

Point-of-Care Guides

Predicting True Penicillin Allergy in Adults

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Clinical Question

In patients reporting a penicillin allergy, is it possible to determine the likelihood of true allergy without formal testing?

Evidence Summary

Penicillin allergy is the most commonly documented drug allergy in medical records, with a prevalence of approximately 10% of all patients.¹ However, in up to 90% of patients with a reported allergy, penicillins are tolerated on allergy testing.² As a consequence of patients being labeled as having a penicillin allergy, alternative (typically broader-spectrum) antibiotic classes are often used, with potentially poorer efficacy and safety profiles. This leads to increased multidrug-resistant organisms, treatment failure, and health care costs and prolonged hospitalizations.³

A formal drug challenge is the preferred test for investigating immunoglobulin E-mediated penicillin hypersensitivity (type I hypersensitivity)⁴; skin testing is also a commonly used validated tool.¹ A number of studies have been performed to develop clinical prediction rules using features of the allergy history to help determine which patients labeled as having a penicillin allergy can safely be given a beta-lactam antibiotic. Despite the high prevalence of patients labeled as having a penicillin allergy, there is an international shortage

of those proficient in conducting formal drug challenges.⁵

A study in a tertiary referral center in the United Kingdom used multivariable logistic regression to identify patients at low risk of type I beta-lactam allergy.⁶ This included patients who had no history of anaphylaxis, who had a reaction more than one year before referral, and who could not recall what the index drug was. Only 1.6% of patients with all of these traits had type I hypersensitivity. Another study derived and validated two algorithms in a retrospective cohort of individuals evaluated for beta-lactam allergy.⁷ Similarly, anaphylaxis, shorter time since the reaction occurred, and reaction onset less than one hour after most recent drug intake were identified as predictors of a true allergy. However, both algorithms had low sensitivity (51% and 60%), precluding their clinical use.⁷

A more recent study derived and validated a clinical prediction rule for penicillin allergy.⁸ The PEN-FAST (penicillin allergy, five or fewer years ago, anaphylaxis/angioedema, severe, treatment) rule was derived from a prospective cohort of 622 allergy-tested patients in Melbourne, Australia, using a multivariable logistic regression model. This identified five independent predictors of an oral challenge positive for penicillin allergy. Discrimination (the ability to separate those with a positive allergy result from those without) was shown to be good in the derivation and internal validation cohort (area under the curve = 0.81). Calibration (agreement between predicted and observed rates of allergy) was also good across multiple measures.

External validation was performed in multicenter retrospective cohorts in Australia (Perth, n = 334; Sydney, n = 80) and the United States (Nashville, Tenn., n = 531), with 94% of participants undergoing an oral penicillin challenge and the remainder undergoing a scratch test or intradermal test alone.⁸

This guide is one in a series that offers evidence-based tools to assist family physicians in improving their decision-making at the point of care.

This series is coordinated by Mark H. Ebell, MD, MS, deputy editor for evidence-based medicine.

A collection of Point-of-Care Guides published in *AFP* is available at <https://www.aafp.org/afp/poc>.

CME This clinical content conforms to AAFP criteria for CME. See the CME Quiz on page 719.

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The study identified three risk factors to include in the clinical prediction rule⁸:

- Allergy event occurring five or fewer years ago (2 points)
- Anaphylaxis/angioedema or severe cutaneous adverse reaction (2 points)
- Treatment required for the episode (1 point)

Total scoring ranged from 0 to 5, allowing for stratification of patients based on risk of a positive result on penicillin allergy testing⁸:

- Very low (0 points): 0.6% risk (1 out of 164)
- Low (1 or 2 points): 5% risk (16 out of 296)
- Moderate (3 points): 19% risk (25 out of 132)
- High (4 or 5 points): 53% risk (16 out of 30)

The investigators chose a cutoff score of less than 3 points, which yielded a sensitivity of 70.7% (95% CI, 57.3% to 81.9%) and specificity of 78.5% (95% CI, 74.9% to 81.9%) in the derivation cohort. A total of 74% of the cohort had a score of less than 3, and, of these patients, only 3.7% (17 out of 460) had a positive test result.⁸ However, different cutoff scores may be considered for risk stratification depending on clinician preference, the setting, and capacity for allergy testing.

The PEN-FAST rule has some clear limitations. Non-White populations were underrepresented in the study cohorts, children were excluded, and the study mainly involved inpatient testing. Even those who scored 0 points, and therefore were stratified as very low risk, had a 0.6% risk of true allergy.⁸

The likelihood of a true allergy in those with a PEN-FAST score of less than 3 points is similar to that for a negative result on skin testing (3.7% vs. 1.9% to 2.9%).^{3,9,10} Therefore, stratifying patients using the PEN-FAST rule may aid in decisions related to immediate antibiotic treatment and referral for allergy testing. Use of the PEN-FAST rule has the potential for significant downstream benefits of improved antibiotic prescribing over the course of the patient-clinician relationship and enhanced antimicrobial stewardship.

Applying the Evidence

A 42-year-old patient presents with signs and symptoms suggesting acute bacterial rhinosinusitis. After consulting local antimicrobial guidelines, you determine that amoxicillin is the first-line antibiotic for acute sinusitis. However, the patient's medical record shows that they have a penicillin allergy. The patient reports that when

they were 14 years old they took amoxicillin/clavulanate (Augmentin), and a maculopapular rash developed on the torso and upper limbs three hours after taking the medication. The patient received an antihistamine and discontinued the antibiotic.

Using the PEN-FAST rule, this patient has a score of 1, for requiring treatment for the potential reaction, and therefore has a low risk (about 5%) of a positive result on allergy testing. You discuss treatment options, the estimate of risk, and other potential benefits and harms with the patient and elicit the patient's preferences. Through this, you make a shared decision to prescribe amoxicillin, and you provide the patient with information on warning signs for allergic reaction and actions to take if this occurs.

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