

CME Review

Penicillin allergy delabeling Opportunities for implementation and dissemination



Upeka Samarakoon, PhD, MPH^{*,†}; John Accarino, MD^{*}; Alyse G. Wurcel, MD, MS^{‡,§};
Jordon Jaggers, MD^{||}; Allen Judd, AB^{*,†}; Kimberly G. Blumenthal, MD, MSc^{*,†,¶}

^{*} Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

[†] Mongan Institute, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

[‡] Division of Geographic Medicine and Infectious Diseases, Department of Medicine, Tufts Medical Center, Boston, Massachusetts

[§] Tufts University School of Medicine, Boston, Massachusetts

^{||} Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

[¶] Harvard Medical School, Boston, Massachusetts

Key Messages

- Penicillin allergy “delabeling” involves the removal of a penicillin allergy from a patient’s medical record after evaluation of the reaction history and often drug challenge, sometimes with preceding skin testing.
- When delabeling is considered in inpatients, current practice is often at the time of antibiotic need, rather than proactively as quality improvement.
- Access to penicillin allergy evaluations and delabeling in the United States is limited.
- Expanding access to penicillin allergy delabeling requires education and training of a nonallergist workforce.
- Penicillin allergy evaluation and delabeling efforts should target expansion to locations and populations that both have a high use of antibiotics and a high risk of adverse effects from broad-spectrum antibiotics.

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ABSTRACT

Although existing as a safety measure to prevent iatrogenic harm, unconfirmed penicillin allergy labels have a negative impact on personal and public health. One downstream effect of unconfirmed penicillin allergy is the continued emergence and transmission of resistant bacteria and their associated health care costs. Recognizing the consequences of inaccurate penicillin allergy labels, professional and public health organizations have started promoting the adoption of proactive penicillin allergy evaluations, with the ultimate goal of removing the penicillin allergy label when the allergy is disproved, also known as penicillin allergy “delabeling.” A penicillin allergy evaluation includes a comprehensive allergy history often followed by drug challenge, sometimes with preceding skin testing. Currently, penicillin allergy delabeling is largely carried out by allergy specialists in outpatient settings. Penicillin allergy delabeling is performed on inpatients, albeit rarely, often at the time of need, as a point-of-care procedure. Access to penicillin allergy evaluation services is limited. Recent studies demonstrate the feasibility of expanding penicillin allergy evaluations and delabeling to internists, pediatricians, emergency medicine physicians, infectious diseases specialists, and clinical pharmacists. However, reducing the impact of mislabeled penicillin allergy will require comprehensive efforts and new investments. In this review, we summarize the current practices of penicillin allergy delabeling and discuss expansion opportunities for penicillin allergy delabeling as quality improvement.

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Reprints: Kimberly G. Blumenthal, MD, MSc, Massachusetts General Hospital, The Mongan Institute, 100 Cambridge Street, 16th Floor, Boston, MA 02114; E-mail: kblumenthal@mgh.harvard.edu.

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Learning Objectives

At the conclusion of this activity, participants should be able to:

- Recognize the importance of penicillin allergy evaluation and de-labeling.
- Identify ways of expanding penicillin allergy de-labeling as quality improvement.

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Physicians involved in providing patient care in the field of allergy/asthma/immunology.

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Introduction

Penicillin-based antibiotics are the most common drug allergy label in the electronic health record (EHR), with a reported prevalence ranging from 6% to 25%.¹ Penicillin allergy labels (PALs) in the EHR may reflect clinician documentation after witnessing a reaction or, more typically, reflect a reaction recorded by a health care team member (eg, medical doctor, nurse practitioner, registered nurse, or medical assistant) after a patient or family member reports a past reaction (Fig 1). Large epidemiologic studies revealed that PAL incidence is greater for women and increases with age.² While several studies report racial and ethnic differences in PAL incidence, conclusions to date are inconsistent.^{2–6} Many PALs are initially recorded during childhood;⁷ recent studies suggest that approximately 75% of children with a PAL acquire this label by 3 years of age and half acquire this label after 1 or even 0 penicillin prescriptions.^{6,8} Given that the PAL was entered without documented penicillin use in some of these children (ie, 0 prescriptions), it is possible that entries may reflect family histories rather than personal histories.⁶ As estimates are on the basis of self-report, the true incidence of penicillin allergy remains unknown.

More than 90% of penicillin allergies are disproved with formal allergy testing. Incorrect PALs may be the result of misinterpretation of a reaction, such as diagnosing amoxicillin allergy when there is an infection-related drug interaction (eg, morbilliform rash from an Epstein-Barr virus infection while taking an aminopenicillin).^{9,10} Even a specialist's assessment cannot reliably differentiate an acute reaction to a penicillin antibiotic from a viral exanthem. The misdiagnosis of penicillin allergy may also occur because most penicillin allergies are remote events or are not observed or diagnosed by clinicians. Because true immunoglobulin E (IgE)-mediated penicillin allergy wanes over time, approximately half of patients lose their allergy within 5 years, and approximately 80% lose their allergy more than 10 years.^{1,11} For all these reasons, a PAL most often is not a true representation of a patient's current allergy status even in patients with a convincing history of an IgE-mediated reaction or a previously positive penicillin allergy skin test.

Even though there are history-based tools to help clinicians safely prescribe penicillins and other β -lactam antibiotics to patients with a PAL, the process is complicated by incomplete EHR documentation and allergy labels with vague or unknown reaction histories.^{12,13} Patients with a PAL receive alternative (non- β -lactam) antibiotics,¹⁴ even when the first-line treatment is a penicillin or other β -lactam antibiotic.^{13,15} Administration of alternative antibiotics to patients with a PAL leads to inferior clinical outcomes,¹⁶ increased adverse drug events including *Clostridioides difficile* infection and surgical site infection,^{14,17} and increased all-cause mortality.¹⁸ Patients with a PAL have increased acquisition of multidrug-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci*.¹⁴ In addition, patients with a PAL use more health care resources and have higher associated health care costs.¹⁹

Penicillin Allergy Evaluation and Delabeling

Given the consequences of PALs, the assessment and removal of inaccurate PALs is now a quality improvement metric and public health necessity.²⁰ Formal penicillin allergy evaluations take less than 3 hours to complete, cost just \$220 per test (\$84 when performed without penicillin skin testing), and can be implemented with relatively low-cost resources and training (Fig 2).²¹ Penicillin allergy evaluations are projected to be a cost-saving intervention across a variety of assumptions.²²

Taking a comprehensive penicillin reaction history is the first step in the clinical evaluation of a patient with a PAL.²³ Allergy history evaluation can be standardized using a point-of-care history form or assessment tool.^{24,25} One purpose of the clinical history is to ensure that penicillin allergy delabeling is not pursued in patients with a reaction that presents a contraindication to delabeling, such as a severe cutaneous adverse reaction, organ-specific reaction (eg, drug-induced liver injury, acute interstitial nephritis), or hemolytic anemia.²⁶ Although a serum sickness–like reaction is no longer a contraindication to penicillin allergy delabeling,²⁶ delabeling patients with possible or confirmed serum sickness–like reactions should be

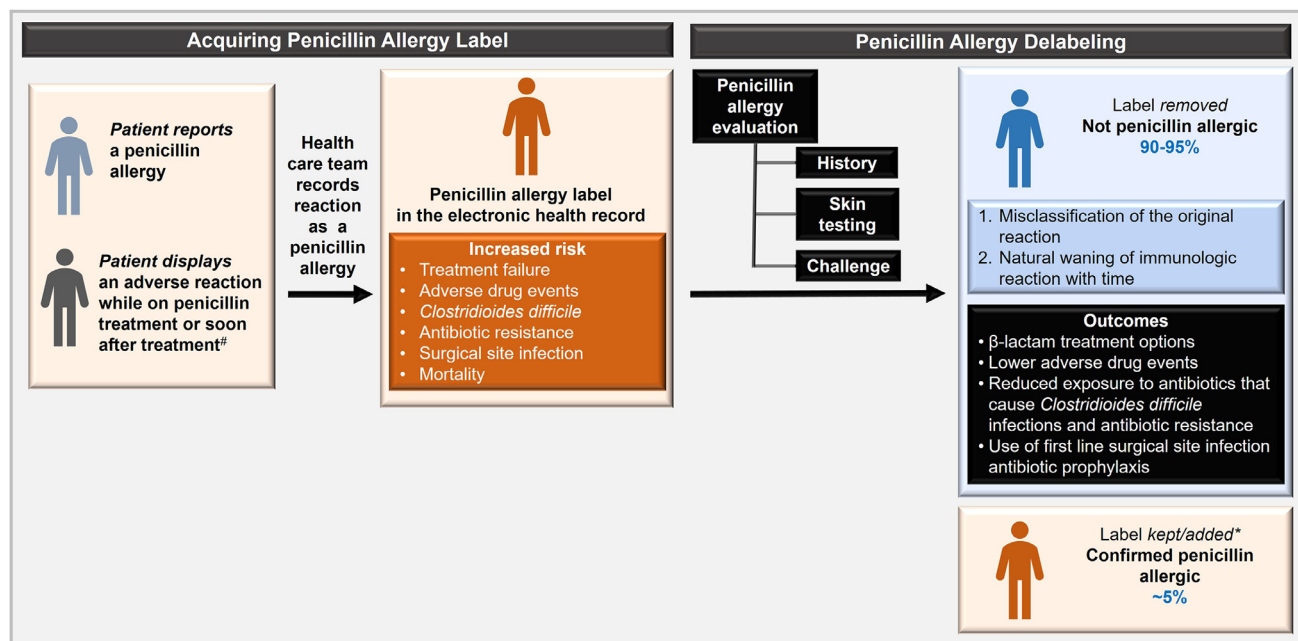


Figure 1. Acquisition of a penicillin allergy label, consequences of a label, and delabeling.

[#] reaction could be drug allergy but could also be from the underlying infection or a drug-infection interaction. * penicillin allergy label may also be kept for patients who have a confirmed penicillin intolerance or adverse effect.

PENICILLIN EVALUATION COMPONENTS	EVALUATION & MANAGEMENT	REQUIRED RESOURCES
	Drug Allergy History	Education and training of staff Standard history form Clinical decision support EHR allergy documentation guidance Evaluation protocols
	Drug Challenge	Procedure informed consent Testing space Observation protocols Education and training of staff Compounding and drug challenge reagent preparation protocols Compounding time (up to 15 minutes) Observation time (eg, 1:1 nursing assignment)
	Skin Testing	Procedure informed consent Skin testing protocols Education and training of staff Skin testing inclusion and exclusion criteria Compounding and skin test reagent preparation protocols Skin test preparation time (up to 15 minutes) Skin tester time (up to 45 minutes per test)
	Counseling & Allergy Documentation	Education and training of staff Counseling regarding outcome and delayed signs and symptoms EHR documentation
REACTION MANAGEMENT	Allergic Reaction	Education and training of staff Access to antihistamines, bronchodilators, corticosteroids, and epinephrine Protocol for reaction management Anaphylaxis treatment protocols High-acuity protocols (eg, call 911, code team) Nursing time (1 to 5 hours) Clinician time (30 minutes to 1 hour)

Figure 2. Resources required to perform penicillin allergy evaluation and delabeling. EHR, electronic health record.

approached with caution given that supportive data were in pediatric populations and a high rate of cutaneous reactions was reported with subsequent courses.²⁷ A comprehensive allergy history also allows for filtering of individuals who are not allergic; for example, history can guide delabeling directly when the PAL was recorded owing to a family history of allergy, an intolerance (eg, fatigue, headache), or if there is documented tolerance to a dose of a type of penicillin subsequent to the last reported reaction.²⁸ Approximately 20% of penicillin allergies may be delabeled on the basis of history alone.²⁸ While allergy history can facilitate rapid delabeling, in select cases, such as patients with anxiety or hesitancy, additional testing may be considered to increase acceptance of penicillin allergy delabeling.²⁶

Oral ingestion of a penicillin (often amoxicillin) in a single- or 2-dose drug challenge, with preceding penicillin skin testing when indicated, is considered the reference standard for evaluation of immediate hypersensitivity reactions to penicillin.^{29–32} In current practice, direct amoxicillin challenges are carried out in individuals with low-risk reaction histories, with the caveat that a standardized, agreed-upon definition of “low-risk” is lacking in current

practice.^{29,32–34} Recently, allergy specialists have led delabeling efforts through direct oral challenges even in patient populations typically considered high risk, such as intensive care unit and obstetric patients.^{35,36} Drug challenges are ideally administered in a clinically stable patient in a controlled environment with medications (antihistamines, corticosteroids, bronchodilators, and epinephrine) and health care personnel accessible. Patients can be delabeled if a full dose of a penicillin is tolerated after 60 minutes. However, tolerating a single full dose of a penicillin does not exclude the possibility of delayed rashes, adverse effects, or other adverse reactions to penicillin during a full course. Given that a benign morbilliform rash occurs in 1% to 3% of delabeled patients with their next full penicillin course, patients should be counseled on this possibility.^{37,38} Extended (multi-day) drug challenges are not recommended as they add limited additional information to the evaluation and run counter to antibiotic stewardship principles.²⁶ A penicillin skin test is generally recommended for medium- and high-risk patients, such as those with reactions like anaphylaxis, angioedema, or shortness of breath or those who are high-risk hosts (eg, sepsis, pregnancy, oxygen requirement,

or unstable cardiac disease).^{39,40} Skin testing as a diagnostic tool performs better in patients who are at higher risk; indeed, false positives are more likely when skin testing is performed in those with lower pretest probabilities of a true allergy.⁴¹ Penicillin skin testing has been successfully used for more than 5 decades and has a negative predictive value of 97% to 99%.^{42–44} Despite high specificity of 96.8% (95% confidence interval, 94.2%–98.3%), penicillin skin tests have poor sensitivity.⁴⁵ In a recent systematic review and meta-analysis of 101 primary studies, skin tests had a summary sensitivity of 30.7% (95% confidence interval, 18.9%–45.9%).⁴⁵

The use of penicillin skin tests in the United States (US) is limited by not having access to a full kit of known antigenic determinants of penicillin allergy. The only reagent both approved by the US Food and Drug Administration and available commercially is benzylpenicilloyl-polylysine (Pre-Pen, AllerQuest LLC). Although data from a multisite US study of 455 patients suggest that skin testing for amoxicillin and minor determinant mixture is useful to detect those with true IgE-mediated penicillin allergy,⁴⁶ these antigens are not available in the US. While it is possible to mix a minor determinant mixture, to skin test with diluted penicillin G as a minor determinant mixture proxy, and to use diluted ampicillin instead of amoxicillin (amoxicillin should not be used for intradermal testing since it is not sterile), this is cumbersome, and skin testing with more than penicilloyl-polylysine is unlikely to be adopted beyond the allergy specialist's office.

Dissemination of Penicillin Delabeling Across Populations

Penicillin allergy evaluations have historically been performed in outpatient settings by allergy specialists;⁴⁷ however, recent expansions have included emergency and inpatient care settings.^{47,48} Penicillin allergy evaluation programs have been implemented successfully in general medical and intensive care units, indicating the value of delabeling on optimizing antibiotic choice.^{49,50} Given the limited access to allergy specialist expertise, delabeling programs across populations and settings may benefit from allergist access remotely through telemedicine. Previous studies have demonstrated the value of drug allergy virtual visits and electronic consults for patients at home or in the hospital.^{51–54}

While many programs were designed and implemented with the help of allergy specialists,^{55,56} a few programs have been managed by nonallergist clinicians.^{49,57,58} The implementation of penicillin allergy delabeling as part of quality improvement programs has been successfully championed by infectious diseases clinicians and pharmacists.^{47,57–59} Pharmacist-led penicillin allergy programs include EHR allergy reconciliation,⁶⁰ penicillin skin testing,⁶¹ and amoxicillin challenges.⁵⁹ Since the first pharmacist-driven penicillin allergy skin testing program was reported in 2004,⁶² many other approaches have been led and implemented by pharmacist colleagues.^{55,63–66} However, given that pharmacists do not have full provider status, their abilities to perform penicillin skin testing and delabel allergies are limited in some US states.^{65,67}

Although all patient populations with a PAL may benefit from penicillin allergy evaluations to confirm or rule out the presence of a true penicillin allergy, specific populations at high risk for antibiotic use or adverse effects from antibiotics should be prioritized for delabeling programs. Below, we highlight some high-priority populations who need further attention, specific access, and resources for delabeling. Example populations in which delabeling programs have been implemented are presented in Table 1.^{29,33,54,68–73}

Obstetrics

Antibiotics are among the most typically prescribed medications during pregnancy.⁷⁴ Approximately one-fourth to one-third of patients will require antibiotics in the peripartum period, including

penicillin G for Group B *Streptococcus* prophylaxis or cefazolin for surgical site infection prophylaxis.⁷⁰ A PAL during pregnancy is associated with substantial morbidity, including increased risk of cesarean delivery, postcesarean wound complications, and longer length of hospital stay.^{75,76} Penicillin allergy evaluations during pregnancy are safe^{69,77,78} and recently recommended by the American College of Obstetrics and Gynecology.⁷⁹ However, penicillin allergy evaluations are infrequently performed during pregnancy, which may reflect a lack of access, patient reluctance, or other barriers.

Surgery

Prophylactic antibiotics are indicated for many surgeries, and both the choice of antibiotic and timing are critical to the efficacy of this prophylaxis. Surgical site infections are tracked and reported to the Centers for Disease Control and Prevention's National Healthcare Safety Network.⁸⁰ When there is a PAL, cefazolin is not regularly used, and instead antibiotics such as clindamycin, vancomycin, or gentamicin are used.¹³ These alternative antibiotic choices impact patients and result in an increased risk of surgical site infections¹³ and, possibly, postoperative *C. difficile* infections.⁸¹ Preprocedure penicillin allergy evaluations can increase cefazolin surgical prophylaxis and have been implemented in general,⁸² cardiac,⁸³ and orthopedic⁷¹ surgical procedures. While delabeling surgery patients will ensure eligible patients receive cefazolin, current guidance does recommend that cefazolin can be directly administered to patients with nonanaphylactic reactions to penicillin without delabeling.²⁶

Oncology

Patients with cancer are typically prescribed antibiotics for prophylaxis, have a higher prevalence of reported antibiotic allergy than the general population,⁸⁴ and are at high risk for developing antibiotic-resistant organisms and complications from broad-spectrum antibiotic use, such as *C. difficile* infection.⁸⁵ Penicillin allergy delabeling efforts in patients with cancer may improve treatment decisions, such as increasing first-line treatment for febrile neutropenia.⁸⁶ Although penicillin skin testing was thought of as potentially inaccurate in immunocompromised hosts because of a high potential for false-negative skin testing, recent studies suggest skin testing is reliable even in those with significant neutropenia and thrombocytopenia.^{73,87} Direct challenge in select groups of immunocompromised patients has also been demonstrated.⁸⁸ Delabeling programs in patients with cancer can be implemented in either outpatient or inpatient settings, ideally before the initiation of chemotherapy or conditioning before hematopoietic stem cell transplant.²³

Pediatrics

Common childhood infections (eg, otitis media) are often managed with penicillins and early-generation cephalosporins. Penicillin reactions in children are largely low-risk (eg, rash, itching) and rarely (<20%) witnessed by clinicians.^{7,8,89} Both a penicillin reaction during childhood and a family drug allergy history have low accuracy in predicting true penicillin allergy.⁸ Given that rashes in children are more likely because of infection-related exanthems or a drug-infection interaction, most reactions reported by parents are low-risk and could be removed by history alone or direct drug challenge.^{7,8} Studies suggest that even children with more recent reactions can undergo delabeling safely with a direct amoxicillin challenge.^{33,34} Currently, direct challenge is the recommended approach in pediatric patients with a history of a benign cutaneous reaction to penicillin.²⁶ Proactive delabeling of children prevents the proliferation of PALs in adults who, as they age and acquire medical problems, may require β -lactam antibiotics.

Table 1
Select Penicillin Allergy Delabeling Studies Across Populations and Settings

Study	Population/ Setting	Study Design	Evaluation Protocol	Number Delabeled (%)	Cases Where Label Remained
Desravines et al, ⁶⁹ 2021	Obstetric / outpatient allergy clinic	Prospective enrollment of pregnant women aged 18 to 55 between 14 0/7 weeks gestation and 36 6/7 weeks of gestation	Skin testing followed by amoxicillin challenge if negative (50 mg then 450 mg, 30 min apart)	43/46 (94)	1 skin test positive, 2 oral challenge positive (both with immediate coughing, chest tightness, vomiting)
Wolfson et al, ⁷⁰ 2021	Obstetric / outpatient allergy clinic	Retrospective cohort study	Skin testing followed by amoxicillin challenge if negative (500 mg × 1)	209/222 (94)	3 skin test positive, 4 did not complete drug challenge, 3 oral challenge positive (1 immediate nonurticarial rash, 2 delayed rash), 1 label remained despite negative challenge
McDanel et al, ⁷¹ 2017	Surgical / adult orthopedic patients referred to outpatient allergy clinic	Retrospective cohort study	Skin testing in all patients, challenge to beta-lactam in certain patients	139/140 (99) after skin test only, 25/25 (100) after challenge	1 indeterminate skin test
Plager et al, ⁷² 2020	Surgical / cardiac surgical patients referred to outpatient allergy clinic	Retrospective cohort study	Skin testing followed by amoxicillin challenge if negative (500 mg × 1)	154/160 (96)	1 skin test positive, 1 did not complete drug challenge, 4 oral challenge positive (1 immediate itching, 3 delayed rash)
Taremi et al, ⁷³ 2019	Oncology / inpatient leukemia and genitourinary medical oncology services	Quality improvement assessment	Skin testing followed by amoxicillin challenge if negative (250 mg × 1)	65/69 (94) Leukemia 30/31(97) GUMO	Leukemia: 1 indeterminate skin test, 2 skin test positive, 1 oral challenge positive (immediate facial flushing and skin rash), GUMO: 1 skin test positive
Foolad et al, ⁸⁷ 2019	Oncology / inpatient leukemia, lymphoma, and solid tumor patients admitted with infectious complications	Prospective enrollment and evaluation of cancer patients receiving aztreonam	Skin testing followed by amoxicillin challenge if negative (250 mg × 1)	46/49 (94)	2 indeterminate skin tests, 1 oral challenge positive (delayed rash)
Mill et al, ³³ 2016	Pediatric / outpatient allergy clinic	Prospective enrollment and evaluation	Two-dose amoxicillin challenge (10% then 90% dose, 20 min apart)	770/818 (94)	48 oral challenge positive (17 immediate mild reactions, 31 nonimmediate reactions)
Vyles et al, ⁶⁸ 2020	Pediatric / emergency department	Prospective enrollment of patients with low-risk history in the emergency department setting	Single-dose 500 mg amoxicillin challenge	36/37 (97)	1 oral challenge positive (immediate mild urticaria)
Tucker et al, ²⁹ 2017	Military / Marine Corps Recruit Depot	Prospective enrollment and evaluation of men between 18 and 25 years	First 74 recruits had skin testing followed by a single-dose amoxicillin challenge (250 mg × 1). Subsequent 328 recruits had direct amoxicillin challenge (250 mg × 1)	397/402 (99)	5 oral challenge positive (all immediate mild cutaneous reactions)
Staicu et al, ⁵⁴ 2018	Telemedicine consultation/ inpatient	Prospective enrollment and evaluation	Skin testing performed by in person allergy/immunology physician assistant followed by remote allergist telemedicine visit	43/50 (86)	4 skin test positive, 3 did not complete the challenge

Abbreviation: GUMO, genitourinary medical oncology.

Military

Delabeling may be considered a key intervention for military medical readiness, given the widespread global availability and use of β -lactam antibiotics. Furthermore, it is considered desirable for military personnel not to have allergies when they are deployed; for example, systemic food allergies are a disqualifying medical condition.⁹⁰ The case for implementing delabeling programs broadly across all services in the Department of Defense has been proposed.⁹¹ A study of incoming marines reported that, among the 5% with a PAL, 99% were safely delabeled with a drug challenge.²⁹ The US military has implemented penicillin allergy evaluation programs at multiple sites, including Walter Reed National Military Medical Center.^{91,92} Regional medical readiness clinics proactively identify active duty service members with a PAL and refer them for evaluations during their annual health assessments, and more than 99% are delabeled.⁹¹

Dissemination of Delabeling Across Settings

Improving antibiotic prescribing is the central focus of antibiotic stewardship programs (ASP) and is critical for optimal management and treatment of patient infections and combating antimicrobial resistance. Although penicillin allergy delabeling is part of the work of ASPs and recommended by the National Quality Forum,⁹³ the American Board of Internal Medicine,⁹⁴ the Centers for Disease Control and Prevention,⁹⁵ the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, and the American Academy of Allergy, Asthma, and Immunology,²³ current estimates suggest that just 1% of Americans with a PAL receive any penicillin allergy evaluation. Therefore, a large gap exists between clinical evidence and practice in penicillin allergy delabeling.

With sufficient training and resources, penicillin allergy delabeling programs can be implemented in any location in which medications are prescribed or administered (Fig 2). As such, testing could extend beyond traditional outpatient, emergency, and inpatient clinical settings (Fig 3). To date, there is no evidence that delabeling has been implemented in a meaningful way across urgent care chains, long-term care facilities, nursing homes, or retail pharmacies.

Ambulatory Care

Approximately 10% of all ambulatory visits result in antibiotic prescriptions, making ambulatory care environments an ideal location to initiate point-of-care penicillin allergy evaluations.⁹⁶ Nonallergist clinicians can be trained to perform safe penicillin allergy evaluations in these settings, with access to decision-making risk stratification tools, vital signs and monitoring equipment, and medications including antihistamines, corticosteroids, bronchodilators, and epinephrine. The risk of an allergic reaction with penicillin allergy testing is comparable to that of allergen immunotherapy, which is administered in primary care clinics in geographic areas that lack allergist access.⁹⁷ Limited clinical knowledge of drug allergy, patient and clinician discomfort with delabeling, and competing interests given a large number of demands on primary care doctors' time are key barriers to delabeling in primary care.^{98–100}

Pediatric ambulatory practices are in a unique position to address penicillin allergy overdiagnosis by improving the initial labeling of potential allergic reactions and implementing penicillin allergy delabeling.⁵¹ Improving initial labeling will involve more detailed documentation of the allergy history in the EHR allergy module, including specific causative drug, date noted, reaction(s), reaction type, severity, and additional details, such as the timing of onset, concurrent infections, comedications, photographs, specialist evaluation, and

management recommendations.¹⁰¹ Key barriers to delabeling programs within pediatrics include limitations in knowledge and comfort,⁸⁹ competing patient needs, and time constraints.¹⁰² Parental resistance may also pose additional obstacles in pediatrics.¹⁰²

Emergency Departments

Antibiotics are the most commonly prescribed medications in the emergency department (ED), which sees a large volume of patients, with approximately 145.6 million ED visits per year in the US.¹⁰³ Patients in the ED include many who do not have access to primary care. Delabeling has been initiated while patients are waiting in the ED (eg, before discharge, or transition to another unit).^{34,104} Given that the ED is equipped to diagnose and manage allergic reactions, the available resources in EDs are ideal to establish delabeling efforts. The feasibility of delabeling in EDs has been previously exhibited.^{34,104,105} However, despite these successes, given issues with ED overcrowding and understaffing, it may be infeasible to prioritize ED-based penicillin allergy evaluations. Furthermore, ED-based penicillin allergy delabeling would negatively impact ED throughput metrics. When delabeling is infeasible, β -lactam allergy guidelines for direct challenges to the indicated β -lactam antibiotic could be used to optimize β -lactam use in the ED setting,¹⁰⁶ and EDs could also serve as a point for the identification of patients with a PAL for a specialist referral on discharge.¹⁰⁶

Inpatient Care

More than half of the patients admitted to hospitals are prescribed antibiotics.¹⁰⁷ Inpatient areas include a variety of personnel who can be trained to perform penicillin allergy evaluations and have access to the requisite resources.⁴⁸ Hospitalists and internal medicine trainees have participated in many inpatient allergy pathways for penicillins and other β -lactam antibiotics.⁴⁷ One acute care β -lactam allergy pathway that directs β -lactam use by full dose, test dose, or only with preceding skin testing is active across 9 academic and community hospitals affiliated with Mass General Brigham health system and has been implemented and studied across many other US hospital systems.^{56,108–110} Studies have previously identified barriers to inpatient skin testing, including inadequate time for testing and competing demands for other assessments that may be performed.¹¹¹ When penicillin skin testing is not feasible or not necessary (ie, the patient is low-risk), drug challenge procedures can be performed.^{56,111,112} Delabeling programs have been implemented on most hospital units to date, including intensive care units.¹¹³ Inpatient delabeling programs benefit from collaboration with ASPs.^{47,58,98,112}

Urgent Care

Urgent care centers treat more than 160 million patients each year, most of whom present with acute, infectious disease-related symptoms such as cough, sore throat, and fever.¹¹⁴ Ideally, point-of-care penicillin allergy delabeling could improve antibiotic prescribing in urgent care. Some of the earliest penicillin allergy data come from specialized urgent care clinics for the treatment of sexually transmitted infections, which are often treated with β -lactam antibiotics.⁴³ An active clinical trial (ClinicalTrials.gov Identifier: NCT04620746) is testing the feasibility of implementing penicillin allergy testing in sexually transmitted infections clinics, the results of which will inform the design and implementation of delabeling programs in this setting.¹¹⁵ With adequate clinical support and aligned economic incentives, urgent care clinics could be the ideal location for expanding penicillin allergy delabeling as quality improvement, although new resources, education, and training would be required.



Figure 3. Penicillin allergy delabeling across the care continuum. Colors indicate the frequency with which penicillin allergy delabeling as quality improvement is implemented in these settings in the United States. Settings in dark blue represent opportunities for the expansion of delabeling as quality improvement.

Long-Term Care Facilities and Nursing Homes

The prevalence of reported penicillin allergy increases with age, and older adults are more likely to suffer the adverse effects associated with the use of alternative antibiotics.² Up to 80% of older adults in nursing homes receive at least 1 course of antibiotics each year, with up to half of the antibiotic courses inappropriately prescribed.¹¹⁶ Using the same approaches used in other settings, penicillin allergy evaluations and delabeling programs in nursing homes would likely benefit older adults and nursing home residents. However, some methods will need to be adapted for these populations given that the reaction history and informed consent will often require health care proxy or care provider interview.

Additional Barriers to Delabeling and Potential Solutions

Although penicillin allergy delabeling is an established evidence-based strategy, many obstacles must be overcome to achieve widespread adoption and integration (Fig 4). Changes and investments must be seen in education, training, testing, policy, innovation, and research. While multilayer barriers to penicillin allergy delabeling exist, there are limited data that identify specific barriers. One previous study found that patients are unaware of the benefits of penicillin

allergy evaluations and that patients who suffered a negative consequence from a PAL were more likely to seek testing.¹¹⁷ Not surprisingly, fear of adverse effects was a barrier identified from the patient's perspective.¹¹⁷ Clinicians seem hesitant to alter a PAL on the basis of their clinical judgment alone and generally have limited experience referring patients with a PAL for evaluation.¹¹⁸ These preliminary findings emphasize the importance of increasing patient and clinician education on the availability, safety, and benefits of penicillin allergy delabeling.¹¹⁷ Advancement of penicillin allergy delabeling as a quality improvement for patients and health care systems will require additional mixed methods research to uncover the full spectrum of barriers and facilitators to this initiative.

The Importance of Health Equity

While some studies described a lower likelihood of a PAL among Black, Latinx/Hispanic, and Asian American individuals than among non-Hispanic White individuals,^{3,5,6,119} other studies document similar or even higher prevalence of PALs in Black individuals.^{4,120} Despite the many unknowns with respect to PALs and health care equity, the 1% of labeled individuals who are receiving allergy specialist evaluations for PALs are largely White, non-Hispanic, educated,

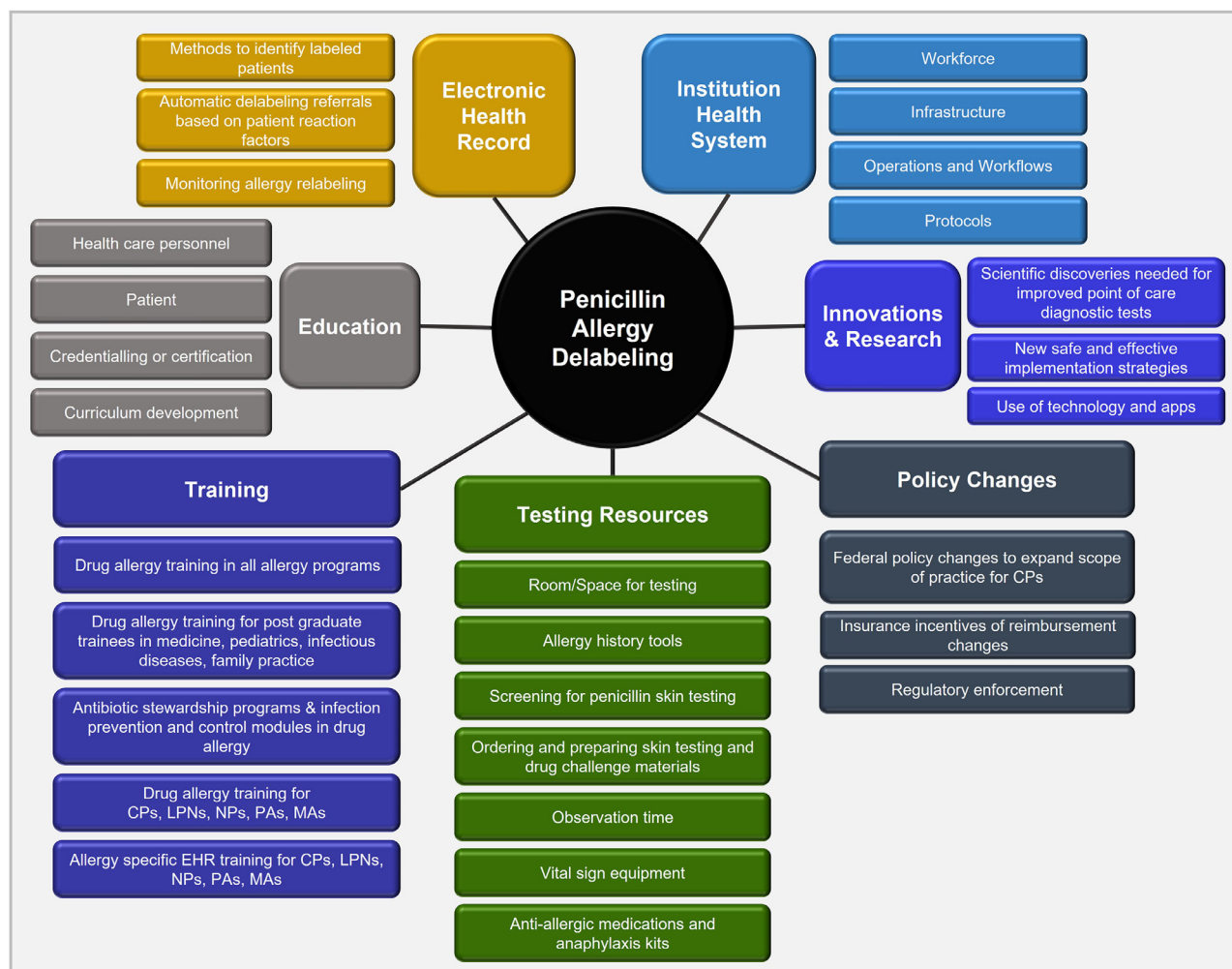


Figure 4. Considerations for expansion of penicillin allergy delabeling into routine care in a radial cluster diagram. CPs, clinical pharmacists; EHR, electronic health record; LPNs, licensed practical nurses; MAs, medical assistants; NPs, nurse practitioners; PAs, physician assistants.

and otherwise healthy.¹²¹ Race, as a social construct, has not been found to be associated with genotypic risk for true immediate hypersensitivity to penicillin.¹²² A recent genomewide association study revealed an association between a genetic marker in the human leukocyte antigen complex, HLA-DRB1*10:01, and specialist-confirmed aminopenicillin allergy; however, conclusive evidence of association with particular ancestries remains unclear.¹²³ To our knowledge, there are no delabeling efforts to date which focus on health equity, despite a disproportionately higher rate of antibiotic-resistant infections affecting minority communities.^{124,125} There is a need to further evaluate factors preventing equitable access to penicillin allergy delabeling.¹²⁶

Conclusion

Penicillin allergy labels (PALs) are ubiquitous but overwhelmingly inaccurate. PALs have unintended negative consequences at the patient, system, and population levels. Expanding access to penicillin allergy evaluations and delabeling requires multipronged approaches, integrated delabeling programs, and cross-specialty collaborations within health systems to prioritize locations and patient populations who are most likely to benefit from delabeling. This effort requires broad investments that can democratize allergist knowledge and skill across settings, locations, and users.

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