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CD Summary

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Penicillin Allergy Delabeling: A Tool for Antibiotic Stewardship

Key Points

- Approximately 10% of the U.S. population reports a penicillin allergy, but fewer than 1% of the population have a true IgE-mediated allergy.
- Inaccurate penicillin allergy labels are associated with greater use of broad-spectrum antibiotics, which increases the risk of *C. difficile* infection, antimicrobial resistance, and negative clinical outcomes.
- A focused allergy history helps clinicians assess a patient's risk of a serious reaction and determine appropriate evaluation.

Background

A significant proportion of antibiotic prescribing is inappropriate, contributing to antimicrobial resistance and increasing the risk of adverse outcomes. Appropriate therapy requires selecting the most effective agent and allergy history can have a significant impact on antibiotic selection. Penicillin is the most commonly reported drug allergy in the U.S.[1,2] Although approximately 10% of the U.S. population reports a penicillin allergy more than 90% of these patients are found not to be truly allergic after formal evaluation.[2] Removing inaccurate penicillin allergy labels, a process known as delabeling, improves antibiotic selection, reduces unnecessary use of broad-spectrum antibiotics, and supports antimicrobial stewardship.[2]

Why the Label Is Often Wrong

Many penicillin allergy labels result from expected side effects, such as nausea, or coincidental events, such as a viral rash incorrectly attributed to an antibiotic. Others originate in childhood, often without documentation of the original reaction.[2]

A family history of penicillin allergy does not increase an individual's risk, yet this misconception commonly leads patients to report a penicillin allergy. Even among patients with a true IgE-mediated penicillin allergy, approximately 80% lose sensitivity after 10 years. Taken together, these factors mean that most reported penicillin allergies do not represent a current, clinically significant allergy.[2,3]

Consequences of Carrying the Label

Penicillins and related beta-lactams are first-line therapy for many common infections. An unverified penicillin allergy label often leads clinicians to prescribe broader-spectrum alternatives that may be less effective, more toxic, more expensive, and more likely to contribute to antimicrobial resistance.[2]

Cohort studies of hospitalized patients found that patients with reported penicillin allergy have higher rates of *C. difficile* infection, methicillin-resistant *Staphylococcus aureus* (MRSA), and longer hospital stays than patients without a reported penicillin allergy.[4,5] In one surgical cohort, a penicillin allergy label was associated with approximately 50% higher odds of surgical-site infection, attributed to use of second-line perioperative prophylaxis.[6]

Benefits and Safety of Delabeling

The Centers for Disease Control and Prevention (CDC) and the American Academy of Allergy, Asthma & Immunology

(AAAAI) recommend systematic penicillin allergy assessment as an important antimicrobial stewardship activity. Delabeling can increase use of narrower-spectrum antibiotics and produces health-system cost savings.[2]

Risk-based penicillin allergy evaluation is safe when patients are selected appropriately. Depending on the reaction history, evaluation may consist of history alone, a direct oral amoxicillin challenge for carefully selected low-risk patients, or referral to an allergist for penicillin skin testing. In a meta-analysis of selected adult and pediatric patients with penicillin allergy labels who underwent supervised drug provocation testing (most after negative preliminary skin testing), severe reactions were rare, occurring in approximately 0.06% of patients. [7]

Some non-severe reactions may be observed following direct oral challenges. In a real-world pediatric graded oral provocation challenge with amoxicillin, 94% (n = 770 of 818) of children tolerated the two-dose 10%/90% method and were delabeled of the penicillin allergy.[13] About 2.1% had an immediate reaction and 3.8% had a nonimmediate reaction. All reported reactions were mild with hives or a macular or papular rash, and none were more severe than the initial suspected reaction.

Who Should Perform Delabeling?

Penicillin allergy evaluation is not limited to allergists. The AAAAI encourages all clinicians to participate in the evaluation of low-risk patients and refer high-risk patients to an allergist.[2,8] Whenever possible, penicillin allergy evaluation should occur proactively during routine care rather than during an acute infection.

Primary care clinicians and pharmacists can often identify, through a brief allergy history, patients whose penicillin allergy label may be removed after appropriate counseling. Examples include cases where the reported "allergy" reflects a predictable side effect or family history alone. The same low-effort interview can identify patients who are appropriate candidates for evaluation.

Recognizing Reaction Patterns

- Symptoms such as headache, gastrointestinal upset or other predictable side effects are generally not consistent with a true allergy.[2]
- *Immediate reactions* may be IgE-mediated and typically occur within minutes to several hours of drug administration. They may include angioedema, bronchospasm, or urticaria.[2,9]
- *Anaphylaxis* is highly likely when two or more of the following symptoms develop within minutes to hours following exposure to the allergen. It is a severe, potentially life-threatening systemic hypersensitivity reaction.[9]
  - Skin or mucosal symptoms (hives, itching, flushing, or angioedema)
  - Respiratory symptoms (wheezing, shortness of breath, cough, stridor, or hypoxemia)
  - Hypotension or signs of end-organ dysfunction
  - Severe gastrointestinal symptoms (crampy abdominal pain or repetitive vomiting).
- *Delayed, T cell-mediated reactions* generally develop over days to weeks following exposure. These reactions may be present as:[2]
  - Benign delayed morbilliform or maculopapular eruption without systemic features
  - Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug reaction with eosinophilia and systemic symptoms (DRESS).

Clinical note: Patients with a history of SCARs or other severe organ-involved delayed reactions should not undergo penicillin allergy testing or oral challenge and should avoid beta-lactam antibiotics unless evaluated by an allergy specialist.[2,9]

Taking a Structured Allergy History

Use a structured allergy history to characterize the patient's reaction. Key questions for the patient include:

- How long ago did the reaction occur?
- Did the reaction require medical treatment or hospitalization?
- What medication was taken when the reaction occurred? Were other medications involved?
- What symptoms occurred, and how soon after taking the medication did the symptoms begin?
- Did symptoms include hives, swelling of the lips, tongue or face; wheezing or shortness of breath?
- Were there painful sores, or skin blistering or peeling?
- Has the patient taken and tolerated penicillin or amoxicillin since the reaction?

The patient's responses can help distinguish nonallergic reactions from IgE-mediated and delayed hypersensitivity reactions, guiding risk stratification and further evaluation.[2]

Assessing Risk

PEN-FAST is a clinical decision tool that estimates the likelihood of a true penicillin allergy in adults.[2,10] PEN-FAST can be completed in less than one minute at the bedside and is freely available online. PEN-FAST complements, rather than replaces, a structured allergy history and clinical judgment. For pediatric patients, risk assessment should be based on a structured history and reaction.[11]

Performing a Direct Oral Amoxicillin Challenge

For carefully selected low-risk patients, direct oral amoxicillin challenge without prior skin testing is recommended in pediatric patients and is a supported option in low-risk adults. Oral challenges should be conducted in a setting with trained staff, a written protocol, appropriate patient monitoring and access to intramuscular epinephrine. [2,9]

For adults, administration of a single therapeutic dose of 250–500 mg of oral amoxicillin, followed by one hour of observation, is generally sufficient to demonstrate immediate tolerance. Dose, number of challenge steps, and observation time vary by age, drug, and clinical setting. For children, challenges are weight-based and often graded.[13] Mild reactions can occur, but serious reactions are rare when patients are selected appropriately. Patients should be counseled to report delayed rash or other symptoms.[2,7] Additional guidance is available through the AAAAI Penicillin Allergy Center.

Cross-reactivity With Other Beta-Lactams

Cross-reactivity is driven largely by similarity of R1 side chains, rather than the beta-lactam ring itself. Current evidence suggests that cross-reactivity among beta-lactams is lower than the historical 10% estimate.[2] Patients with an unverified, nonanaphylactic penicillin allergy can generally receive cephalosporins without prior testing. For patients with a history of SCARs or organ-involved delayed reactions, avoid beta-lactams or obtain allergy-specialist guidance.[2]

For More Information

- PEN-FAST calculator: https://qxmd.com/calculate/calculator_752/pen-fast-penicillin-allergy-risk-tool
- CDC: Clinical features of penicillin allergy: www.cdc.gov/antibiotic-use/hcp/clinical-signs/index.html
- AAAAI Penicillin Allergy Center: education.aaaai.org/penicillin-allergy-center/penicillin
- SHEA CE course, Penicillin Allergy Management — Removing Barriers to Optimal Antibiotic Prescribing: learningce.shea-online.org

TABLE 1. PENICILLIN ALLERGY RISK STRATIFICATION AND RECOMMENDED

Risk category	Example history	Recommended approach
Nonallergic	• Family history only (no personal reaction) • Predictable side effects such as headache, nausea, diarrhea	• No formal evaluation needed • Prescribe penicillins at standard dose • Remove allergy label *Optional: single oral amoxicillin challenge for patients who would like reassurance.*
Low	• Benign delayed morbilliform or maculopapular rash without mucosal involvement, blistering, or other features of SCAR. • Remote childhood reaction with no indication of anaphylaxis or SCAR. • Unknown reaction more than 10 years ago, not requiring medical care (e.g. "My mom told me I had a reaction as a baby").	• Direct oral amoxicillin challenge under medical observation, without prior skin testing. • OK to administer cephalosporins at full dose. • After negative challenge: Remove allergy label and prescribe penicillin.

Moderate/High	• Anaphylaxis or angioedema any time in the past
	• Any of the following the past 5 years:
	  o angioedema
	  o hives, itching, flushing
	  o wheezing
	  o hypotension
	  o severe GI symptoms
	  o urticaria
	• Unknown reaction within the past 10 years, or any reaction that required medical care.
		• Refer to allergist for penicillin skin testing and assessment.
		• Retain allergy label awaiting final determination by the allergist.
		• While awaiting evaluation: cephalosporins with a dissimilar R1 side chain (e.g., cefazolin, ceftriaxone, cefepime), carbapenems and aztreonam may be considered.

Severe risk. Contraindication to evaluation	• Severely delayed reactions:
	  o Stevens-Johnson syndrome (SJS)
	  o Toxic epidermal necrolysis (TEN)
	  o Drug reaction with eosinophilia and systemic symptoms (DRESS)
	  o Drug induced interstitial nephritis, hemolytic anemia, thrombocytopenia, hepatitis
		• Retain allergy label.
		• Skin testing and oral challenge contraindicated.
		• Avoid beta-lactams or consult with specialist.

Adapted from University of Washington CSiM Antibiotic Guide, updated October 2025.
Sources: Khan DA et al. J Allergy Clin Immunol. 2022;150:1333–1393.

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