

Los Angeles County Department of Public Health Antibiotic Stewardship Program

Adult Low-Risk Penicillin Allergy Delabeling Toolkit for Hospitals



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* American Academy of Allergy Asthma and Immunology



Introduction

The Center for Disease Control (CDC), American Academy of Allergy Asthma and Immunology (AAAAI), the Society of Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) recognize that over-labeling patients as penicillin allergic is a significant public health concern. Patients labeled with a penicillin allergy are frequently treated with overly broad-spectrum alternative antibiotics placing them at greater risk for exposure to antibiotic resistance. Furthermore, the avoidance of beta-lactam antibiotics in a penicillin-allergic patient results in suboptimal treatment outcomes and increased adverse events. Healthcare institutions and clinicians who prescribe antibiotics are strongly urged to implement penicillin allergy delabeling programs and protocols. For patients with a low-risk penicillin allergy history (defined below, see page 5), delabeling can be safely accomplished by obtaining a good allergy history and administering an oral amoxicillin challenge.

Facts about penicillin allergy which result in mislabeling patients as penicillin allergic

- Penicillin allergy is the most common drug allergy reported, representing millions of people in the U.S. who consider themselves allergic to penicillin.
- Approximately 10% of patients report having had a reaction to a penicillin antibiotic in the past. And as many as 15% of patients or more in hospitals report having a penicillin allergy.
- More than 90% of patients with a reported penicillin allergy do not have a true IgE-mediated allergy (i.e., allergies that could lead to anaphylaxis) when confirmed by skin testing. This means the actual rate of true allergy to penicillin is <1% of patients.
- The disparity between the number of patients with “self-reported” penicillin allergy (10% or more) and those who are truly penicillin allergic (< 1.0%) is due to the following:
 - **Penicillin allergy goes away over time where 50% of patients will no longer be allergic after 5 years and 80% after 10 years. Nearly all patients will no longer be allergic after 20 years.**
 - Many cutaneous reactions can be the result of an underlying infection (e.g., a viral exanthem) which may occur while receiving antibiotics.
 - Mislabeled of an adverse event or family history as a penicillin allergy.

Harms associated with a penicillin allergy label

- Patients with gram-negative bloodstream infections who report having a penicillin allergy and receive non-beta-lactam regimens are more likely to experience treatment failure than patients who receive beta-lactams (*Jeffres et al. [Consequences of avoiding b-lactams in patients with b-lactam allergies: J All Clin Immunol. 2015; 137:4](#)*)
- Patients who have a penicillin allergy have an increased risk of all-cause mortality (14%) compared with patients who are not penicillin allergic. (*Blumenthal KG et al. [Recorded Penicillin Allergy and Risk of Mortality: A Population-Based Matched Cohort Study. J Gen Intern Med. 2019 34:9](#)*)
- Patients with reported penicillin allergies receiving non-beta-lactam antibiotics are more likely to develop surgical site infections than patients without a penicillin allergy (*Blumenthal KG et al. [The](#)*

[Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk](#). *Clinical Infectious Diseases*. 2018 Jan 18;66)

- Patients with malignancies who report beta-lactam allergies have longer hospitalizations, increased mortality, are more likely to require readmission and experience *C. difficile* infections in comparison to those who do not report a penicillin allergy. (Kuan-Hsiang Gary Huang et al. [The Impact of Reported Beta-Lactam Allergy in Hospitalized Patients with Hematologic Malignancies Requiring Antibiotics](#). *Clin Inf Dis* 2018 67:1)
- Patients with penicillin allergy are three times more likely to experience an adverse event in comparison to patients who are not penicillin allergic. (McFadden D, et al. [Impact of Reported Beta-Lactam Allergy on Inpatient Outcomes: A Multicenter Prospective Cohort Study](#) *Clin Infect Dis* 2016. 63:7)
- Patients with penicillin allergy are more likely to experience exposure to resistant bacteria. (Blumenthal. [Risk of Methicillin Resistant Staphylococcus Aureus and Clostridium Difficile in Patients with a Documented Penicillin Allergy: Population Based Matched Cohort Study](#) *BMJ* 2018)

NOTE: There is considerable concern about life threatening anaphylaxis when a penicillin allergic patient is exposed to a penicillin. Among patients experiencing an acute IgE-mediated allergy to a penicillin, less than 1 in 1000 experience anaphylaxis which can be life threatening in some cases (David Vyles and Eric Macy, [Expert Review of Anti-infective Therapy,17:6, 429-435](#)). Death due to anaphylaxis is extremely rare, less than 0.002% (Eric Macy and N. Franklin Adkinson. [J Allergy Clin Immunology Pract. February 2023](#)). **The risk of significant harm associated with avoidance of penicillin is much greater.**

Benefits of inpatient penicillin allergy delabeling in low-risk patients

- A hospital-wide penicillin delabeling program implemented an amoxicillin or penicillin V oral challenge program in patients identified with a low-risk penicillin allergy. Over six months, 97% (192/200) of patients were successfully delabeled. An additional 155 patients were delabeled based on their allergy history alone. Other findings were increased narrow spectrum beta-lactam antibiotic use (OR 10.5); improved appropriate antibiotic use (OR 2.13) and reduced use of restricted antibiotic (OR 0.38). (Chua et al. [The Penicillin Allergy Delabeling Program: A Multicenter Whole-of-Hospital Health Services Intervention and Comparative Effectiveness Study](#) *CID* 2021 Aug 2;73(3):487-496)
- A hospital program using either amoxicillin challenge (administered in three doses) or penicillin skin testing was implemented in patients with low-risk penicillin allergy. Of 100 patients tested, 48 received oral challenge and 52 received skin testing. Among patients given oral challenge, one had an immediate reaction (swelling under the eyes which resolved with diphenhydramine) and an additional two had a delayed reaction (Non-IgE mediated). Beta-lactams were safely administered to 56/100 patients with avoidance of 783 days of second-line antibiotic therapy. Estimated drug cost savings was \$23,375.27. (Ramsey et al. [Direct Challenges to Penicillin-Based Antibiotics in the Inpatient Setting](#). *J Allergy Clin Immunol Pract* 2020 8:7)

Recommendations from the AAAAI 2022 Practice Parameter for Drug Allergies

The AAAAI updated drug allergy guidance specifically acknowledges that a label of penicillin allergic is not benign and that patients with a history of penicillin allergy are more likely to be treated with less effective, more toxic, or more expensive antibiotics resulting in increased mortality, longer hospital stays, and increased cost. A proactive effort to delabel patients as penicillin allergic is strongly encouraged. Selection of patients for penicillin allergy delabeling can be done safely by primary care clinicians and other trained health care professionals by obtaining a detailed allergy history of the reaction and assessment of patient comorbidities. Direct oral challenge with amoxicillin without skin testing is suggested for most patients with a low-risk history of benign and/or remote reactions. Penicillin skin testing may be reserved for higher risk patients with a history of anaphylaxis, or a recent reaction suspected to be IgE-mediated (e.g., immediate onset urticaria). Patients with a history of severe cutaneous adverse reactions (SCAR) including Stevens Johnson syndrome and toxic epidermal necrolysis; generalized exanthematous pustulosis; drug rash with eosinophilia with systemic symptoms (DRESS), serum sickness, hemolytic anemia or other immune related organ-specific reactions are not candidates for skin testing and/or oral challenge. Specific AAAAI recommendations for management of low-risk penicillin allergies include:

- ✓ Recommend proactive penicillin allergy delabeling by clinicians including primary care practitioners
- ✓ Recommend that allergist-immunologists collaborate with hospitals and health care systems to implement beta-lactam allergy assessment pathways to improve antibiotic stewardship outcomes
- ✓ Consideration for direct amoxicillin challenge in adults with low-risk penicillin allergy histories
- ✓ Suggest use of 1- or 2-step drug challenges for low-risk patients
- ✓ Suggest penicillin skin testing for patients with a history of anaphylaxis or a recent reaction suspected to be IgE-mediated and not necessary for patients with low-risk penicillin allergies
- ✓ Suggest use of placebo challenges in patients with subjective symptoms (e.g., itching without visible rash) or multiple reported drug allergies

Taking a penicillin allergy history: questions to ask

Penicillin allergy history needed for determining level of risk

(Adapted from: [Vyles, and Macy; Expert Reviews of Anti-infective Therapy 2019, Vol 17:6](#))

| Questions | Comments |
|-------------------------------|---|
| Essential Questions | |
| Antibiotic name | The specific drug needs to be listed |
| Time to symptoms | Any significant IgE-mediated reaction typically presents within the first hour after oral exposure and always within 30 minutes of a parenteral exposure; T cell related benign reactions typically occur 2-5 days after the first dose; SCAR*, immune-mediated reactions and serum sickness may have delayed onset up to 4 weeks |
| Symptoms | Benign rash, hives, SOB, GI upset, anaphylaxis, headache, SCAR*, immune mediated reactions, serum sickness, DRESS, SJS, TEN, other benign reactions, unknown reaction |
| Date/year of index exposure | The longer the time since the index exposure, the lower the probability there is any clinically significant anti-beta-lactam IgE present |
| Other Useful Questions | |
| Route of exposure | Oral or IV |
| Time to symptom resolution | Individual hives only last hours in a single site. T-cell mediated rashes may be evident days-weeks. SCAR* takes weeks to resolve. SJS and TEN must affect at least 10% and 30% of BSA, respectively |
| Treatment given | None, just stopped drug; antihistamine, epinephrine, systemic or topical steroids use |
| Hospitalization required | SCAR* is almost always associated with hospitalization and systemic symptoms |

Patient criteria for amoxicillin challenge based on allergy history

The following penicillin allergy history is considered “low risk” and acceptable for an amoxicillin challenge

- Non- immediate cutaneous reaction only (without features suggestive of SCAR*)
- Immediate cutaneous reaction (hives only without symptoms of anaphylaxis such as bronchospasm or hypotension) AND occurred more than 5 years ago
- Patient does not recall the specific penicillin allergic reaction and the event was long ago
- Patients with history suggestive of an intolerance and worried about an allergic reaction
- No oral challenge is needed in patients with a history of intolerance (GI upset, headache, yeast infection, etc.) or if there is a record of having previously tolerated a penicillin at a time after the allergic reaction.
- Patients with significant comorbidities should be approached carefully with consideration for risk vs benefit

The following is NOT considered “low-risk” and unacceptable for amoxicillin challenge:

- History of anaphylaxis or a recent reaction (within 5 years) suspected to be IgE-mediated (e.g., immediate onset urticaria)
- Severe cutaneous adverse reactions (SCAR*) including Stevens-Johnson syndrome and toxic epidermal necrolysis; generalized exanthematous pustulosis; drug rash with eosinophilia with systemic symptoms (DRESS), serum sickness, hemolytic anemia or other immune related organ-specific reactions are not candidates for oral challenge.

***SCAR: features include blistering over a large surface area, skin sloughing, mucosal involvement AND almost always involves systemic symptoms requiring hospitalization**

Amoxicillin challenge and delabeling procedure

An amoxicillin challenge is a simple procedure where a single dose of amoxicillin 250mg is administered orally followed by 60 minutes of observation. In the hospital, observation is typically done by a nurse instructed to check for symptoms of an allergic or adverse reaction every 15-30minutes following oral amoxicillin administration. Patients should also be instructed to notify their nurse if they may be experiencing a reaction. If no reaction occurs, then the patient may receive a penicillin antibiotic by any route (see below criteria for a positive reaction). Beta-blockers need to be held on the day of the oral challenge in case epinephrine is required for a reaction. Antihistamines should be held at least three days, and ideally five days, prior to the oral challenge to prevent a false negative result. Although the oral route is preferred, patients who are unable to take enteral medications can receive the challenge by intravenous route.

Alternatively, the oral challenge can be done in 2 steps starting with a 10th of a dose (e.g., amoxicillin 25mg) or if more convenient, one quarter of a dose, with observation as above for 30-60 minutes followed by a full dose (e.g., amoxicillin 250mg) and observation for one additional hour. The two-step oral challenge could be used routinely or considered in selected circumstances such as a patient with a significant comorbidity who needs to receive immediate treatment with a beta-lactam. Also consider including an order for an antihistamine as needed for a reaction during the amoxicillin challenge.

Patients who are successfully delabeled need to have their medical record updated accordingly and informed they are not allergic and can take any penicillin. They should also be made aware there is still a risk for future adverse events, just like any other patient who is administered a penicillin antibiotic. Patients who are not adequately informed or updated following the amoxicillin challenge will be at greater risk of reintroduction of their penicillin allergy label into the medical record and unnecessary avoidance of penicillin in the future.

AAAAI criteria for determining a positive allergic reaction during the amoxicillin challenge

| Reaction Type | Symptoms |
|---------------|---|
| Positive | urticaria, angioedema, exanthem, wheezing, hypoxia, hypotension, anaphylaxis* |
| Possible | flushing, vomiting, cough, abdominal cramping, persistent pruritis without rash, fever, mouth, or eye soreness |
| Doubtful | dizziness, tachycardia, subjective lip/tongue swelling, subjective throat tightness, lump in throat, dyspnea, transient pruritis without rash, headache |

*By definition, anaphylaxis requires a sign or symptom from at least two of the following systems: skin, cardiovascular, respiratory, and gastrointestinal.



Hospital Antibiotic Stewardship Program recommendations for penicillin allergy delabeling

(source: AHRQ)

Given the high burden of penicillin allergy labeling, adverse consequences and, severe lack of enough allergy specialists to address all patients with penicillin allergy, the following strategies are recommended:

- ✓ Incorporate penicillin allergy evaluation and delabeling into hospital guidelines, pathways, and order sets
- ✓ Educate nurses about questions they should ask at initial intake and consider having a “soft” entry to be confirmed by providers for a “hard” entry
- ✓ Ensure a system is in place to actively remove any inaccurate penicillin allergy label
- ✓ Educate patients and providers about the importance of maintaining delabeling so this is not reversed in the medical record
- ✓ Institute pharmacist screening of allergies and/or delabeling
- ✓ Where available consider auto-allergy consults and/or referrals to an allergist

Elements of a hospital policy for amoxicillin challenge in patients with low-risk penicillin allergy

(Note: content is for example only and should be tailored as needed)

| General |
|---|
| Committee(s) Approval/Authors and Reviewers/Approval Date/Planned Review Date |
| Background/Statement of Purpose |
| <p>The Center for Disease Control (CDC), American Academy of Allergy Asthma and Immunology (AAAAI), the Society of Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) recognize that over labeling patients as penicillin allergic is a significant public health concern. Patients labeled with a penicillin allergy are frequently treated, with overly broad-spectrum alternative antibiotics placing them at greater risk for exposure to antibiotic resistance. Avoidance of beta-lactam antibiotics in a penicillin-allergic patient results in suboptimal treatment outcomes, increased adverse events, and higher costs. About 10% of the population is labeled as penicillin allergic however less than 1% are truly allergic. Given the high burden of over labeling and severe lack of allergy specialists available to address all patients, a hospital protocol for delabeling patients will be established.</p> <p>The purpose of this policy is to identify patients who have a “low-risk” penicillin allergy label for administration of an oral amoxicillin challenge and if negative, remove the penicillin allergy from the medical record.</p> |



Implementation Team

The following individuals are responsible for the development, and implementation of the penicillin delabeling program. Names and responsibilities are listed below:

- *Allergy Specialist*: Development of protocol, staff education, outcome assessment
- *Infectious Diseases Specialist*: Development of protocol, staff education, outcome assessment
- *Antibiotic Stewardship Pharmacist*: Assistance with protocol development, implementation
- *Nurse (lead or administrator)*: Assistance with protocol development, implementation
- *Administrator*: Oversight, assure consensus and resource availability
- *Medication Safety Committee Chair*: TBD
- *Other*: TBD

Definitions/Inclusion Criteria/Exclusion Criteria

Inclusion Criteria for “low-risk” penicillin allergy:

- Non- immediate cutaneous reaction only (without features suggestive of SCAR)
- Immediate cutaneous reaction (hives only without symptoms of anaphylaxis such as bronchospasm or hypotension) AND occurred more than 5 years ago
- Patient does not recall the specific penicillin allergic reaction and the event was long ago
- Patients with history suggestive of an intolerance and worried about an allergic reaction
- No oral challenge is needed in patients with a history of intolerance (GI upset, headache, yeast infection, etc.) or if there is a record of having previously tolerated a penicillin at a time after the allergic reaction

Exclusion Criteria:

- History of anaphylaxis or a recent reaction (within 5 years) suspected to be IgE-mediated (e.g., immediate onset urticaria). Patients with a history of Severe cutaneous adverse reactions (SCAR) including Stevens Johnson syndrome and toxic epidermal necrolysis; generalized exanthematous pustulosis; drug rash with eosinophilia with systemic symptoms (DRESS), serum sickness, hemolytic anemia or other immune related organ-specific reactions are not candidates for oral challenge.
- Pregnancy (ACOG recommends consulting an allergist)
- Comorbidity (consider risk versus benefit and/or two step oral challenge)
- Recent Beta-blocker use
- Recent Antihistamine use

Oral amoxicillin challenge: Administration of a single dose of amoxicillin 250mg followed by 60 minutes of nurse observation for an immediate allergic reaction. The oral amoxicillin challenge is not restricted to any specific area of the hospital or level of care.

Observation during the oral amoxicillin challenge: Nurse assessment of vital signs and for presence of an allergic reaction every 20 minutes X3 following administration of amoxicillin challenge.

Allergic reaction during the amoxicillin challenge: skin rash, hives, subjective itching, facial edema, syncope, difficulty breathing, vomiting, diarrhea.

Procedure/Orders for Amoxicillin Challenge

Prescriber:

- Patient history review and assessment of “low-risk” allergy and candidacy for amoxicillin challenge
- Discuss amoxicillin challenge purpose and procedure with the patient prior to the challenge
- Order for amoxicillin 250mg by mouth X1 dose
- Order for nurse to obtain vital signs (temp, HR, BP, RR including parameters to call prescriber) and observe for an allergic reaction every 20 minutes X3 following oral amoxicillin administration
- Order diphenhydramine 25-50mg PO/IV as needed for an allergic reaction during amoxicillin challenge
- Update allergies in the medical record per results of the amoxicillin challenge
- Patient counseling based on the results of the oral challenge and ability to receive a penicillin and future risk of an allergic reaction and/or adverse event, etc.

Nurse:

- Administer oral amoxicillin dose
- Monitor vitals and for allergic reaction per orders
- Contact prescriber if an allergic reaction occurs per orders
- Contact prescriber if no reaction occurred after the 60-minute observation period is completed

Antibiotic Stewardship Pharmacist:

- Routine identification of patients with penicillin allergy
- Screen (daily/weekly/all patients/certain patients) for patients with “low-risk” allergy history and referral to primary care physician or team for oral amoxicillin challenge (may include or describe a screening tool)
- Assist prescribers and nurses with oral amoxicillin challenge procedure

Patient Education

Determine plan for counseling and/or education including written materials, videos, etc.

Staff Education

Determine plan for educating physicians, nurses and pharmacists about penicillin allergy and amoxicillin challenge including in-services, printed materials, resources, etc.

Data Collection and Reporting

Determine a plan for QI through assessment of progress toward goals, and identification of barriers. Scope of data collection should be achievable and tailored to available resources.

References

https://education.aaaai.org/sites/default/files/media/2022-09/AAAAI-Compiled%20Penicillin%20Allergy%20References%20September%202022_1.pdf

Resources

- 1) [2023 “Grey-Literature” Review of Penicillin Allergy Delabeling Resources](#)
- 2) [Penicillin Allergy Impact and Management Infectious Diseases Clinics of North America 2023](#)
- 3) [AAAAI Penicillin Allergy Center](#)
- 4) [AAAAI 2022 Drug Allergy Practice Parameter Update](#)
- 5) [AAAAI Penicillin Allergy Essential Reference List September 2022](#)
- 6) [Allergist Finder Tool](#)
- 7) [Scottish Antimicrobial Prescribing Group Penicillin Allergy Toolkit](#)
- 8) [Experience and lessons learned Implementing a multi-hospital penicillin allergy program at Massachusetts General](#)
- 9) [PENFAST allergy assessment tool](#)
- 10) [CDC penicillin allergy fact sheet](#)

