

Management of Influenza Vaccination In Patients With Suspected Egg Allergy

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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 seasonal and swine flu (H1N1) vaccines (both the inactivated injectable and live-attenuated intranasal vaccine preparations), are produced by propagation of the influenza virus in chicken egg amniotic fluids, and as a result contain egg protein, which can pose a potential risk 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 reactions to influenza vaccines do occur, vaccine components, including 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, when, in fact, most would likely be able to tolerate influenza vaccination.¹¹ Therefore, patients with suspected egg allergy may benefit from being carefully evaluated by an allergist/immunologist for optimal management of their influenza vaccination options.

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 as well as 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. Five major allergens have been characterized in hen's egg, four of which are egg white proteins (ovomucoid, oval-

bumin, ovotransferrin and lysozyme); whereas chicken serum albumin is the major allergen in egg yolk.¹⁸ Fortunately, almost all children with egg allergy develop tolerance to egg ingestion by late childhood (68% by age 16 years).¹⁹

Although the majority of egg-allergic individuals react to the ingestion of less well cooked eggs (such as scrambled eggs), many may tolerate the ingestion of extensively heated (baked) egg products (such

as cakes, muffins, waffles).²⁰⁻²² A possible explanation for this dichotomy resides in the differential sensitivity to thermal denaturation that exists between egg proteins.²³ Many patients may be predominantly sensitized to ovalbumin, which is the egg protein most sensitive to thermal denaturation. By contrast, ovomucoid, the immunodominant protein in egg white, retains its potency as an allergen despite extensive heating. Consequently, individu-

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

Source	Recommendation (2009)
FDA News Release[4] CDC[6]	People with severe or life-threatening allergies to chicken eggs, or to any other substance in the vaccine, should not be vaccinated. 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 (eg, 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 (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI) 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

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	
	0.5ml	0.25ml	0.5ml	0.25ml
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.

a Doses administered 15 minutes apart.

b Doses administered 30 minutes apart.

c Observe for at least 30 minutes after final dose.

FS = full strength influenza vaccine

als 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 to the native egg protein present in the 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 and/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/or shock. In individuals where the history or testing is unclear or where the clinical correlation of a positive test for specific IgE to egg is questionable, the gold standard of diagnosis remains a double-blind, placebo controlled, oral challenge procedure (which is an outpatient based procedure, only performed when benefits outweigh risks, including anaphylaxis.) An alternative procedure is an open (non blinded) food challenge. However, it should be noted that it is not advisable for parents to administer to children an oral egg challenge at home because of the potential risk of anaphylaxis.

Diagnostic cutoffs have been reported, for skin test size and for *in vitro* measures, which may assist the clinician in deciding to forgo a food challenge in patients when

a high risk of reaction is present.^{24,25} However, 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 (rather than *in vitro* measures), followed by ingestion challenge when attempting to establish the loss of egg sensitivity.

Batch-to-batch variability of egg content in extant influenza vaccines necessitates an informed and cautious approach to vaccination of an egg allergic individual.

MANAGEMENT OF INFLUENZA VACCINATION IN PATIENTS WITH SUSPECTED EGG ALLERGY

Although the quantity of egg protein in the influenza vaccine may be a significant contributing factor to the risk for a vaccine reaction in egg allergic patients, the exact content is usually not reported and can 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, preliminary data suggests vari-

ability in the content of egg protein ranging from 0.0005-1.2168 micrograms/mL. [Li, J. Personal Communication. Nov. 15, 2009] Based on prior clinical studies, if the amount of egg protein is known to be \leq 1.2 micrograms/mL, the vaccine 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.¹¹

Although a history of tolerating cooked egg ingestion may seem reassuring, there is concern that this history may not unequivocally predict low risk with vaccination. This results from a number of case reports of egg allergic patients, who tolerated the ingestion of well cooked egg (as described above), but who experienced 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 as well as skin testing to the vaccine in order to resolve the question.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 2) It is initially performed by the prick technique, which usually suffices,⁹ but may be followed by more sensitive, properly diluted, intradermal testing in order to exclude the possibility of a reaction in patients with suspected severe egg allergy. Even if all test results are negative, 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.

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 3)³The 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 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 first dose. 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.

CONCLUSION

Patients with suspected egg allergy who require influenza vaccine should be appropriately evaluated by an allergist/immunologist. Tolerance of the ingestion of cooked egg may not predict tolerance of egg proteins present in the influenza vaccine. Batch-to-batch variability of egg content in extant influenza vaccines necessitates an informed and cautious approach to vaccination of an egg allergic individual. For most individuals with egg allergy, 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. 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.

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The author and spouse/significant other have no financial interests to disclose.

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