evaluated by an allergist/immunologist. In most cases, if the benefits are felt to outweigh the risks, precautionary measures are available that can enhance safe vaccine administration. A case of influenza vaccine management in a child with egg allergy is presented. Clinical characteristics, diagnostic testing, case management, and natural history are reviewed. Clinical Pearls and Pitfalls include: (1) Batch-to-batch variability of egg content in extant influenza vaccines necessitates an informed and cautious approach to vaccination of an egg-allergic individual. (2) Due to denaturation of some egg proteins through heating, tolerance of "baked egg" products may not predict tolerance of "native egg" proteins present in the influenza vaccine. (3) Intradermal skin testing with influenza vaccine diluted 1:10 may be irritating to the skin and result in false positive results. (4) If skin test to the vaccine is positive, vaccination may still be cautiously administered, if necessary, in a graded-dose protocol, as presented herein. (5) Most patients with egg allergy are likely to develop egg tolerance by late childhood.

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Key words: Anaphylaxis, children, egg allergy, egg-specific IgE, H1N1, influenza vaccine, skin test, swine flu

Question:

The parents of a 13-year-old male with a history of egg allergy, atopic dermatitis, asthma, and allergic rhinitis present to your clinic, seeking advice regarding influenza vaccination. A history of egg allergy is elicited, originally manifesting as generalized urticaria with associated vomiting following the ingestion of a small amount of scrambled eggs at age 17 months. Initial work up revealed a positive skin test to egg white and an egg-specific immunoglobulin E (IgE) of 11 kU/L. In recent years, the child has been able to tolerate the ingestion of egg as an ingredient in cake, muffins, and waffles without adverse reaction. His parents desire to know whether he has "outgrown" his egg allergy and if he can safely receive the seasonal and H1N1 influenza vaccines. A recent egg-specific IgE test, ordered by the pediatrician, reveals a level of 0.70 kU/L. There is no history of an adverse reaction to any previous vaccinations.

In which of the following settings is it appropriate to administer the influenza vaccine to an egg-allergic child without further evaluation? (One or more answers may be correct.)

- A. The child has previously received the influenza vaccine without adverse reaction.
- B. The child is able to ingest egg as a prominent ingredient in baked goods such as muffins, but has not reattempted scrambled egg ingestion.
- C. The child is skin-test negative to egg white and egg yolk.
- D. The vaccine ovalbumin content is $<1.2 \mu\text{g/mL}$.
- E. If the intranasal live-attenuated vaccine is available, it is preferable to the trivalent inactivated influenza vaccine.

INTRODUCTION

The H1N1 influenza pandemic presents a challenge for clinicians to thoroughly evaluate options for influenza vaccination in patients who have been labeled as "egg allergic." All currently available influenza vaccines, including the swine flu (H1N1) vaccine, are produced by propagation of the influenza virus in chicken egg amniotic fluids. As a result, all currently available influenza vaccines contain egg protein and pose a potential risk, particularly to individuals with egg allergy. Fortunately, anaphylactic reactions to vaccines are very rare and are estimated to occur at an incidence of approximately 1 per million doses.^{1,2} When IgE-mediated reac-

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Table 1 Current (2009) recommendations regarding influenza vaccination in patients with suspected egg allergy

Source	Recommendation (2009)
FDA news release ⁴	People with severe or life-threatening allergies to chicken eggs, or to any other substance in the vaccine, should not be vaccinated.
CDC ⁶	TIV is contraindicated and should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine unless the recipient has been desensitized. LAIV is contraindicated in persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs.
AAP policy statement ⁸	Children who should not be vaccinated with TIV (or LAIV) include those who have a history of hypersensitivity, including anaphylaxis, to eggs, to any previous influenza vaccine dose, or to any of the vaccine components
AAP red book ⁷	Neither TIV, nor LAIV should be administered to anyone with severe allergic reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) to chicken, egg proteins, or any other component of the vaccines. Less severe or local manifestations of allergy to egg or feathers are not contraindications.
BSACI position statement ⁹	No egg-allergic patient should be refused swine influenza vaccination without full assessment and discussion of the risks and benefits. Patients who only develop local symptoms after consuming lightly cooked (scrambled) eggs should be vaccinated as usual.
AAAAI treatment guidelines ¹⁰	Many people with diagnosed or suspected egg allergy can receive influenza vaccination safely, if precautions are followed. A graded dose protocol can be used to administer the vaccine in sensitive patients.
Joint Task Force on Practice Parameters ³	Even if vaccine or vaccine component skin test results are positive, the vaccine may still be administered, if necessary, in graded doses.

The Joint Task Force on Practice Parameters represents the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology.

AAP = American Academy of Pediatrics; BSACI = British Society of Allergy and Clinical Immunology; CDC = Centers for Disease Control and Prevention; FDA = Food and Drug Administration; LAIV = live-attenuated influenza vaccine; TIV = trivalent inactivated influenza vaccine.

tions to influenza vaccines do occur, vaccine components, such as egg protein, gelatin, or antibiotics are the most likely causes.³ Consequently, egg allergy is a frequently stated contraindication to influenza vaccination (Table 1).^{4–10} A resultant concern is that many egg-allergic patients are unnecessarily restricted from vaccination. It is likely that most would be able to tolerate influenza vaccination.¹¹ Therefore, there is a need for patients with suspected allergy to egg to be carefully evaluated by an allergist/immunologist for optimal management.

EGG ALLERGY

Egg allergy is one of the most common causes of food allergies, affecting 1–2% of young children.^{12,13} It

represents the second most common food allergy in children and the first most common food allergy in children with atopic dermatitis.¹⁴ In addition, early sensitization to egg is a marker of later sensitization to aeroallergens¹⁵ and the development¹⁶ and persistence¹⁷ of asthma. Clinical manifestations of egg allergy result from an IgE-mediated hypersensitivity reaction to protein components of the whites or yolks of hen's egg. Almost all young children with egg allergy are likely to develop egg tolerance (defined as tolerance to the ingestion of concentrated egg) by late childhood (68% by age 16 years), with the exception being patients with an initial egg-specific IgE greater than 50 kU/l.¹⁸

Five major allergens have been characterized in hen's egg, which are designated Gal d 1–5.¹⁹ Most people who are allergic to hen's eggs have IgE antibodies that react to one of the following four egg white proteins: (1) ovomucoid (Gal d 1), (2) ovalbumin (Gal d 2), (3) ovotransferrin (Gal d 3) and (4) lysozyme (Gal d 4). Ovomucoid has been shown to be the immunodominant protein in egg white, whereas chicken serum albumin (Gal d 5) is the major allergen in egg yolk. Allergic sensitivity may occur to proteins present in either the egg white, egg yolk, or both. A small number of individuals who are allergic to eggs will develop allergic sensitivity to chicken or other poultry meats.¹⁹

Although the majority of egg-allergic individuals may tolerate the ingestion of extensively heated (baked) egg products (such as cakes, muffins, waffles), they may react to ingestion of less well-cooked eggs (such as scrambled eggs).^{20–22} A possible explanation for this dichotomy may reside in the differential sensitivity to thermal denaturation between ovalbumin and ovomucoid.²³ Many patients may be predominantly sensitized to ovalbumin, a more thermolabile allergen, known not only to be more sensitive to thermal denaturation, but also to show reduced IgE binding following extensive heating. By contrast, ovomucoid is able to retain its antibody-binding capacity despite extensive heating. Consequently, individuals tolerating egg in baked products, but not tolerating scrambled or raw egg may potentially still be at risk for the development of an allergic reaction following influenza vaccination. However, if an individual can eat lightly cooked egg (such as a spoonful of scrambled eggs) without any reaction, egg allergy is considered resolved, and the risk of an allergic reaction to the influenza vaccine is considered to be most unlikely.⁹

Diagnosis of egg allergy is generally made by a careful clinical history in combination with skin-prick testing or serologic testing for specific IgE. Symptoms consistent with egg allergy are of immediate onset, usually within minutes, and may include flushing, pruritus, urticaria, angioedema, wheezing, dyspnea, vomiting, and shock. The occurrence of these types of symptoms in association with positive diagnostic tests is sufficient for the diagnosis of egg allergy. In individuals where the history is unclear or where the association of egg allergy is suspect (such as in cases of atopic dermatitis), the gold standard of diagnosis remains a double-blind, placebo-controlled, oral challenge procedure, the diagnostic sensitivity of which may be enhanced by using less extensively heated (i.e., lightly cooked scrambled) eggs. Due to the potential of enteric infection with undercooked eggs, pasteurized egg products are recommended for oral challenge.²⁴ An alternative procedure in young children is an open (nonblinded) food challenge, which is acceptable in clinical practice. However, it is not advisable for par-

ents to administer to children an oral egg challenge at home because of the risk associated with an un supervised allergic reaction.

Diagnostic testing can be useful in cautiously predicting the clinical response to oral egg challenge. For example, it has been suggested that oral egg challenges not be performed in egg-allergic patients whose skin-prick tests result in a wheal diameter of >5 mm and >7 mm (in children <2 years old and >2 years old, respectively) because these results have been associated with a 90% chance of reacting to egg on subsequent food challenge.²⁵ Likewise, egg-specific IgE levels of >2 kU/L and >7 kU/L (in children <2 years old and >2 years old, respectively) are associated with a 95% positive predictive value of a positive challenge.²⁶ The caveat is that cutoff values such as these cannot be relied on for use in clinical practice because the range of reported cutoff values varies considerably, in part due to the different populations studied and different methodologies employed.¹⁹ However, these cutoffs may assist the clinician in forgoing a food challenge in patients with a high risk of reaction.^{27,28} For most clinicians, it would be more important to have reliable diagnostic cutoffs that predict a negative oral challenge. In this regard, the *in vitro* measurement of specific IgE to egg has poor negative predictive value. Therefore, it is best to rely on a negative skin-prick testing followed by ingestion challenge when attempting to establish the loss of egg sensitivity.

MANAGEMENT OF INFLUENZA VACCINATION IN PATIENTS WITH SUSPECTED EGG ALLERGY

Although the content of egg protein in the influenza vaccine may be a significant factor contributing to the risk for vaccine reaction in egg-allergic patients, this is often a moot point because the amount of egg protein present in the influenza vaccine is usually not known and has been reported to be highly variable, differing from year to year, as well as from manufacturer to manufacturer and lot to lot. For the 2009–2010 seasonal influenza/H1N1 formulations, variability in the content of egg protein in 14 samples has been reported to range from 0.0005 to 1.2168 $\mu\text{g}/\text{mL}$ (Li, J., Mayo Clinic, personal communication. Nov. 15, 2009) However, if the amount of egg protein is known to be $\leq 1.2 \mu\text{g}/\text{mL}$, current recommendations are that it can safely be administered, either in a 2-dose protocol (Table 2) and subsequently as a single dose, without the need for vaccine skin testing. This recommendation is based on tolerance of the two-dose protocol in 83 egg-allergic children administered an influenza vaccine that contained no more than 1.2 $\mu\text{g}/\text{mL}$ of egg protein.¹¹ A single booster injection 1 month after the initial vaccination was tolerated by all 34 recipients who needed a second dose.

Table 2 Examples of graded-dose protocols for influenza vaccine administration

Target Dose	Example of a Five Dose Protocol ^a		Example of a Two Dose Protocol ^b	
	0.5 ml	0.25 ml	0.5 ml	0.25 ml
Dose 1	0.05 ml 1:10	0.025 ml 1:10	0.05 ml FS	0.025 ml FS
Dose 2	0.05 ml FS	0.025 ml FS	0.45 ml FS ^c	0.225 ml FS ^c
Dose 3	0.1 ml FS	0.050 ml FS		
Dose 4	0.15 ml FS	0.075 ml FS		
Dose 5	0.2 ml FS ^c	0.10 ml FS ^c		

Graded-dose protocols should be performed under direct medical supervision with emergency medications and equipment to promptly treat an anaphylactic reaction. Target dose is age dependant. Refer to specific product information for appropriate target dosing.

^aDoses administered 15 min apart.

^bDoses administered 30 min apart.

^cObserve for at least 30 min after final dose

FS = full strength influenza vaccine.

Table 3 Skin testing to egg and influenza vaccine

Testing Agent	Step 1 Prick skin test	Step 2 (optional) ^b Intradermal skin test
Egg white	full strength	not indicated
Egg yolk	full strength	not indicated
H1N1 influenza vaccine	full strength ^a	1:100
Seasonal influenza vaccine	full strength ^a	1:100
Positive control	histamine	histamine
Negative control	saline	diluent

^aIf there is a history of previous life threatening anaphylaxis resulting from prior influenza vaccine, consideration can be given to first prick testing to a diluted vaccine, then if negative, to the full strength vaccine.

^bThe degree to which intradermal testing may result in false positive results is unknown. It is left to the discretion of the practitioner to decide whether skin-prick testing alone will suffice.

Although a history of tolerating cooked egg ingestion is somewhat reassuring, there is some concern that this history may not unequivocally predict low risk with vaccination. There are a number of case reports of egg allergic patients, who tolerate the ingestion of well cooked egg (as described above), but who experience anaphylactic reactions upon exposure to unheated egg protein (as may be present in the influenza vaccine).^{20–22} Consequently, when there exists a question of egg allergy, it is recommended to consider skin testing (or *in vitro* measurement of specific IgE antibody) to egg allergen as well as skin testing to the vaccine to help resolve the problem.¹⁰ Skin testing to egg is preferred over *in vitro* testing because of superior sensitivity, faster results, and lower cost. Skin testing for IgE sensitivity to the vaccine is most clearly indicated if the clinical history is consistent with prior anaphylaxis from egg ingestion.^{9,10}

When evaluating for the presence of specific IgE to the influenza vaccine, skin testing is the only option

available (Table 3). It is initially performed by the skin-prick technique, which usually suffices,⁹ but may be followed by more sensitive intradermal testing to exclude the possibility of a reaction in patients with suspected severe egg allergy. When performing intradermal testing to the influenza vaccine, it is important to be aware that dilutions of the vaccine at 1:10 vol/vol frequently irritate the skin and are more likely to produce false positive results, whereas dilutions of 1:100 vol/vol have been demonstrated to be nonirritating.²⁹ A negative skin test to the vaccine at a 1:100 dilution denotes a negligible chance of IgE sensitivity, and the vaccine can be administered in the standard manner.³ Regardless of negative test results, whenever a past history suggests a potential risk for an anaphylactic reaction, it is prudent to administer the vaccine under direct physician observation, with epinephrine and other supportive measures available. Additionally, depending on coexisting risk factors such as asthma, history of severe egg anaphylaxis, or strongly positive

egg skin test, the clinician may elect to administer the influenza vaccine using a two-dose graded protocol, even if the influenza vaccine skin test is negative.

Positive skin test results to the influenza vaccine do not necessarily contraindicate vaccine administration. If benefits outweigh risks, consideration can be given to administering the vaccine in a graded five-dose protocol (Table 2).³ The decision to undertake this procedure should be performed after obtaining patient consent, and under direct medical supervision, in a clinical setting equipped to assess and manage anaphylaxis.

SECOND VACCINE DOSING

A word of caution is necessary in situations where a second dose of vaccine is required in egg-allergic patients. Because of the lot-to-lot variability in egg protein content of the various influenza vaccine preparations, it is possible that the second dose of the vaccine may contain significantly more egg protein content than the dose first administered. Therefore, in egg-allergic patients, receiving a second dose of vaccine after tolerating a first dose, unless the source of the vaccine is from the same manufacturer's lot as the first dose, it is prudent to proceed with repeat vaccine skin testing, and to repeat the graded dosing protocol (if skin test positive). The same caveat applies to the administration of influenza vaccination in subsequent years. An alternative approach is to forego the repeat skin test and to proceed directly with graded dosing.

INTRANASAL VACCINE PREPARATIONS

The live-attenuated intranasal influenza vaccine is manufactured in the same fashion as the inactivated injectable vaccine and thus contains components of egg, gelatin, and antibiotics. It is often a less appealing option for certain allergic individuals due to its recommended precautionary use in patients with asthma and in those under 5 years of age who have recurrent wheezing, due to the potential of the vaccine to exacerbate the underlying condition.

CONCLUSION

Patients with suspected egg allergy who require influenza vaccine can pose a significant challenge and should be appropriately evaluated by an allergist/immunologist. In most cases, if the benefits are felt to outweigh the risks, cautionary measures are available that can enhance safe vaccine administration. For mild egg allergy, the vaccine may be administered following routine vaccination precautions. For more severe egg allergy, especially with positive vaccine skin test results, the vaccine should be administered using a graded-dose protocol.

Answer: C, D

Pearls

- Egg allergy is the second most common food allergy in children and the first most common food allergy in children with atopic dermatitis.
- Due to thermolability of some egg proteins, the majority of children with egg allergy are able to tolerate the ingestion of heated egg in the form of baked products, but react to less well cooked products.
- Most patients with egg allergy are likely to develop egg tolerance by late childhood (teens), with the exception of patients with an initial egg-specific IgE greater than 50 kU/L.
- Even patients with severe egg allergy may take advantage of the benefits of influenza vaccination through a careful approach to testing and protocol-driven administration of the vaccine.
- If the egg protein content of the influenza vaccine is known to be $<1.2 \mu\text{g/mL}$, vaccine administration may proceed without skin testing using a two dose-protocol.
- If skin testing to the vaccine is positive, the vaccine may still be cautiously administered, if necessary, in graded doses.

Pitfalls

- Tolerance of the ingestion of cooked egg may not predict tolerance of egg proteins present in the influenza vaccine.
- Intradermal skin testing with influenza vaccine diluted 1:10 may be irritating to the skin and result in false positive results.
- Because the influenza vaccine contains gelatin and other potential allergens in addition to egg protein, tolerance to egg does not guarantee tolerance to the vaccine.
- Due to lot-to-lot variability of egg proteins in the influenza vaccination, previous safe administration of the vaccine does not denote future tolerance, requiring thoughtful consideration of vaccine administration in the egg allergic individual with each vaccination.

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