

Drug and Vaccine Allergy



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KEYWORDS

• Allergy • Beta-lactam • Penicillin • Egg allergy • Influenza vaccination

KEY POINTS

- Children labeled as allergic to penicillin should undergo penicillin skin testing and oral challenge to identify the vast majority who are not currently penicillin-allergic.
- Children with a distant history of a mild reaction to penicillin can safely be administered oral cephalosporins.
- Reactions to carbapenems among children with penicillin allergy are rare, and such medications can be administered cautiously under observation.
- Leaving egg-allergic patients unvaccinated against influenza leaves them at risk for morbidity and mortality from influenza.
- Studies involving thousands of egg-allergic subjects, including hundreds with histories of severe reactions to the ingestion of eggs, have shown a low rate of minor reactions that is not different from nonegg-allergic controls.
- Current guidelines from the American Academy of Pediatrics (AAP) and Centers for Disease Control and Prevention (CDC) recommend that egg-allergic patients receive annual influenza vaccine and be observed for 30 minutes afterward; however, given the safety data, even this precaution may be unnecessary.

INTRODUCTION

It is important to identify children who are allergic to drugs and vaccines, because administration of these substances to such children can lead to serious, even life-threatening systemic allergic reactions (anaphylaxis). Recent updates of practice parameters on adverse reactions to drugs¹ and vaccines² provide excellent resources on these topics.

However, it is also important not to overdiagnose such allergy (ie, label children as allergic when they are not), because this deprives them of the most appropriate treatment. This article specifically reviews allergic reactions to beta-lactam antibiotics and the administration of influenza vaccine to egg-allergic recipients. These are areas where recent evidence has allowed the administration of these treatments to children from whom they had previously been withheld.

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Immunol Allergy Clin N Am 35 (2015) 221–230

<http://dx.doi.org/10.1016/j.iac.2014.09.013>

immunology.theclinics.com

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BETA-LACTAM ANTIBIOTICS

Penicillin and its derivatives are regarded as the most common cause of drug allergy,¹ due to propensity to cause such reactions, but also because of frequent use. However, the incidence of penicillin allergy appears to be falling over time, perhaps related to the less frequent use of penicillin by the potentially more sensitizing parenteral route in the outpatient setting.^{3,4} Approximately 6% of children are reported to be allergic to penicillin.⁵ However, only approximately 4% to 9% of such children have positive immediate type (immunoglobulin E [IgE]) skin tests to penicillin reagents.⁶⁻⁹ The remainder were either never allergic to penicillin or the allergy was lost with the passage of time.¹⁰ Those who were never allergic may have been mislabeled, because they suffered a nonimmunologic side effect from the medication such as emesis, or because they suffered an adverse event that was coincidental to, but not caused by the penicillin administration. Thus, most children labeled as penicillin-allergic are not, and are inappropriately denied treatment with this class of antibiotics. The use of alternative antibiotics may be associated with suboptimal treatment and higher costs and may promote antibiotic resistance.¹¹ Thus, a strong argument can be made for testing such patients in advance of need in order to identify the vast majority who are not currently allergic to penicillin.^{1,10}

It had previously been advocated that penicillin skin testing be performed in patients with suspected penicillin allergy only at the time of infection and only when there were no acceptable alternatives.¹² The rationale for this recommendation was based in part on a concern that skin testing and challenge with penicillin could resensitize previously allergic children who had lost sensitivity over time, placing them at risk for allergic reactions when administered penicillin in the future. However, such resensitization is rare with orally administered penicillins,^{6,9} although it may be somewhat higher after parenterally administered penicillin.¹³

Penicillin is a small molecule and must act as a hapten with a protein carrier to have a large enough size and high enough valency to elicit an IgE-mediated response. Penicillin is metabolized to so-called major and minor determinants. The majority of the drug is metabolized to the penicilloyl (major) determinant, while the remainder is metabolized to penilloate and penicilloate (minor) determinants. Unmetabolized benzylpenicillin, known as penicillin G, is also typically regarded as a minor determinant. Penicillin G has always been available as a skin test reagent simply as a dilution of the drug used for treatment. The penicilloyl (major) determinant is available commercially as benzylpenicilloyl polylysine, where multiple penicilloyl determinants (haptens) are linked to an amino acid polymer (carrier). Penilloate and penicilloate (minor) determinants have never been available commercially in the United States, although many allergists with access to laboratory facilities have generated these reagents from penicillin G through acid and alkaline hydrolysis, respectively.¹⁴ The rationale for including penilloate and penicilloate minor determinants for skin testing patients with suspected penicillin allergy is that some patients with such histories will have positive skin test results only to these reagents.^{6,15} Some centers perform penicillin skin testing with the readily available benzylpenicilloyl polylysine and penicillin G, and if negative perform an oral amoxicillin challenge under observation to identify those patients who are clinically allergic to penicillin despite negative skin test with these 2 reagents, some of whom would presumably have had positive skin tests to penilloate, penicilloate, or amoxicillin.¹⁶ However, when 496 patients with suspected penicillin allergy but negative benzylpenicilloyl polylysine and penicillin G skin tests underwent amoxicillin challenge, only 4 (0.8%) were positive, all developing only hives within 1 hour. The authors calculated that 3375 patients would have to be tested with a panel

also including penilloate, penicilloate, and amoxicillin to avoid 1 additional positive oral challenge with amoxicillin.¹⁶ Thus, until such time as a minor determinant mixture is commercially available, skin testing with benzylpenicilloyl polylysine and penicillin G, and if negative, observed oral amoxicillin challenge, is a reasonable approach to the evaluation of penicillin allergy.

A common clinical scenario is for a child to develop up a rash, often urticarial, several days into a course of penicillin. Thus, the nature of this adverse event (urticaria) is consistent with an IgE-mediated mechanism, but the timing (delayed) is not, given that the typical IgE-mediated reaction should occur within minutes to hours of the first dose in a previously sensitized child. Children also often develop maculopapular rashes in this setting, which can be difficult to distinguish from urticarial reactions without a careful history and physical examination. Nonetheless, given the potential danger of a more serious reaction with subsequent exposure if the child does have an IgE-mediated penicillin allergy, such children are typically labeled as penicillin-allergic and do not receive the drug again in the future. A study published in 2011 examined the likelihood of penicillin allergy in this clinical situation.¹⁷ Eighty-eight children who had developed urticarial (53%) or maculopapular (47%) rashes an average of 4.9 days into the course of treatment with a beta-lactam antibiotic underwent intra-dermal penicillin skin tests and an oral challenge test (OCT) with the culprit antibiotic testing 2 months later. The skin test results were positive in 11 of the 88 patients (12.5%), yet 7 of these patients did not develop a rash on OCT. Six of the 88 patients (6.8%) developed a rash on OCT, 4 urticarial and 2 maculopapular. Three of the 4 patients who developed urticarial reactions on OCT had positive skin tests, as did 1 of the 2 patients who developed a maculopapular rash. Thus, most children who develop a delayed-onset rash during the course of treatment with a beta-lactam antibiotic are not allergic to the antibiotic and will not develop a rash on subsequent exposure. Penicillin skin testing and oral challenge performed 1 or 2 months after the event will confirm the absence of allergy in most children so that they need not be inappropriately labeled as penicillin-allergic.

Penicillins and cephalosporins are both beta-lactam class antibiotics, and thus there is at least the theoretic potential that a child who is allergic to penicillin would also react to cephalosporins due to immunologic cross-reactivity (ie, that IgE antibodies directed against a particular penicillin epitope would also bind a similar cephalosporin epitope). However, most penicillin-allergic children tolerate cephalosporins.¹⁸ The potential for cross-reactivity appears largely related to the similarity of side chains on various penicillins and cephalosporins.¹⁸ There are several other factors that may increase the risk of a reaction to a cephalosporin in a penicillin-allergic child. The severity of a past anaphylactic reaction may predict the severity of a future reaction; penicillin allergy tends to wane over time, and anaphylactic reactions are more common with parenteral (as opposed to oral) administration. Thus, in a child with a recent history of a severe reaction to penicillin, caution is warranted with the administration of a parenteral cephalosporin, particularly one with a side chain similar to the penicillin that caused the initial reaction. On the other hand, a child with a distant history of a mild reaction to penicillin will almost certainly tolerate administration of an oral cephalosporin, particularly one with a side chain dissimilar to the penicillin that caused the initial reaction.

Carbapenems and monobactams are beta-lactam antibiotic classes with chemical structures that are dissimilar to other beta-lactam antibiotics, and the rate of cross-reactivity between these antibiotics and penicillin is low. One-hundred-eight children with histories of immediate-type allergic reactions to penicillin and positive penicillin skin tests were skin tested with the carbapenem meropenem.¹⁹ Only 1

child had a positive meropenem skin test and was not challenged; however the remaining 107 children had negative meropenem skin tests and tolerated a meropenem challenge. Similarly, 124 children with histories of immediate-type allergic reactions to penicillin and positive penicillin skin tests were skin tested with the carbapenem imipenem.²⁰ Only 1 child had a positive imipenem skin test and was not challenged. Interestingly, this was the same child who had a positive skin test to meropenem in a study described previously. However, the remaining 123 children had negative imipenem skin tests and tolerated an imipenem challenge. Thus, in a child with a history of penicillin allergy who is to receive a carbapenem, skin testing with penicillin reagents and the carbapenem proposed for administration may be considered; however, given the low rate of cross-reactivity, cautious administration of the carbapenem under observation may be an acceptable alternative. Patients who are allergic to penicillin have not shown skin test reactivity or clinical reactions to the monobactam aztreonam.²¹

ADMINISTRATION OF INFLUENZA VACCINE TO EGG-ALLERGIC CHILDREN

Most influenza vaccines are literally grown in chicken eggs.^{22,23} Although the virus is subsequently purified, some residual egg protein remains in the final product. For decades, it had been assumed that administration of influenza vaccines containing this residual egg protein to egg-allergic recipients would result in systemic allergic reactions. For this reason, egg allergy had been considered a contraindication to the receipt of influenza vaccine. This approach may be regarded as conservative or prudent, because it avoids this risk of an allergic reaction. However, it neglects the risk of remaining unimmunized. Each year in the United States, over 20,000 children are hospitalized with influenza, and over 100 children die from the disease.^{24,25} Thus, not vaccinating egg-allergic children with influenza vaccine avoids the theoretic risk of an allergic reaction, but leaves the children at risk of hospitalization or death from influenza.

Many studies have been conducted to assess the risk of administration of egg-based influenza vaccines to egg allergic recipients.²⁶⁻⁵³ Most such recipients are children, as egg allergy is quite common among children, but almost always outgrown. The inclusion criteria for these studies have included both a recent history of reaction to the ingestion of egg, where the nature and timing of this reaction are consistent with an IgE-mediated event, as well as demonstration of IgE antibody either by immediate-type allergy skin testing or serum-specific IgE antibody to egg. Some studies excluded patients with histories of anaphylactic as opposed to less severe allergic reactions to egg; however, most studies specifically included those with anaphylactic egg allergy. Many studies included skin testing with the influenza vaccine as part of the study protocol. Although some studies withheld the vaccine from egg-allergic patients with positive vaccine skin tests, in the majority of studies, the vaccine was administered even to those with positive vaccine skin tests. Some studies took the precautionary step of administering 10% of the vaccine dose followed by a 30-minute observation, after which, if no reaction occurred, the remaining 90% of the vaccine dose was given. Other studies administered the vaccine as a single (100%) age-appropriate dose in the usual manner. Some studies have also included control groups of nonegg-allergic children who were also carefully observed for adverse reactions after immunization.

Collectively, these studies evaluated 4315 patients with egg allergy, including 656 with severe reactions to the ingestion of egg. Including booster doses, 4872 doses of influenza vaccine were administered to these patients. No anaphylactic reactions

were reported. Occasional patients developed hives or mild wheezing; however, the rate of these reactions was similar in control patients without egg allergy. These rare reactions were no more common in patients who were skin test positive to the vaccine than in those who were skin test negative. The vaccine was tolerated equally well whether given in divided doses or as a single dose.

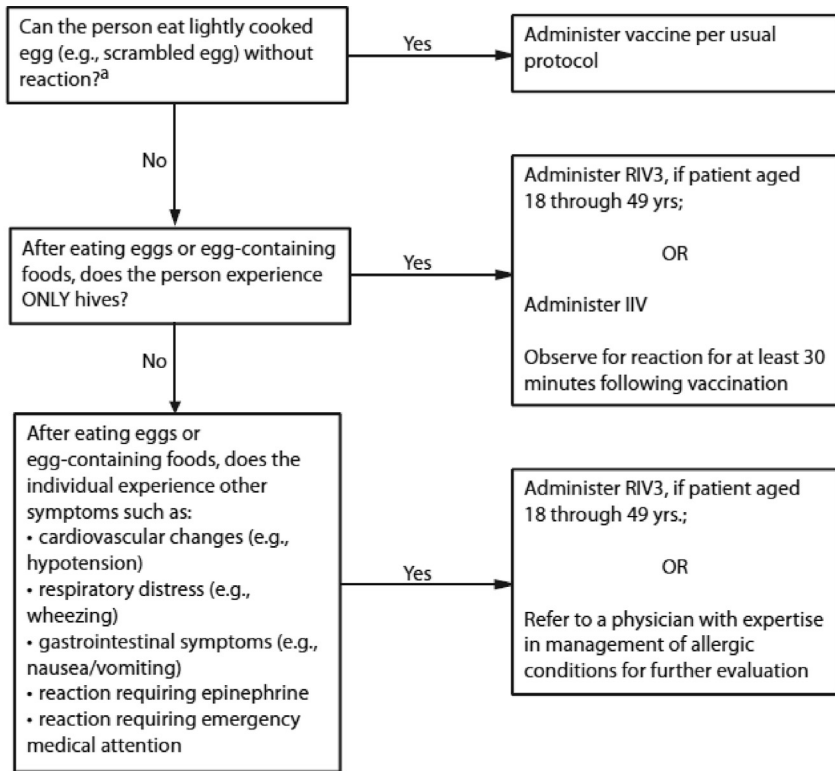
The actual amount of egg protein in the various influenza vaccines has also been measured by the manufacturers and in independent laboratories. Although other egg proteins may be present in the vaccine, the particular egg protein measured in the vaccines is ovalbumin, with the concentration typically expressed as micrograms of ovalbumin per milliliter or per 0.5 mL vaccine dose. According to the manufacturers, all currently available influenza vaccines contain less than 1 μg of ovalbumin per 0.5 mL dose.²³ Analysis in independent laboratories has often revealed levels of ovalbumin much lower than the amounts claimed by the manufacturers.^{54–56}

It is likely that the reason that egg-allergic patients can receive the egg-containing influenza vaccine without reaction is that the amount of egg protein present in the vaccine is simply not high enough to induce a reaction. Although there are no dose–response studies on the injection of egg protein as occurs with vaccination, attempts have been made to establish the lowest dose of egg protein that could elicit a reaction in egg-allergic patients by ingestion.^{57,58} The lowest amount of egg protein ever reported to provoke an allergic reaction is 130 μg .⁵⁷ A calculated dose of egg protein that “would be predicted to elicit no reaction in 99% of the allergic population [and]...would likely provoke mostly mild allergic reactions in the remainder of the patients” is 30 μg .⁵⁸ Thus, although not subject to digestion, the at most 1 μg of egg protein present in the influenza vaccine is likely below the threshold required to elicit an allergic reaction.

These considerations have led to major changes in official guidance regarding the administration of influenza vaccines to egg allergic recipients. Beginning in 2011, both the CDC’s Advisory Committee On Immunization Practices (ACIP)⁵⁹ and the AAP’s Committee on Infectious Diseases⁶⁰ began recommending that egg-allergic patients should receive annual influenza vaccines, with the latter stating “Although both trivalent influenza vaccine (TIV) (now called IIV, inactivated influenza vaccine) and LAIV (live attenuated influenza vaccine) are produced in eggs, recent data have shown that influenza vaccine administered in a single, age-appropriate dose is well tolerated by nearly all recipients who have egg allergy. More conservative approaches, such as skin testing or a 2-step graded challenge, are no longer recommended.” In subsequent influenza seasons, since this change in recommendation, there has been no disproportionate reporting of allergic reactions after influenza vaccine.²³

Recently 2 new influenza vaccines have been introduced that are not grown in eggs. One is made from virus grown in cell culture,⁶¹ and the other consists of recombinant hemagglutinin proteins produced in an insect cell line.⁶² There is no mention of egg allergy in the package inserts for either of these 2 vaccines. The cell culture-based vaccine is approved for patients 18 years of age and older. The recombinant vaccine is approved for patients 18 to 49 years of age. Thus, these vaccines are acceptable alternatives for egg-allergic adults; however, this constitutes a tiny fraction of the population of egg-allergic patients, most of whom are children. It may be tempting to use one of these to vaccines off label (ie, outside the approved age range) for children with egg allergy; however, this is not appropriate. The safety and effectiveness of these vaccines have not been demonstrated in younger patients, and antibody responses to the recombinant vaccine in children ages 6 months to 3 years were less than those generated to a standard influenza vaccine. Further, the safety of egg-based vaccines has been demonstrated in egg-allergic children.

Recommendations from the CDC and AAP for the 2013 to 2014 influenza season^{22,23} are summarized in Fig. 1. This algorithm points out that patients who can consume egg directly without reaction are not egg-allergic and require no special precautions for influenza vaccination. Most patients who have had allergic reactions to the ingestion of egg have had hives as their only symptom. Such patients can receive influenza vaccine in a primary care setting with a 30-minute observation period afterward. It is recommended that patients who have had more severe reactions to the ingestion of egg, or who are sensitized but who have never knowingly ingested egg and thus whose reaction severity cannot be known, be referred to an allergist. The 2012 update of the adverse reactions to vaccines practice parameter for allergists recommends that influenza vaccine be administered (as a single, age-appropriate dose without prior vaccine skin testing) to patients with egg allergy of any severity (including anaphylaxis) with a 30-minute observation period afterward.² However, given the



Abbreviations: IIV = inactivated influenza vaccine; RIV3 = recombinant influenza vaccine, trivalent

^a Persons with egg allergy might tolerate egg in baked products (e.g. bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy. For persons who have no known history of exposure to egg but who are suspected of being egg-allergic on the basis of previously performed allergy testing, consultation with a physician with expertise in the management of allergic conditions should be obtained prior to vaccination. Alternatively, RIV3 may be administered if the recipient is aged 18 through 49 years.

Fig. 1. Recommendations regarding influenza vaccination of persons who report allergy to eggs. IIV, inactivated influenza vaccine; RIV3, recombinant influenza vaccine, trivalent. (From Advisory Committee on Immunization Practices, United States, 2013–2014 influenza season.)

overwhelming safety data on the administration of egg-based influenza vaccines to egg-allergic recipients, a statement endorsed by the Joint Task Force on Practice Parameters has recommended that all patients with egg allergy receive annual influenza vaccination without any special precautions.⁶³ Although all studies published to date have examined the safety of inactivated influenza vaccines (IIV) in egg-allergic recipients, the LAIV for intranasal administration contains less than 0.24 µg of ovalbumin per 0.2 mL dose²³ and would also not be expected to cause reactions in egg-allergic subjects.

FUTURE CONSIDERATIONS/SUMMARY

Given the general principle that patients who are allergic to a particular allergen should avoid exposure to the allergen, it seemed reasonable for children with a prior history of reactions to penicillin not to receive subsequent courses of beta-lactam antibiotics and for egg-allergic children not to receive influenza vaccines containing egg protein. However, this conservative approach is not without risks of its own. Denying patients treatment with beta-lactam antibiotics when they are able to tolerate them leads to their treatment with antibiotics that may be less effective and more expensive and have greater side effects. Denying egg-allergic patients influenza vaccines when they are able to tolerate them leaves them at risk of the morbidity and mortality associated with the disease itself. Thus, children with a history of penicillin allergy should undergo penicillin skin testing and oral challenge to identify those who never were or are no longer allergic, allowing them to be treated with beta-lactam antibiotics, and children with egg allergy of any severity should receive annual influenza vaccination. In the future, efforts could be directed toward applying the same approach to other drugs and vaccines. For example, sulfa allergy is also commonly reported. If reliable skin test reagents could be developed for sulfonamide antibiotics, testing and challenge might reveal that most of these patients are also not allergic to this antibiotic. Similarly, for patients reporting egg allergy, yellow fever vaccine skin testing and graded dose and are currently recommended; however, carefully conducted studies such as those performed with influenza vaccine might determine that these precautions are unnecessary. Allergists routinely provide an important service in determining what patients are allergic to and need to avoid, but can also provide an equally important service in determining what patients are not allergic to and need not avoid.

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