

CLINICAL COMMENTARY

The Importance of Penicillin Skin Testing in Patients with a History of Penicillin Allergy

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This review presents information about the importance of penicillin skin testing in the evaluation of patients who report an allergy to penicillin.

Approximately 10% of patients report a history of penicillin allergy. However, more than 90% of these patients are able to tolerate penicillin.^{1,2} Patients often attribute a family history of penicillin allergy to themselves or an adverse reaction, such as nausea, diarrhea, or a non-pruritic maculopapular rash as evidence of a penicillin allergy. The label of penicillin allergy leads to increased use of second line antibiotics, such as fluoroquinolones, clindamycin, and third generation cephalosporins. Overuse of broad spectrum antibiotics in patients labeled with a penicillin allergy increases the rate of *Clostridium difficile*, vancomycin-resistant *Enterococcus*, and methicillin resistant *Staphylococcus aureus*.^{3,4} Therefore, penicillin allergy is increasingly being recognized as a public health concern. Correctly diagnosing penicillin allergy in hospitalized patients could reduce antibiotic resistance and hospital costs.⁵⁻⁸

Multiple studies have shown that patients rapidly lose their penicillin sensitivity over time.⁹ Both the age of the patient and the time since the reaction correlate inversely with the rate of a positive penicillin skin test.² Since older patients are more likely to be hospitalized and require antibiotics,¹⁰ penicillin skin testing is especially useful in older individuals with a history of penicillin allergy.

Another health care scenario where penicillin allergy often arises is in pregnant women with group B streptococcus colonization. Two studies have shown that the majority of pregnant women reporting penicillin allergy have negative penicillin skin testing and can tolerate GBS prophylaxis without adverse reaction.^{11,12}

Penicillin skin testing to major and minor determinants is a safe and validated way to evaluate patients with a history of an immediate reaction to penicillin. The negative predictive value of penicillin skin testing, if performed with major and minor determinants, approaches 100%.^{13,14} Although serum-specific IgE testing to penicillin, amoxicillin, and ampicillin is commercially available, the predictive values of these tests are unknown. Therefore, these blood tests are not acceptable alternatives to skin testing. Moreover, results from serum-specific IgE typically take about one week to return, which

reduces its utility in the inpatient setting. If the blood test were positive, an IgE-mediated hypersensitivity would be assumed. If the test were negative, however, the negative predictive value is unknown; therefore, the safety of proceeding with penicillin treatment is unknown.

The history is important when evaluating patients with a history of penicillin allergy. The timing and description of the reaction are important to assess the type of reaction that occurred. As described by Gell and Coombs, a type 1 reaction is IgE-mediated and occurs minutes to hours after exposure to the offending agent. This type of reaction can be severe and can present with acute urticaria, angioedema, respiratory distress, and hypotension. If the patient's adverse reaction to penicillin was not immediate, then penicillin skin testing is not indicated. However, if the patient is not sure of the timing of the reaction, then it is reasonable to proceed with penicillin skin testing. If the patient has a history of a type 4 reaction, such as a blistering or desquamating rash, skin testing is not indicated and avoidance of all similar antibiotics is necessary. Skin testing is not indicated if the patient developed toxic epidermal necrolysis, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), severe hepatitis, interstitial nephritis, or hemolytic anemia, as penicillin skin testing does not assess for these types of reactions. The offending medication must be avoided indefinitely due to the severity of these reactions. If the patient reports a delayed reaction that includes a morbilliform or other non-life threatening reaction, then an oral challenge to penicillin can be considered. It is also important to inquire about other medications the patient was taking at the time of the reaction. If the patient does not remember the reaction, another historical aspect is to ask if the patient has ever received another penicillin or cephalosporin by giving examples to the patient (i.e., amoxicillin, Augmentin, Keflex, etc). If they have received any of these medications since the initial reaction and had no adverse effect, this supports the possibility that the patient is no longer allergic.

Penicillin allergy evaluation can be safely performed before the need for antibiotic treatment. Skin testing is not associated with re-sensitization.^{15,16} In a patient with a history of penicillin allergy who has tolerated one or more courses of penicillin, repeat skin testing does not need to be performed as re-sensitization after treatment with penicillin is rare.¹⁷

A common misconception is that the β -lactam ring is the cause of allergy to penicillin. During metabolism in the body, the beta lactam ring is cleaved to form potentially allergenic compounds. In vitro cross-reactivity between penicillin and cephalosporins is mainly due to the R side chain.¹⁸ Prior to 1980, the reaction rate in patients with a history of penicillin allergy and positive penicillin allergy was 10-20%. Since 1980, the incidence of clinical cross-reactivity between penicillin and cephalosporins is now \sim 2%.¹⁸⁻²¹ The high reaction rate prior to 1980 is likely due to the fact that some first generation cephalosporins were contaminated with penicillin. The predictive value of skin testing to cephalosporins is unknown; therefore, it is not routinely used in the clinical setting. Penicillin skin testing cannot predict the risk of a reaction to a cephalosporin except if the cephalosporin shares a side chain with the penicillin, such as with ampicillin and cephalixin or amoxicillin and cefadroxil. If the patient has a history of allergy to a cephalosporin, then use of a cephalosporin with a different side chain is usually acceptable.

Carbapenems and monobactams can be safely used in patients with a history of penicillin allergy.²²⁻²⁵ An exception is the cross-reactivity that has been demonstrated between aztreonam and ceftazidime.

In conclusion, penicillin skin testing is a safe and reliable way to evaluate patients with a history of penicillin allergy. This testing should be considered in any patient whose reaction was remote (>10 years ago), in older individuals (especially >50 years of age), and in any patient undergoing elective surgery.

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