Penicillin Allergy Impact and Management

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KEYWORDS

• Penicillin allergy • Drug allergy • Delabeling • Oral challenge

KEY POINTS

- Penicillin allergy labels negatively impact patient outcomes. Efforts should be made to reduce this risk through clarifying or eliminating these labels where appropriate by all health care personnel.
- Penicillin and antibiotic allergy assessment tools and clinical decision rules are validated for risk stratification to assist with prescribing and delabeling.
- Low risk direct oral penicillin challenge can be implemented in the outpatient or inpatient setting to aid delabeling with an Antimicrobial Stewardship focus.

INTRODUCTION

Beta-lactam allergy is frequently encountered in hospitalized patients and community practice, with up to 1 in 4 patients reporting an antibiotic allergy "label," with 1 in 10 patients reporting a penicillin allergy.[1,2] This label has been associated with inappropriate antibiotic usage leading to adverse outcomes such as *Clostridioides difficile* infections (CDI), surgical site infections (SSIs), antimicrobial resistance (eg, methicillin resistant *Staphylococcus aureus*), patient mortality, and excess hospital costs.[1] The described impacts are potentially avoidable health consequences, as only 1 in 10 patients are truly allergic.[3] The act of removing antibiotic allergies, in particular beta-lactam allergies, is described as "delabeling"—the revision of a patient-reported antibiotic allergy via testing or medical reconciliation.[4] The traditional testing method, especially in an infectious diseases' (ID) context, has been via skin testing (skin prick

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and intradermal) followed by oral challenge (ie, provocation).[5–8] Modern approaches have incorporated point-of-care risk assessment, followed by direct oral challenge in those considered to have low-risk phenotypes.[9,10] Reducing the impact of beta-lactam allergies from an ID and antimicrobial stewardship (AMS) perspective requires greater understanding of antibiotic allergy (1) mechanisms, (2) cross-reactivity, (3) risk assessment, and (4) point-of-care delabeling strategies.

DEFINITIONS

Penicillin and Beta-lactam Allergy Mechanism Definitions

Reaction types are important to understand and to clarify through allergy assessment. Types of reactions are described below and in **Table 1**.

Immediate hypersensitivity reactions typically occur within 1 hour and are most likely IgE-mediated with presentations of urticaria, bronchospasm, angioedema, and/or anaphylaxis. Non-IgE mediated reactions that occur immediately or within 6 hours after the dose are uncommon; however, they are classified as immediate hypersensitivity. Anaphylaxis is a form of immediate hypersensitivity, defined as an acute systemic allergic reaction that involves more than 1 organ system. Consensus criteria for diagnosis do not exist; however, there are visual representations from national guidance created in an effort to simplify the diagnosis.[11]

Delayed hypersensitivity reactions are thought to involve drug-specific T cells that can take days and, in rare cases, weeks to present. Often, they are benign cutaneous reactions; however, more severe cutaneous reactions (SCARS) can occur. Severe cutaneous reactions include drug reactions with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP).

Penicillin and Beta-lactam Allergy Testing Definitions

An understanding of the modern approaches to penicillin and beta-lactam allergy testing is required prior to implementation into AMS programs, as outlined below.

Table 1
The immunologic mechanisms and clinical manifestations of commonly encountered beta-lactam immune-mediated allergies

Immunologically Mediated Mechanisms	
Type I, immediate hypersensitivity (IgE-mediated)	Urticaria, angioedema, bronchospasm, anaphylaxis, cardiovascular collapse
Type II, cytotoxic reaction	Hemolytic anemia, petechia, thrombocytopenia
Type III, immune-complex reaction	Small-vessel vasculitis, serum sickness, arthus reaction
Type IV: cellular mediated (delayed)	Contact dermatitis, exanthems
T-cell mediated mechanisms	
DRESS	Epidermal edema, lymphadenopathy, atypical lymphocytosis, fever, eosinophilia, and infiltration of skin and internal organs
SJS-TEN	Epidermal necrosis, subepidermal bullae, and involvement mucosal membranes
AGEP	Fever, neutrophilic leukocytosis, sterile pustules in stratum corneum and epidermis, dermal edema, and infiltration of immune cells

Oral drug challenge (ie, provocation)

Administration of a drug orally to determine tolerance. This can be done with one dose of drug, multiple doses, or multiple days of administration with observation for symptoms following dose or doses (**Figs. 1** and **2**). Other common names for this testing are "drug provocation tests," "graded challenge," or "test dose". A direct oral challenge is the administration of drug to assess for allergic reaction without prior skin testing.

- 1-step: A single full dose of drug is administered followed by monitoring for symptoms of allergic reaction. This 1-step strategy is recommended by the Drug allergy: A 2022 practice parameter update by both the America Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology[12]; however, a 2-step test may be required for reimbursement in some regions.
- 2-step: A multistep process in which 10% to 25% of the treatment dose is administered followed by observation and if no adverse reactions are observed, the remainder of the treatment dose is administered followed by observation.
- Multi-day drug challenges are typically not recommended as studies have shown single day challenges to be sufficient.
- Nocebo effect: Placebo-controlled drug challenges are recommended in patients with subjective drug allergy symptoms or multiple allergies as drug challenges can be anxiety producing and there is data demonstrating objective reactions can occur when placebo is administered rather than the suspected allergen.[12] These placebo-associated reactions, termed a nocebo effect, can include symptoms such as flushing, wheezing, tachycardia, urticaria, and vomiting, occurring between 8% and 11% of patients receiving placebo.[13,14]

Skin testing

Penicillin skin test (PST) is a process to evaluate penicillin allergy by pricking or injecting skin with dilute penicillin followed by monitoring, typically initially with a skin prick testing (SPT) followed by intradermal testing (IDT) using standardized published

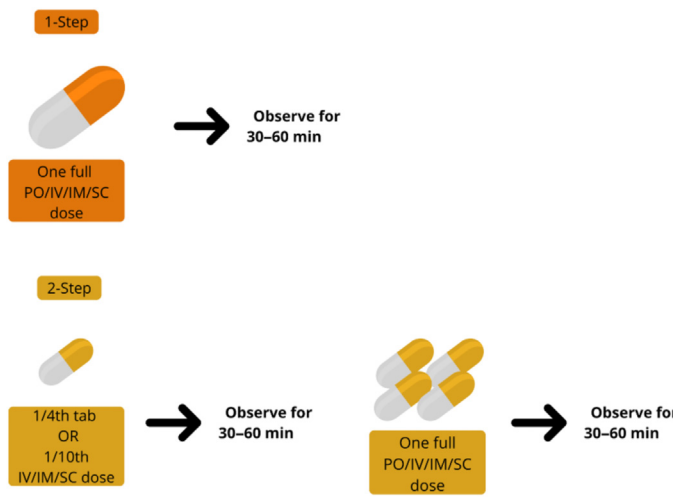
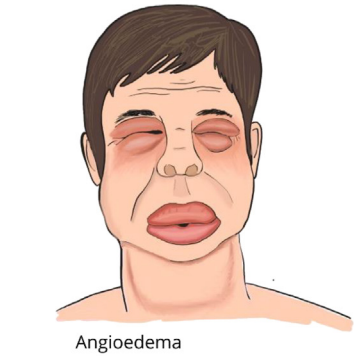
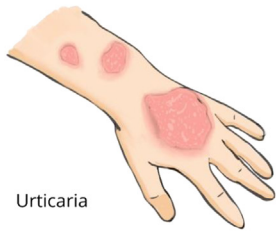


Fig. 1. Oral drug challenge: 1-step and 2-step testing followed by appropriate monitoring. (Illustration reprinted with permission from: Desirae E. Hanna, Pharm.D., BCPS (@rxpalette); Clinical Pharmacist, Duke University Hospital.)





Criteria for positive reaction:

Angioedema
Urticaria
Exanthem
Wheezing
Hypoxia
Hypotension
Anaphylaxis

Criteria for possible reaction:

Flushing
Vomiting
Cough
Abdominal cramping
Persistent pruritus without rash
Fever
Mouth or eye soreness

Criteria for doubtful reaction:

Dizziness
Tachycardia
Subjective lip/tongue swelling
Subjective throat tightness
Lump in throat
Dyspnea
Transient pruritus without rash
Headache

Fig. 2. Signs and symptoms to indicate a positive, possible, or doubtful reaction. (Illustration reprinted with permission from: Desirae E. Hanna, Pharm.D., BCPS (@rxpalette); Clinical Pharmacist, Duke University Hospital.)

concentrations of drugs.[4] Negative skin testing must be followed by oral challenge to confirm the presence or absence of true allergy.

Delabeling

The act of removing a drug allergy through allergy history, drug challenge, and/or skin testing. *Direct delabeling* is the removal without testing via medical reconciliation alone.

Desensitization

Inducing drug tolerance through exposure to incrementally increasing doses of drug. This procedure does not eliminate or clarify existing allergies, rather it allows for administration of the drug following desensitization and with consistent drug exposure.

DISCUSSION

Burden and Impacts

The same year Fleming, Florey, and Chain were awarded the Nobel Prize for the discovery of penicillin, the first case of anaphylaxis to penicillin was reported.[15] At that time the authors call out the "toxic, microbiogenic, and allergic side effects occurring in man as a result of large amounts of penicillin increasingly used in medical and veterinary practice," an early call to steward these agents.[15] The rate of death from anaphylaxis associated with penicillins was reported by the WHO to be 0.002% in 1968 and has been reported to have decreased even further since that time.[15] Despite this very low rate, there is considerable fear of this rare reaction and with 10% to 20% of patients reporting a penicillin allergy, many of which do not have the reaction

specified, alternative therapies are selected. Over 95% of patients with reported penicillin allergy tolerate beta-lactams when carefully evaluated[5,16]; however, this often-inaccurate label negatively impacts patient care and outcomes as alternative antibiotics that are less effective, more costly, and more toxic are selected including fluoroquinolones, clindamycin, vancomycin, and cephalosporins.[17] These agents have been repeatedly shown to put patients at higher risk for *C. difficile* infections, methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) infections, and SSIs.[1,18]

In a cohort of over 300,000 ambulatory patients with a penicillin allergy label (N = 63,690) matched 1:5 on age, sex, and study entry time to patients without a penicillin allergy label (N = 237,167), Blumenthal and colleagues[19] found an increased incidence of *S. aureus* and *C. difficile* in patients with penicillin allergies (**Table 2**). This same cohort additionally demonstrated the high rates of non-beta-lactam antibiotic utilization in penicillin allergic patients which the authors attribute to increasing the risk for *S. aureus* and *C. difficile.* The authors in this study found a 14% increased risk of death among those with a penicillin allergy label.[20,21] Although there are limitations to this study, the cohort was adjusted for Charlson Comorbidity Index, antibiotic prescription, and health care utilization and followed patients over 6 years. Colonization and infection with *S. aureus* and *C. difficile* are associated with substantial morbidity and mortality; thus proactive efforts to reduce these risks however possible are important. Many of the risk factors for either pathogen are unmodifiable; however, delabeling penicillin allergies through assessments or active testing is a modifiable risk for most patients given the high risk of mislabeled patients.

Similar negative impacts are seen in hospitalized patients. Macy and colleagues[21] conducted a 1:2 matched cohort study of 51,582 with a penicillin allergy label, admitted for any diagnosis, matched to non-penicillin allergy labeled patients based on discharge diagnosis, sex, age, and date of admission. In this study, an increase length of stay (LOS) of 0.59 days was observed in patients with a penicillin allergy with the biggest impact (0.80 days LOS increase) in females over age 50 years. The penicillin allergic patients had more *C. difficile*, VRE, and MRSA infections than control patients determined by clinical isolates or associated ICD-9 codes.[17] These negative patient outcomes are costly both to the patient and the health care system. Although just over half a day increase in LOS may seem minor, when applied to this population it accounted for over 30,000 extra hospital days.[17] Based on average cost per hospital day at the time of $2123.56 the extra LOS resulted in over $64 million in health care expenditures.[17] These costs do not include the additional cost of the acquired

Table 2
The microbiological, patient and hospital impacts of a beta-lactam allergy

Factor	Increased Risk to Patient
Clostridioides difficile	23% inpatient[17] 26% outpatient[19]
MRSA infection	14% inpatient[17] 69% outpatient[19]
VRE infection	30% inpatient[17]
Length of stay	0.59 d[17]
Surgical site infection	50%[18]
Increased risk of death	14%[20]
Death during hospitalization	1.6 (crude OR 1.56, 95% CI 1.20–2.04)

infections associated with the penicillin allergy label. There is substantial cost savings, estimated at $1915 per patient per year (in US dollars) and improvement to patient outcomes associated with delabeling.[22]

Additional adverse effects associated with the penicillin allergy label were found when evaluating the impact on surgical prophylaxis with a 51% increased risk of SSI when analyzing a cohort of over 8000 patients and 9000 procedures.[18] Not only does this have substantial impact on the patient, but there is also substantial cost to the institution with each SSI costing $12,000 to $24,000.[18] There is also impact to the perception of hospital quality as the SSI data for certain surgical types is available to the public.[18] The authors estimate that 1 SSI could be prevented by reviewing and clarifying allergies per 112 to 124 patients.[18] The majority of patients can have their allergy removed through detailed history that requires minutes or if additional testing is required only hours to prevent the morbidity and mortality associated with SSI.

The negative effects of the antibiotic allergy label substantially impact both ambulatory and inpatient cohorts; thus, it is imperative that the assessment strategies described below are used throughout all health care settings.

MANAGEMENT

Allergy History

Allergy assessments are critical to determining which patients are truly allergic and to delabel those with inaccurate labels. It is the responsibility of all members of the clinical team (eg, nurses, prescribers, pharmacist, etc.) to proactively interview patients regarding allergy status to ensure the medical record is correct as this data changes antibiotic choices.[16] A critical component of this process is education of both the patient and family as well as the patient's clinical team. There are key components to an allergy history that are essential for appropriate phenotyping and ensuring correct delabeling strategy, as outlined below.[23]

Severity and Type of Reaction

1. Do you remember the details of the reaction?
2. How was the reaction managed? Did it require treatment or hospitalization?

Timing

3. How long after taking the antibiotic did the reaction occur?
4. How many years ago did the reaction occur?

Antibiotic Use Since Reaction

5. Are there other antibiotics that you have taken without problems since the reaction?

Key areas for provider and patient education about beta-lactam allergies include reasons for mislabeling, risk of adverse reaction of both the labeled beta-lactam and alternative agent, as well as newer understanding of the natural history of immune-medicated hypersensitivity reactions. There are many reasons for mislabeling including simply coding a nonimmunologic adverse reaction as an allergy (eg, diarrhea with amoxicillin-clavulanic acid)—type A adverse drug reaction (ADR). Additionally, some patients who had an allergic reaction may no longer be allergic as penicillin-specific IgE-mediated reactions wane over time with up to 80% of patients losing the anti-penicillin IgE antibodies after 10 years.[24,25] Overall there are many fewer positive PST results than historically likely due to improved drug manufacturing processes

and elimination of penicillins from cephalosporin preparations as this accounted for 5% of cross-reactivity with early cephalosporins.[22] For some patients there may have been an interaction of infectious agents (eg, viruses) with antibiotics that caused a cutaneous reaction, or in fact direct cutaneous manifestation of a pathogen.[12,24]. Thus, historic allergies may not predict future reactions. Sharing this knowledge can help to alleviate fears of the patient and clinical teams and allow for good history taking and comfort with removing allergy labels where appropriate. Allergy assessments and education should be proactively offered in all health care settings and should be part of standard education for all health care workers.

RISK ASSESSMENT

Assessment Tools

Ascertaining the beta-lactam allergy phenotype is the first point-of- call to assigning risk—defined as the likelihood of persistent immune-mediated allergy. There has been increased focus on defining low- and high-risk beta-lactam allergies to further aid the assignment of management AMS strategies—prescribing and delabeling. Assessment tools have primarily been expert derived; however, there has been increased use of validated toolkits as outlined in **Table 3**. In the ID/AMS setting, Devchand and colleagues[27] (Australia) developed the Antibiotic Allergy Assessment Tool (AAAT) that has been widely used in hospital-based programs,[10,54] and adapted for pediatrics.[31] AAAT can be used by a range of stakeholders to risk-stratify antibiotic allergies (sensitivity of 91.8% and specificity of 97.5%) (see **Table 3**).[27,28]

Shenoy and colleagues[34] presented an expert opinion algorithm for extrapolating penicillin allergy assessment into risk stratification (see **Table 3**), which has been referenced and adapted for widespread clinical use. This is endorsed by the American Academy of Allergy, Asthma and Immunology (AAAAI), Infectious Diseases Society of America (IDSA), and Society of Healthcare Epidemiology of America (SHEA). In regard to penicillin allergy, Ramsey and colleagues have also used a penicillin allergy history algorithm (PAHA), incorporated as a standardized history-taking tool. This tool in effect risk stratifies patients into high risk (avoid penicillin) and low/moderate risk (perform testing).[38,55] One limitation of these tools is they have been designed primarily for penicillin allergy; however, they likely can be extrapolated to other beta-lactams. The universal features that are considered low-risk across all 3 assessment tools are: type A adverse drug reaction, family history, skin rash greater than 10 to 20 years previous.

Clinical Decision Rules

The search for point-of-care risk assessment tools has led to the derivation of a range of clinical decision rules for antibiotic allergy. The 5 published clinical decision rules for penicillin or beta-lactam allergy from across Europe, USA, and Australia are demonstrated in **Table 3**. The negative predictive values (NPV) for true penicillin allergy range from 80% to 96.3%, with 4 of the 5 tools providing a validated low-risk criterion (see **Table 3**).

PEN-FAST is the only prospectively derived clinical decision rule that has been subsequently externally validated. PEN-FAST is a 3-point clinical criterion derived from a published cohort study in Melbourne (Australia),[7,10] with subsequent external validation in penicillin allergy tested cohorts from Sydney (Australia), Perth (Australia), and Nashville (USA).[47] The variables associated with a positive penicillin allergy test result on multivariable analysis were subsequently summarized in the PEN-FAST mnemonic: PENicillin allergy, Five or fewer years ago (2 points), Anaphylaxis/angioedema, Severe cutaneous adverse reaction (SCAR) (2 points), and Treatment required for allergy

Table 3
Penicillin allergy risk assessment and clinical decision rules

Author/ Region[a]	Primary Derivation	User Group	Population	Assessment Outcome	Outputs	Sensitivity (%)	Specificity (%)	External Validation or Usage	Special Population Adaption
Assessments tools									
Staicu et al[26] (USA)	Expert opinion	Hospital clinicians Pharmacists	Adult inpatients	Mild-moderate/ severe	Beta-lactam utilization[c]	-	-	USA[8]	-
Devchand et al[27] (Australia)	Expert opinion	Doctors Nurses	Adult inpatients/ outpatients[b]	No risk/low/ moderate/high *Low risk criteria:* childhood rash, MPE > 10 y, unknown > 10 y	Testing[c]	91.8%	97.5%–97.9%	Australia[10,28–30]	Pediatric adapation[31]
Blumenthal et al[32] (USA)	Expert opinion	Allergists	Outpatients (n = 426)	Low/intermediate/ high Low risk criteria: mild cutaneous or unknown > 5 y	Testing and beta-lactam utilization[c]	95.1%	-	USA[33]	Perioperative assessment[33]
Shenoy et al[34] (USA)	Expert opinion[d,e]	Clinicians	Not specified	Low/medium/high Low risk criteria: type A, pruritis without rash, unknown reactions > 10 y without IgE features, family history	Testing[c]	-	-	USA[35,36] Canada[36]	General Practice[37]

Ramsey et al[38] (USA)	Expert opinion	Pharmacists	Adult inpatients (n = 50)	No specific grading Low risk criteria: type A, family history	Testing[b] and penicillin utilization	94%	NA	USA[35]	-
Roberts et al[39] (UK)	Expert opinion	Pharmacists	Pediatric outpatients (n = 104)	Low/possible IgE/ allergic/severe	DOC	91%	-	-	-
Reichel et al[40] (Germany)	Expert opinion	Allergists	Outpatients (n = 200)	Low/moderate/ high Low risk—isolated urticaria, type A, childhood rash	Testing[c]	-	-	-	-
Bediako et al[41] (USA)	Expert opinion	Nursing	Inpatients (n = 235)	Low/high	Direct delabeling[c]	-	-	-	-
Sijpe et al[42] (Belgium)	Expert opinion	Pharmacy	Inpatients (n = 197)	Correct/ undetermined/ incorrect	Direct delabeling[c]	-	-	-	-
Manning et al[36] (Canada)	Expert opinion[f]	Pharmacists	Inpatients (N = 48)	Low/medium/high Low: unknown reaction or side effect; poorly described non-anaphylactic symptoms, delayed (>72 h) rash without IgE features	Allergy documentation	-	-	-	-

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Table 3
(*continued*)

Author/ Region[a]	Primary Derivation	User Group	Population	Assessment Outcome	Outputs	Sensitivity (%)	Specificity (%)	External Validation or Usage	Special Population Adaption
Clinical decision rules									
Chiriac et al[43,44] (France)	Retrospective data—multivariable logistic regression	Allergists	Outpatients (n = 2101)	5-point criteria No validated low-risk criteria identified	Testing[c]	51% 83% NPV	75% 40% PPV	-	-
Siew et al[45] (UK)	Retrospective data—multivariable logistic regression	Allergists	Outpatients (n = 1092)	Low-risk criteria—no anaphylaxis, reaction > 1 y previous, inability to recall index drug	Testing[c]	80.6% NPV (98.4% low risk only)	-	-	-
Stevenson et al[46] (Australia)	Retrospective—multivariable logistic regression	Allergists	Outpatients (n = 447)	Low-risk criteria: non-SCAR rash OR rash without angioedema and > 1 y previous	Testing[c]	80.6% (NPV 97.1%)	60.8%	-	-

Trubiano et al[47] (Australia/ USA)	Prospective data—multivariable logistic regression	ID/allergist	In/outpatients (n = 945)	3-point clinical criteria (max score 5) Low/moderate/ high low risk criteria: PEN-FAST score < 3	Testing[c]	70.7% (NPV 96.3%)	78.5%	US[48]/Europe[49]	Virtual care[50] Pediatrics[51] Pregnancy[52]
Sabato et al[53] (Europe)	Multivariable logistic regression	Allergists	Outpatients (n = 410)	1-1-1 criterion—rash within 1 h after first and regression within 1 d	Testing	85% 80% NPV	85%	-	-

DOC, direct oral challenge for low-risk phenotypes; IDT, penicillin intradermal testing; NPV, negative predictive value; PPV, positive predictive value; SPT, penicillin skin prick testing.

Low risk was defined as an assessment outcome that led to or recommended direct oral penicillin challenge.

[a] The assessment tool was used in AMS context.

[b] Expert opinion derived and applied to real-case scenarios (n = 8) from a prospective inpatient and outpatient testing database by 40 end users.

[c] An output of allergy testing could be direct oral penicillin challenge and/or skin testing. An additional outcome is direct delabeling—the removal of an allergy by medical reconciliation alone (eg, confirmed post safe re-exposure, non-immune-mediated side effect history).

[d] Approved and endorsed by IDSA, AAAAI, and SHEA.

[e] The terms "low" and "very low" were not used in this assessment tool, the outcomes were given regarding the testing modality not the severity.[38]

[f] Adapted from Providence Health Care in British Columbia and Shenoy et al.[34]

episode (or unknown) (1 point). A score of less than 3 points on the PEN-FAST tool translates to a low risk of penicillin allergy, as only 17 of 460 patients (3.7%) are positive on testing [area under the curve (AUC), 0.805; NPV 96.3% (95% CI, 94.1%–97.8%)]. PEN-FAST has subsequently been externally validated in European[56] and North American outpatient allergy cohorts.[48] Specialist positive validation has been demonstrated in pregnancy[52]; however PEN-FAST failed to be effective in a pediatric cohort.[51]

In regard to the other published clinical decision rules, Stevenson and colleagues[46] identified a reported penicillin allergy of benign rash more than 1 year previous as a low-risk criterion (97.1% NPV, sensitivity 80.6%, specificity 60.8%). Siew and colleagues[45] generated a low-risk criteria consisting of (1) no anaphylaxis, (2) reaction more than 1 year ago, and (3) no recall of index drug (NPV 98.4%). Chiriac and colleagues[43] produced a clinical decision rule that was unable to predict allergy (AUC, 0.67; sensitivity, 51%; NPV, 83%). Recently, Sabato and colleagues[53] produced the 1-1-1 criterion (rash within 1 hour after 1st dose and regression within 1 day) with an NPV of 80%. With clinician decision rules for penicillin and beta-lactam allergy continuing to emerge clinicians and AMS programs can select and adapt the tool that is best suited to their health service and patient population.

Approaches to Delabeling: Skin Testing

PST has been a standard practice for delabeling in the USA; however, the most recent practice parameter emphasizes the use of drug challenge over skin test as the reference standard for patients without anaphylaxis or severe cutaneous skin reactions.[12] For patients with a history of anaphylaxis or recent reaction suspected to be IgE mediated, a PST is recommended. Patients with a negative penicillin skin test and oral amoxicillin challenge should be considered to be at the same risk of penicillin allergy as the general population.[57] Knowledge of how to perform and evaluate a penicillin skin test can be obtained through a training course or in published references.[34] In addition to the benefits of reducing the risks associated with penicillin allergy, multiple studies have demonstrated health care cost reduction associated with PST.[58] Penicillin allergy testing can be done across the health care continuum safely including in the ambulatory, emergency, and inpatient settings (**Table 4**). If patients cannot be cleared of their allergy label through assessment alone or oral challenge, a PST should be used with relatively few contraindications (exceptions: SCAR, recent allergic reactions, concurrent antihistamines, etc.). Pregnancy should not eliminate the option for PST as it has been associated with reducing the risk of this label (eg, longer hospitalizations, increased morbidity, complications) as this test has been repeatedly demonstrated to be safe in pregnancy.[63] Proactive testing of pregnant women should be offered to those who test positive for group B Streptococcus.[64]

Skin testing approaches to cephalosporins have evolved, with increasing publications from Australia, North America, and Europe.[65–67] Although standardized testing for cephalosporins has not yet been achieved, nonirritating concentrations have been published and widely used.[68,69] Variability in the published cephalosporin intradermal concentrations varies from 2 mg/mL to 20 mg/mL for immediate hypersensitivity.[53] The similarity between penicillin and cephalosporin allergy appears to be in the loss of sensitivity over time–time since reaction predicting skin test positivity with a reported aOR 0.71 (95% CI 0.56, 0.9).[67] In general, cephalosporin skin testing appears to have a lower sensitivity than penicillin testing in IgE-mediated reactions,[1,4,70] whereas in high-risk phenotypes (eg, anaphylaxis) skin testing retains a high positive predictive value.[70] Data for direct oral challenge to penicillin in low-risk phenotypes continues to emerge, however similar data remains absent for cephalosporins.[71] The use of test

Table 4
Penicillin skin test location of test administration

Intensive Care Unit[59]	
Intervention	PST in conjunction with allergy consultation
Results	• Negative skin test: 88.6% • Indeterminate test: 10.4% • 81.5% of patients with negative test had antibiotic changed to beta-lactam
Emergency department[60]	
Intervention	PST by 2 ED physicians trained by allergist (N = 150)
Results	• Negative skin test: 91.3% • Recommended first-line therapy was a beta-lactam in 70% of patients • Cost saved per patient est. $73.80 (95% CI, $17.17–$130.43)
Preoperative[61]	
Intervention	○ A hospital with established preoperative evaluation clinic implemented a pathway for patient with penicillin allergy ○ Same-day skin testing was performed by a nurse and test was interpreted by an on-site allergist ○ Reviewed experience from 1072 patients
Results	• Negative skin test: 95% • Patients with negative versus positive PST ○ ↓ vancomycin (16% vs 30%, $P < 0.01$) ○ ↓ non-β lactam antibiotics (3% vs 24%, $P < 0.01$) • No adverse events
Ambulatory Care[62]	
Intervention	○ Prospective observational study with patient identification during routine prescription filling ○ Patients educated and offered allergy referral (N = 503) ○ 71 patients were seen in clinic
Results	• 503 patients were enrolled • 71 patients (14%) evaluated by allergist • 94% (N = 67) had a negative PST • Future treatment with β-lactam was more common in group evaluated by allergist (66% vs 26%, $P < 0.0001$)

dose procedures as a guideline-based approach has been successfully deployed in North American experiences.[72] However, at present direct oral challenge data without prior skin testing for primary cephalosporin allergies remains limited and this approach is not routinely performed or hence recommended.

Approaches to Delabeling:Direct Oral Challenge

Antimicrobial stewardship programs continue to play a significant role in the implementation of direct oral challenge programs for beta-lactam allergy, in particular penicillin allergy.[4] Although early evidence demonstrated that use of skin prick and intradermal testing prior to oral challenge performed by ID and AMS pharmacist led programs was successful,[6,8,73] there has been a shift to the utilization of direct oral challenge programs without prior skin testing. The available published literature of direct oral challenge programs is demonstrated in **Table 5**. There are more than 3000 published oral challenges reported from 21 studies in the literature, with a significant body of the literature performed by nonallergists (8/21 studies) and positive oral challenge rate of ranging from 0% to 10% (average 3.17%) (see **Table 5**).

Table 5
Direct oral challenge in the inpatient and outpatient adult population

Author	Study Design	Population	N	Risk Assessed	ICH	Low-Risk Definition	Follow-up	Oral Challenge (Full Dose)	Immediate Positive	Delayed Positive	Total Positive
Tucker et al[74] (USA)	Retrospective single center cohort study	Adult outpatients	328	A/I	No	All reactions EXCLUDING. SCAR/hepatitis/ hemolytic anemia/ nephritis	-	1-step amoxicillin (250 mg)	1.5% [a] (5/328)	0% (0)	1.5% (5/328)
Trubiano et al[29] (Australia)	Prospective multicenter cohort study	Adult outpatients	46	ID	Yes	ANY OF Type A ADR/ unknown reaction >10 y/ benign childhood rash/nonurticarial rash/MPE >10 y prior EXCLUDING History of drug associated anaphylaxis/ hemodynamically unstable	5 d	1-step penicillin/ amoxicillin (250 mg)—2 h observation	0% (0)	0% (0)	0% (0)
Banks et al[75] (USA)[f]	Retrospective single center cohort study	Adult outpatients	708	A/I		ANY OF benign rash/ GI Symptoms/ headache/benign somatic symptoms/ unknown AND >1 y EXCLUDING Blistering rash, nephritis, hepatitis, hemolytic anemia	-	1-step amoxicillin (250 mg)	1.1% (8/708) [a,b]	0% (0)	1.1% (8/708)
		Adult outpatients	806	A/I			-	1-step amoxicillin (250 mg)	1.2% (15/806) [a]	0.8% (10/806) [a]	2% (25/806)

Iammatteo et al[76] (USA)	Retrospective single center cohort study	Adult and pediatric outpatients	155	A/I	U	All reactions EXCLUDING Bronchospasm or laryngeal edema requiring intubation/ anaphylactic shock/ SCAR, AIN, hepatitis, hemolytic anemia, cutaneous/ mucosal blisters, hypersensitivity vasculitis, pneumonitis, pulmonary fibrosis and serum sickness)/ antihistamine use/ pregnancy	1 mo	2-step amoxicillin (500 mg)—2 h	2.6% (4/155) [a]	0% (0)	2.6% (4/155)
Kuruvilla et al[77] (USA)	Retrospective single center cohort study	Adult outpatients	20	A/I	U	ANY OF nonspecific benign rash/remote unknown reaction/ benign somatic symptoms AND >1 y EXCLUDING Blistering rash/ hemolytic anemia/ organ involvement/ steroids/ antihistamines	-	1-step amoxicillin (500 mg)—1 h observation	0% (0)	0% (0)	0% (0)
Stevenson et al[46] (Australia)	Retrospective multicenter cohort study	Adult outpatients	167	A/I	U	"Low-risk" defined by center-specific protocols EXCLUDING Pregnancy/significant cardiorespiratory disease	3–7 d	1 or 2-step amoxicillin or implicated penicillin	3.6% (6/167)	0% (0)	3.6%[b] (6/167) [d,e]

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Table 5
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Author	Study Design	Population	N	Risk Assessed	ICH	Low-Risk Definition	Follow-up	Oral Challenge (Full Dose)	Immediate Positive	Delayed Positive	Total Positive
Mustafa et al[78] (USA)	Prospective single center RCT	Prospective single center RCT—adult/ pediatric outpatients	79	A/I	U	ANY OF skin rash/ hives/itching/ unknown AND >10 y AND nil emergency medical attention EXCLUDING Age < 5 y/pregnancy/ SCAR	-	2-step amoxicillin (400 mg)—1 h observation	3.8% (3/79) [a]	0% (0)	3.8% (3/79)
Savic et al[79] (UK)	Prospective single center	Adult perioperative outpatients	56	Nurse	U	ANY OF GI/nonitchy rash/no hospital admission/thrush/ unknown AND >15 y EXCLUDING Unstable asthma/ pregnancy/ breastfeeding	5–7 d	3-step amoxicillin then 3 days (500 mg)	2% (1/56) [a]	0% (0)	2% (1/56)
Devchand et al[28] (Australia)	Prospective single center	Adult inpatients	20	Nurse/ pharmacist	Yes	Childhood exanthema Rash > 10 y Unknown > 10 y EXCLUDING History of drug associated anaphylaxis/ hemodynamically unstable	24 h	1-step penicillin VK or amoxicillin (250 mg) – 2-h observation	Nil	5% (1/20) [a]	5% (1/20)

Blumenthal et al[80] (USA)	Retrospective multicenter	Adult inpatients	76 (6)[a]	AI/internal medicine/ nurse	U	ANY OF minor rash (not hives)/MPE/ recorded allergy which patient denies	-	1-step or 2-step amoxicillin	-	-	3.9%[b] (3/76)
Du Plessis et al[81] (NZ)	Prospective single center	Adult inpatients	34	Pharmacist	U	Delayed onset rash AND > 5 y EXCLUDING COPD/asthma/ significant cardiovascular disease/beta-blockers, ACE inhibitors/ hemodynamically unstable/> 70 y	1 mo + 1 y	5-step amoxicillin (500 mg)	-	8.8% (3/34) [a]	8.8% (3/34)
Li et al[82] (Australia)	Prospective singe center	Adult inpatients	56	A/I	Yes	Type A reaction (nonimmune mediated) OR immune-mediated reaction EXCLUDING Anaphylaxis (<10 y)/ IgE mediated <1 y/ hemolytic anemia/ serum sickness/ SCAR/pregnancy/ hemodynamically unstable	3 d	3-step amoxicillin (500 mg)—3-h observation (Then 3 days)	0% (0)	3.6% (2/56) [a]	3.6% (2/56)

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Table 5
(*continued*)

Author	Study Design	Population	N	Risk Assessed	ICH	Low-Risk Definition	Follow-up	Oral Challenge (Full Dose)	Immediate Positive	Delayed Positive	Total Positive
Ramsey et al[55] (USA)	Prospective single center	Adult inpatients	48	A/I/Pharm	U	ANY OF rash/hives/itching/unknown AND >20 y AND nil emergency medical attention EXCLUDING Pregnancy	2 wk	3-step amoxicillin (500 mg)—1.5-h observation	2% (1/48) [a]	4% (2/48) [a]	6.25% (3/48)
Stone et al[83] (USA)	Prospective single center	Adult critical care inpatients	54	A/I	U	ANY OF urticaria only >5 y/self-limited rash/GI only/remote childhood reaction with limited details/family history of alone/avoidant due to fear of allergy/known tolerance of penicillin post-reaction/other symptoms non-allergy	Chart review at 7 mo	1-step amoxicillin (250 mg)	0% (0)	0% (0)	0% (0)

Chua et al[10] (Australia) Trubiano et al[84] (Australia)	Prospective multicenter study (identical hospitals)	Adult inpatients	200 478[e]	ID	Yes	ANY OF type A ADR where direct delabeling not accepted by patient/unknown reaction >10 y/ benign childhood rash/injection site reaction/MPE >10 y EXCLUDING History of drug associated anaphylaxis/ hemodynamically unstable	90 d	1-step penicillin / amoxicillin (250 mg)—1.5–2 h observation	1.5% (3/200[c]) 2.3% (11/478)	1.5% (3/200) 1% (9/478)	3% (6/200) 4% (458/478)
Lin et al[85] (Netherlands)	Prospective single center	Adult inpatients	42	Internal medicine/ pharm	U	Mild rash, rhinitis or GI > 1 y OR 1–2 immediate symptoms of any severity > 10 y EXCLUDING Day treatment patients	-	1-step amoxicillin 500 mg—1 h observation	0% (0)	4.7% (2/42)	5% (2/42) [a,b]
Steenvoorden et al[86] (Norway)	Prospective single center	Adult inpatients	54	Internal medicine	U	ANY OF benign rash OR symptoms unlikely to be allergic etiology OR no recollection of reaction EXCLUDING Penicillin-IgE mediated, SCAR, critical illness, recent anaphylaxis (any)	-	2-step amoxicillin (75 mg/250 mg) —1 h observation	1.9% (1/54)	3.7% (2/54)	5.5% (3/54) [a]

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Table 5
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Author	Study Design	Population	N	Risk Assessed	ICH	Low-Risk Definition	Follow-up	Oral Challenge (Full Dose)	Immediate Positive	Delayed Positive	Total Positive
Fransson et al[87] (Denmark)	Prospective cohort study	Adult patients	202	A/I	U	Low-risk cutaneous exanthema	-	1-step amoxicillin and 4 d prolonged	2.4% (5/202)	7% (15/202)	10% (20/202)
Koo et al[88] (USA)	Prospective single center	Adult critical inpatients	205	A/I	Y	ANY OF isolated urticaria > 5 y ago; self-limited cutaneous rash (mild); GI symptoms only; remote childhood action; family history; fear avoidance	-	1-step amoxicillin 250 mg	0% (0)	0.1% (2/203)	0.1% (2/203)
Ghassemian et al[50] (Canada)	Prospective single center	Adult virtual outpatients	23	A/I	Y	PEN-FAST score 0–2	7 mo	1-step amoxicillin	0% (0)	0% (0)	**0%**
Total			3323								

A/I, allergy/immunology; AIN, acute interstitial nephritis; COPD, chronic obstructive pulmonary disease; ID, infectious diseases; RCT, randomized control trial; MPE, maculopapular exanthema; ADR, adverse drug reaction; ICH, immunocompromised host; GI, gastrointestinal; SCAR, severe cutaneous adverse reactions; U, unknown; Pharm, pharmacist.

[a] No serious adverse events (SAE)—As defined by not requiring intensive-care support, adrenaline therapy, SCAR or readmission to hospital.

[b] Unspecified if onset of reaction post challenge was immediate or delayed.

[c] Non-immune-mediated ADR.

[d] Unknown descriptions of positive challenges.

[e] First 200 oral challenges patients from the this published study presented in prior publication by Chua et al.[10]

[f] Non-peer-reviewed data, 708 patients from Walter Reed National Military Cent and Marine Corps Recruit Depot.

Adapted from Rose and colleagues 2020.[9]

As AMS programs turn their focus to inpatient challenges there are inpatient factors that are often perceived barriers to undertaking direct oral challenge post risk assessment as a low-risk phenotype. These are outlined below.

1. Concurrent therapies

Antihistamine therapies, cardiovascular therapies, and immunosuppressants (including corticosteroids) are often considered relative contraindications to testing/challenge. Performing beta-lactam allergy testing is considered a safe and effective AMS strategy in an immunocompromised cohort,[89] with a recent review by Waldron and colleagues[90] highlighting that immunosuppression does not impact testing outcomes. H2 antagonists (eg, ranitidine) do not appear to impact testing, whereas H1 antagonists may impact,[91] and should be avoided in patients with high-pretest probability of true allergy. Beta-blockers remain a relative contraindication in drug allergy testing; however, in low-risk cohort studies these have not been excluded.[84,92]

2. Single versus multistep direct oral challenges

There is evidence that supports the application of both single and multistep (2–3 steps) challenges.[12] Although there are no head-to-head studies comparing safety and efficacy with the positive challenge rate. This is not significantly different between cohorts (see **Table 5**), and therefore for direct oral challenges a single step can be performed.

3. Patient selection

In a whole-of-hospital program in Australia only 29% of assessment patients transitioned to direct oral challenge.[10] In a subsequent analysis, the authors found that the predictors of proceeding to oral challenge were patients admitted with an infective diagnosis, surgical patients, or those with a history of childhood penicillin exanthema. Those who used a narrow spectrum penicillin in the next 12 months post delabeling were patients with an infective diagnosis, surgical patients, or immunocompromised hosts.[93] Therefore, although whole-of-hospital surveillance programs with linked direct oral challenges protocols are ideal, a practical approach is for clinicians to target the named groups that are likely to be immediately amenable to challenge and subsequently benefit.

Approaches to Delabeling:Resensitization

Because of the nature of immediate type allergic reactions to beta-lactams occurring after exposure to the allergen, there has been historic concern that skin testing and oral challenge would offer that re-exposure and thus resensitize a patient that may have over time lost the penicillin-specific antibodies. This theoretic concern was evaluated in a study of 46 patients with a history of penicillin allergy that were cleared of this label with PST and then were given a 10 days course of penicillin V potassium followed by another PST.[94] Two additional 10 day courses and 2 additional PSTs were performed, each 4 weeks after the 10 day course of penicillin V potassium was complete.[94] Zero patients converted from a negative skin test to a positive or indeterminant skin test despite repeated re-exposure to penicillin.[94] In a larger study of 568 patients with negative PST followed by at least one course of oral penicillin, zero of these patients experienced serious reactions following re-exposure.[12]

Hospital Locations for Assessment and Delabeling

All locations where patients interact with health care providers should be viewed as an opportunity to add clarity to allergy labels. The allergy assessment process takes

moments and can improve clinical outcomes for years to come. Minimal training is needed to have a good allergy history and this activity should be a standard part of all intake and assessment processes as a patient traverses the health care setting. Additional methods for ensuring allergies are not inadvertently re-added to the medical record should be put into place such as in the example below which fires when a penicillin allergy label is re-entered after being removed from the EMAR (Fig. 3A).

With the EMR connecting prescription data from many encounter types, it becomes easier to gain helpful data to inform allergy discussions with patients. For example, patients may have received a beta-lactam without realizing the medication was within the same antibiotic class as the medication they initially reacted to. This data can be reviewed with the patient to ensure tolerance and lead to allergy label removal in appropriate cases. Additional tools such as a flag for patient with a recent prescription for a penicillin and a penicillin allergy can facilitate identifying patients with a high potential for penicillin allergy label removal after completing a full allergy assessment (Fig. 3B).

Stakeholder Engagement for Beta-lactam Allergy Delabeling

There are a multitude of references with easy to use tools that can facilitate initiation of allergy assessment activities.[80] Allergy histories can be obtained by a multitude of professionals within the health care system including pharmacists, pharmacy technicians, prescribers, nurses, and trainees. Trainees can in fact use this opportunity to learn more about quality improvement as MacFadden and colleagues[95] reported in this prospective multisite cohort in which ID trainees found 75% of the ID consult patients with reported penicillin allergy could tolerate a beta-lactam. These trainees also found patients with a reported beta-lactam allergy that received an alternative agent had a 3-fold increase in odds of adverse effects including readmission with same infection, acute kidney injury, *C. difficile* infection, and drug-related adverse effects. Pharmacists are also well positioned to routinely assess and clarify allergies through the medication reconciliation process in the ambulatory setting or on inpatient admission or discharge. Pharmacist-led allergy assessment programs have also been associated with reduced high-CDI risk antibiotics both inpatient and on discharge with trends toward increase overall survival and CDI-free survival as reported by Turner and colleagues.[8] This program used pharmacy interns, in addition to pharmacists, to obtain allergy histories that were then verified prior to leaving a formalized progress note in the EMR. This use of pharmacist extenders further expanded the reach and impact of the program.

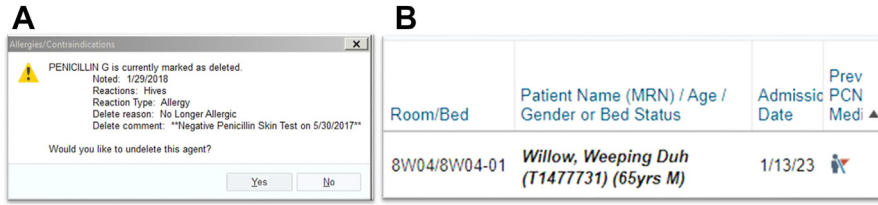

Fig. 3. Best practice alert for electronic medical record when penicillin allergy re-entered. (*A*) Epic 2023 Epic Systems Corporation Best Practice Alert (BPA) fires to staff who attempt to re-enter a penicillin allergy on a patient who had a negative PST or allergy was removed from assessment. This BPA fires inpatient or outpatient. The BPA also fires the stewardship team. (*B*) Utilization of Epic© 2023 Epic Systems Corporation logic to flag patients with penicillin allergy and receipt of penicillin within the previous 5 years.

Approaches to Prescribing: Cross-Reactivity

There has been increased focus over the last 30 years in the cross-reactivity between penicillin and cephalosporin allergy. Initially reported as 10%,[96] modern systematic reviews and meta-analysis demonstrated that the rate of cross-reactivity is closer to 2.1% when examining beta-lactams with limited structural cross-reactivity and primarily related to the R1 side chain[97] (**Fig. 4**). In particular numerous global cohort studies have demonstrated that cefazolin hypersensitivity, in particular IgE mediated, appears to be isolated in nature with patients tolerating other penicillins and cephalosporins that do not share a same/similar R1 side chain.[70,98–100] Guidelines are increasingly recommending the use of non-cross-reactive cephalosporins in patients with a primary penicillin allergy, except for in severe delayed reactions (eg, SCAR) where all beta-lactams should currently be avoided,[1,12,101] or prescribed only following specialist consultation.

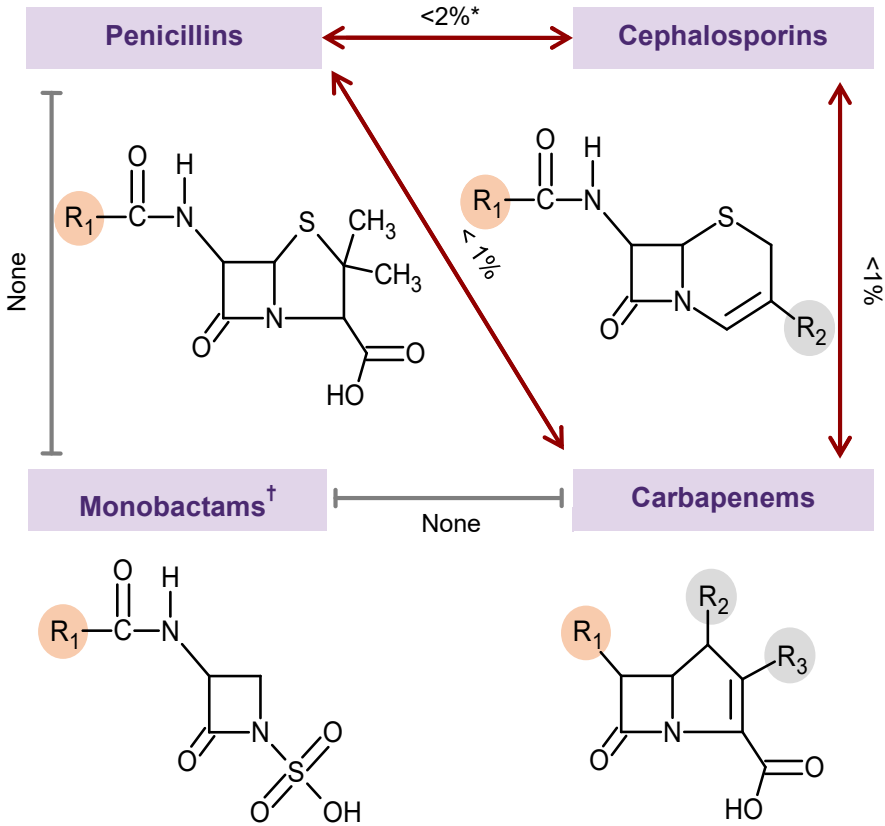

Fig. 4. Cross-reactivity between beta-lactams. Structure of conserved regions and side chains of common β-lactam antibiotics. β-Lactams consist of a 4-member β-lactam ring, the penicillins connected to a 5-member thiazolidine ring, and cephalosporins to a 6-member dihydrothiazine ring. Penicillins have 1 side chain (R1), whereas cephalosporins have 2 side chains (R1, R2).[4,96] Similarity between the R1 side chains can cause cross-reactivity. In settings where allergy testing is not available and a beta-lactam antibiotic is the preferred drug, antimicrobials to avoid based on potential cross-reactivity due to identical or similar R1 side chains are amoxicillin or ampicillin allergy—avoid cefalexin and cefaclor; ceftriaxone allergy—avoid cefotaxime, cefepime, and cefuroxime; ceftazidime allergy—avoid aztreonam.

SUMMARY

The assessment and testing of beta-lactam allergy has transformed into a new pillar of antimicrobial stewardship. There are demonstratable links between beta-lactam allergy, and in particular penicillin allergy, with poor prescribing, antimicrobial resistance, and inferior patient outcomes. Subsequent integration of beta-lactam allergy cross-reactivity principles into international therapeutic guidelines has improved the utilization of alternative beta-lactams in those reporting a primary penicillin allergy, based on the core principles of side-chain cross-reactivity. Further, the focus on delabeling as a primary stewardship intervention in the outpatient and inpatient space has elevated this intervention as a "weapon" of AMS programs using a wide stakeholder group and range of testing strategies (PST, cephalosporin skin testing, and direct oral challenge). The current body of evidence supports the integration of beta-lactam allergy assessment and delabeling into current AMS practice.

CLINICS CARE POINTS

- Penicillin allergy labels are associate with negative outcomes such as Clostridioides difficile infections (CDI), surgical site infections (SSIs), antimicrobial resistance (eg, methicillin resistant Staphylococcus aureus), patient mortality, and excess hospital costs.
- Antibiotic allergies should be clarified for all patients, and eliminated where possible, with the validated tools described in this article.

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REFERENCES

1. Blumenthal KG, Peter JG, Trubiano JA, et al. Antibiotic allergy. Lancet 2019; 393(10167):183–98.
2. Trubiano JA, Chen C, Cheng AC, et al. Antimicrobial allergy 'labels' drive inappropriate antimicrobial prescribing: lessons for stewardship. Journal of antimicrobial chemotherapy 2016;71(6):1715–22.
3. Trubiano JA, Adkinson NF, Phillips EJ. Penicillin Allergy Is Not Necessarily Forever. JAMA 2017;318(1):82–3.
4. Trubiano J, Phillips E. Antimicrobial stewardship's new weapon? A review of antibiotic allergy and pathways to 'de-labeling'. Curr Opin Infect Dis 2013;26(6): 526–37.
5. Gadde J, Spence M, Wheeler B, et al. Clinical experience with penicillin skin testing in a large inner-city STD clinic. JAMA 1993;270(20):2456–63.
6. Heil EL, Bork JT, Schmalzle SA, et al. Implementation of an Infectious Disease Fellow-Managed Penicillin Allergy Skin Testing Service. Open Forum Infect Dis 2016;3(3):ofw155.
7. Trubiano JA, Thursky KA, Stewardson AJ, et al. Impact of an Integrated Antibiotic Allergy Testing Program on Antimicrobial Stewardship: A Multicenter Evaluation. Clin Infect Dis 2017;65(1):166–74.

8. Turner NA, Wrenn R, Sarubbi C, et al. Evaluation of a Pharmacist-Led Penicillin Allergy Assessment Program and Allergy Delabeling in a Tertiary Care Hospital. JAMA Netw Open 2021;4(5):e219820.
9. Rose MT, Slavin M, Trubiano J. The democratization of de-labeling: a review of direct oral challenge in adults with low-risk penicillin allergy. Expert Rev Anti Infect Ther 2020;18(11):1143–53.
10. Chua KYL, Vogrin S, Bury S, et al. The Penicillin Allergy Delabeling Program: A Multicenter Whole-of-Hospital Health Services Intervention and Comparative Effectiveness Study. Clinical infectious diseases 2020;73(3):487–96.
11. Manivannan V, Campbell RL, Bellolio MF, et al. Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. Ann Allergy Asthma Immunol 2009;103(5):395–400.
12. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. J Allergy Clin Immunol 2022;150(6):1333–93.
13. Bavbek S, Aydın Ö, Sözener Z, et al. Determinants of nocebo effect during oral drug provocation tests. Allergol Immunopathol 2015;43(4):339–45.
14. Iammatteo M, Ferastraoaru D, Koransky R, et al. Identifying Allergic Drug Reactions Through Placebo-Controlled Graded Challenges. J Allergy Clin Immunol Pract 2017;5(3):711–7.
15. Idsoe O, Guthe T, Willcox RR, et al. Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. Bull World Health Organ 1968;38(2):159–88.
16. Lee CE, Zembower TR, Fotis MA, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. Arch Intern Med 2000;160(18):2819–22.
17. Park MA, Solensky R, Khan DA, et al. Patients with positive skin test results to penicillin should not undergo penicillin or amoxicillin challenge. Journal of Allergy and Clinical Immunology 2014;135(3):816–7.
18. Blumenthal KG, Ryan EE, Li Y, et al. The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk. Clin Infect Dis 2018;66(3):329–36.
19. Blumenthal KG, Lu N, Zhang Y, et al. Risk of meticillin resistant Staphylococcus aureus and Clostridium difficile in patients with a documented penicillin allergy: population based matched cohort study. BMJ 2018;361:k2400.
20. Blumenthal KG, Lu N, Zhang Y, et al. Recorded Penicillin Allergy and Risk of Mortality: a Population-Based Matched Cohort Study. J Gen Intern Med 2019;34(9):1685–7.
21. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. Journal of allergy and clinical immunology 2014;133(3):790–6.
22. Castells M, Khan DA, Phillips EJ. Penicillin Allergy. N Engl J Med 2019;381(24):2338–51.
23. Devchand M, Trubiano JA. Penicillin allergy: a practical approach to assessment and prescribing. Aust Prescr 2019;42(6):192–9.
24. Blanca M, Torres MJ, Garcia JJ, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. Journal of allergy and clinical immunology 1999;103(5 Pt 1):918–24.
25. Finke SR, Grieco MH, Connell JT, et al. Results of Comparative Skin Tests with Penicilloyl-Polylysine and Penicillin in Patients with Penicillin Allergy. Am J Med 1965;38:71–82.

26. Staicu ML, Brundige ML, Ramsey A, et al. Implementation of a penicillin allergy screening tool to optimize aztreonam use. Am J Health Syst Pharm 2016;73(5):298–306.
27. Devchand M, Urbancic KF, Khumra S, et al. Pathways to improved antibiotic allergy and antimicrobial stewardship practice: The validation of a beta-lactam antibiotic allergy assessment tool. J Allergy Clin Immunol Pract 2019;7(3):1063–5.
28. Devchand M, Kirckpatrick C, Stevenson W, et al. Evaluation of a pharmacist-led penicillin allergy de-labelling ward-round – A novel antimicrobial stewardship intervention. J Antimicrob Chemother 2019;74(6):1725–30.
29. Trubiano JA, Smibert O, Douglas A, et al. The Safety and Efficacy of an Oral Penicillin Challenge Program in Cancer Patients: A Multicenter Pilot Study. Open Forum Infect Dis 2018;5(12):ofy306.
30. Caughey GE, Shakib S, Inglis JM, et al. External validation of beta-lactam antibiotic allergy assessment tools: implications for clinical practice and workforce capacity. J Allergy Clin Immunol Pract 2019;7(6):2094–5.
31. Rischin KJ, Mostaghim M, Rao A, et al. ESCAPE-Allergy: Evaluating screening for children and adolescents with penicillin allergy. J Paediatr Child Health 2021;58(1):83–9.
32. Blumenthal KG, Huebner EM, Fu X, et al. Risk-based pathway for outpatient penicillin allergy evaluations. J Allergy Clin Immunol Pract 2019;7(7):2411–4.
33. Plager JH, Mancini CM, Fu X, et al. Preoperative penicillin allergy testing in patients undergoing cardiac surgery. Ann Allergy Asthma Immunol 2020;124(6):583–8.
34. Shenoy ES, Macy E, Rowe T, et al. Evaluation and Management of Penicillin Allergy: A Review. JAMA 2019;321(2):188–99.
35. Song YC, Nelson ZJ, Wankum MA, et al. Effectiveness and Feasibility of Pharmacist-Driven Penicillin Allergy De-Labeling Pilot Program without Skin Testing or Oral Challenges. Pharmacy (Basel) 2021;9(3):127.
36. Manning J, Pammett RT, Hamour AO, et al. Assessing Use of a Standardized Allergy History Questionnaire for Patients with Reported Allergy to Penicillin. Can J Hosp Pharm 2021;74(2):104–9.
37. Gateman DP, Rumble JE, Protudjer JLP, et al. Amoxicillin oral provocation challenge in a primary care clinic: a descriptive analysis. CMAJ Open 2021;9(2):E394–9.
38. Ramsey A, Staicu ML. Use of a Penicillin Allergy Screening Algorithm and Penicillin Skin Testing for Transitioning Hospitalized Patients to First-Line Antibiotic Therapy. J Allergy Clin Immunol Pract 2018;6(4):1349–55.
39. Roberts H, Soller L, Ng K, et al. First pediatric electronic algorithm to stratify risk of penicillin allergy. Allergy, asthma, and clinical immunology 2020;16(1):103.
40. Reichel A, Roding K, Stoevesandt J, et al. De-labelling antibiotic allergy through five key questions. Clin Exp Allergy 2020;50(4):532–5.
41. Bediako H, Dutcher L, Rao A, et al. Impact of an inpatient nurse-initiated penicillin allergy delabeling questionnaire. Antimicrob Steward Healthc Epidemiol 2022;2(1):e86.
42. Van De Sijpe G, Gilissen L, Vandebotermet M, et al. Non-invasive delabeling and refining of beta-lactam allergy labels in inpatients to optimize antimicrobial stewardship. Allergy 2022;77(10):3157–9.
43. Chiriac AM, Wang Y, Schrijvers R, et al. Designing Predictive Models for Beta-Lactam Allergy Using the Drug Allergy and Hypersensitivity Database. J Allergy Clin Immunol Pract 2018;6(1):139–48.

44. Brusco NK, Bury S, Chua KYL, et al. Penicillin Allergy Delabeling Program: an exploratory economic evaluation in the Australian context. Intern Med J 2021; 53(1):74–83.
45. Siew LQC, Li PH, Watts TJ, et al. Identifying Low-Risk Beta-Lactam Allergy Patients in a UK Tertiary Centre. J Allergy Clin Immunol Pract 2019;7(7):2173–81.
46. Stevenson B, Trevenen M, Klinken E, et al. Multicenter Australian Study to Determine Criteria for Low- and High-Risk Penicillin Testing in Outpatients. J Allergy Clin Immunol Pract 2020;8(2):681–9.
47. Trubiano JA, Vogrin S, Chua KYL, et al. Development and Validation of a Penicillin Allergy Clinical Decision Rule. JAMA Intern Med 2020;180(5):745–52.
48. Su C, Kuster J, Belmont A, et al. Evaluating a Penicillin Allergy Clinical Decision-Making Tool to Enhance Penicillin Allergy De-labeling. J Allergy Clin Immunol 2023;151(2).
49. Piotin A, Godet J, Trubiano JA, et al. Predictive factors of amoxicillin immediate hypersensitivity and validation of PEN-FAST clinical decision rule. Ann Allergy Asthma Immunol 2021;128(1):27–32.
50. Ghassemian A, Sadi G, Mak R, et al. Virtually supported penicillin allergy delabelling during COVID-19. Allergy, asthma, and clinical immunology 2023; 19(1):17.
51. Copaescu AM, Vogrin S, Shand G, et al. Validation of the PEN-FAST Score in a Pediatric Population. JAMA Netw Open 2022;5(9):e2233703.
52. Mak R, Yuan Zhang B, Paquette V, et al. Safety of direct oral challenge to amoxicillin in pregnant patients at a Canadian tertiary hospital. J Allergy Clin Immunol Pract 2022;10(7):1919–21.
53. Sabato V, Gaeta F, Valluzzi RL, et al. Urticaria: The 1-1-1 Criterion for Optimized Risk Stratification in beta-Lactam Allergy Delabeling. J Allergy Clin Immunol Pract 2021;9(10):3697–704.
54. Clarke J, Graham N. Paediatric antibiotic allergy assessment, testing and delabelling. 2020; https://www.childrens.health.qld.gov.au/wp-content/uploads/PDF/guidelines/gdl-01076.pdf.
55. Ramsey A, Mustafa SS, Holly AM, et al. Direct Challenges to Penicillin-Based Antibiotics in the Inpatient Setting. J Allergy Clin Immunol Pract 2020;8(7): 2294–301.
56. Piotin A, Godet J, Grandbastien M, et al. Predictive factors of amoxicillin IgE-mediated hypersensitivity and validation of PEN-FAST clinical decision rule. Ann Allergy Asthma Immunol 2021;128(1):27–32.
57. Macy E. The clinical evaluation of penicillin allergy: what is necessary, sufficient and safe given the materials currently available? Clin Exp Allergy 2011;41(11): 1498–501.
58. Sacco KA, Bates A, Brigham TJ, et al. Clinical outcomes following inpatient penicillin allergy testing: A systematic review and meta-analysis. Allergy 2017; 72(9):1288–96.
59. Arroliga ME, Radojicic C, Gordon SM, et al. A prospective observational study of the effect of penicillin skin testing on antibiotic use in the intensive care unit. Infection control and hospital epidemiology 2003;24(5):347–50.
60. Raja AS, Lindsell CJ, Bernstein JA, et al. The use of penicillin skin testing to assess the prevalence of penicillin allergy in an emergency department setting. Ann Emerg Med 2009;54(1):72–7.
61. Park M, Markus P, Matesic D, et al. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. Ann Allergy Asthma Immunol 2006;97(5):681–7.

62. Park MA, McClimon BJ, Ferguson B, et al. Collaboration between allergists and pharmacists increases β-lactam antibiotic prescriptions in patients with a history of penicillin allergy. Int Arch Allergy Immunol 2011;154(1):57–62.
63. Wolfson AR, Schatz MX. Management of the Pregnant Patient with Beta-Lactam Allergy. Curr Allergy Asthma Rep 2023;23(3):189–94.
64. Philipson EH, Lang DM, Gordon SJ, et al. Management of group B Streptococcus in pregnant women with penicillin allergy. J Reprod Med 2007;52(6):480–4.
65. Antunez C, Blanca-Lopez N, Torres MJ, et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. Journal of allergy and clinical immunology 2006;117(2):404–10.
66. Buonomo A, Nucera E, Pecora V, et al. Cross-reactivity and tolerability of cephalosporins in patients with cell-mediated allergy to penicillins. Journal of investigational allergology & clinical immunology 2014;24(5):331–7.
67. Stone CA Jr, Trubiano JA, Phillips EJ. Testing Strategies and Predictors for Evaluating Immediate and Delayed Reactions to Cephalosporins. J Allergy Clin Immunol Pract 2020;9(1):435–44.
68. Testi S, Severino M, Iorno ML, et al. Nonirritating concentration for skin testing with cephalosporins. Journal of investigational allergology & clinical immunology 2010;20(2):171–2.
69. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2013;68(6):702–12.
70. Khan DA, Banerji A, Bernstein JA, et al. Cephalosporin Allergy: Current Understanding and Future Challenges. J Allergy Clin Immunol Pract 2019;7(7):2105–14.
71. Cooper L, Harbour J, Sneddon J, et al. Safety and efficacy of de-labelling penicillin allergy in adults using direct oral challenge: a systematic review. JAC-Antimicrobial Resistance 2021;3(1).
72. Blumenthal KG, Shenoy ES, Varughese CA, et al. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. Ann Allergy Asthma Immunol 2015;115(4):294–300.
73. Leis JA, Palmay L, Ho G, et al. Point-of-care Beta-lactam Allergy Skin Testing by Antimicrobial Stewardship Programs: A Pragmatic Multicenter Prospective Evaluation. Clin Infect Dis 2017;65(7):1059–65.
74. Tucker MH, Lomas CM, Ramchandar N, et al. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. J Allergy Clin Immunol Pract 2017;5(3):813–5.
75. Banks TA, Tucker M, Macy E. Evaluating Penicillin Allergies Without Skin Testing. Curr Allergy Asthma Rep 2019;19(5):27.
76. Iammatteo M, Alvarez Arango S, Ferastraoaru D, et al. Safety and Outcomes of Oral Graded Challenges to Amoxicillin without Prior Skin Testing. J Allergy Clin Immunol Pract 2019;7(1):236–43.
77. Kuruvilla M, Shih J, Patel K, et al. Direct oral amoxicillin challenge without preliminary skin testing in adult patients with allergy and at low risk with reported penicillin allergy. Allergy Asthma Proc 2019;40(1):57–61.
78. Mustafa SS, Conn K, Ramsey A. Comparing Direct Challenge to Penicillin Skin Testing for the Outpatient Evaluation of Penicillin Allergy: A Randomized Controlled Trial. J Allergy Clin Immunol Pract 2019;7(7):2163–70.
79. Savic L, Gurr L, Kaura V, et al. Penicillin allergy de-labelling ahead of elective surgery: feasibility and barriers. British journal of anaesthesia 2019;123(1):e110–6.

80. Blumenthal KG, Li Y, Hsu JT, et al. Outcomes from an inpatient beta-lactam allergy guideline across a large US health system. Infection control and hospital epidemiology 2019;40(5):528–35.
81. du Plessis T, Walls G, Jordan A, et al. Implementation of a pharmacist-led penicillin allergy de-labelling service in a public hospital. Journal of antimicrobial chemotherapy 2019;74(5):1438–46.
82. Li J, Shahabi-Sirjani A, Figtree M, et al. Safety of direct drug provocation testing in adults with penicillin allergy and association with health and economic benefits. Ann Allergy Asthma Immunol 2019;123(5):468–75.
83. Stone CA Jr, Stollings JL, Lindsell CJ, et al. Risk-stratified Management to Remove Low-Risk Penicillin Allergy Labels in the ICU. Am J Respir Crit Care Med 2020;201(12):1572–5.
84. Trubiano JA, Vogrin S, Copaescu A, et al. Direct oral penicillin challenge for penicillin allergy delabeling as a health services intervention: A multicenter cohort study. Allergy 2022;77(3):1038–42.
85. Lin L, Nagtegaal JE, Buijtels P, et al. Antimicrobial stewardship intervention: optimizing antibiotic treatment in hospitalized patients with reported antibiotic allergy. J Hosp Infect 2020;104(2):137–43.
86. Steenvoorden L, Bjoernestad EO, Kvesetmoen TA, et al. De-labelling penicillin allergy in acutely hospitalized patients: a pilot study. BMC Infect Dis 2021; 21(1):1083.
87. Fransson S, Boel JB, Mosbech HF, et al. Safe De-Labeling of Patients at Low Risk of Penicillin Allergy in Denmark. Int Arch Allergy Immunol 2022;183(6): 640–50.
88. Koo G, Stollings JL, Lindsell C, et al. Low-risk penicillin allergy delabeling through a direct oral challenge in immunocompromised and/or multiple drug allergy labeled patients in a critical care setting. J Allergy Clin Immunol Pract 2022;10(6):1660–3.
89. Trubiano JA, Slavin MA, Thursky KA, et al. Beta-Lactam and Sulfonamide Allergy Testing Should Be a Standard of Care in Immunocompromised Hosts. J Allergy Clin Immunol Pract 2019;7(7):2151–3.
90. Waldron JL, Trubiano JA. Antibiotic allergy labels in immunocompromised populations. Transpl Infect Dis 2022;24(5):e13955.
91. Shah KM, Rank MA, Dave SA, et al. Predicting which medication classes interfere with allergy skin testing. Allergy Asthma Proc 2010;31(6):477–82.
92. Fung IN, Kim HL. Skin prick testing in patients using beta-blockers: a retrospective analysis. Allergy, asthma, and clinical immunology 2010;6(1):2.
93. Trubiano JA, Vogrin S, Mitri E, et al. The Who, What, When and Where of Inpatient Direct Oral Penicillin Challenge - Implications for health services implementation. Clin Infect Dis 2023;ciad156.
94. Solensky R, Earl HS, Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. Arch Intern Med 2002;162(7):822–6.
95. MacFadden DR, LaDelfa A, Leen J, et al. Impact of Reported Beta-Lactam Allergy on Inpatient Outcomes: A Multicenter Prospective Cohort Study. Clin Infect Dis 2016;63(7):904–10.
96. Trubiano JA, Stone CA, Grayson ML, et al. The 3 Cs of Antibiotic Allergy-Classification, Cross-Reactivity, and Collaboration. J Allergy Clin Immunol Pract 2017;5(6):1532–42.

97. Picard M, Robitaille G, Karam F, et al. Cross-reactivity to cephalosporins and carbapenems in penicillin-allergic patients: Two systematic reviews and meta-analyses. J Allergy Clin Immunol Pract 2019;7(8):2722–38.
98. Blumenthal KG, Youngster I, Shenoy ES, et al. Tolerability of cefazolin after immune-mediated hypersensitivity reactions to nafcillin in the outpatient setting. Antimicrobial agents and chemotherapy 2014;58(6):3137–43.
99. Li J, Green SL, Krupowicz BA, et al. Cross-reactivity to penicillins in cephalosporin anaphylaxis. British journal of anaesthesia 2019;123(6):e532–4.
100. Uyttebroek AP, Decuyper II, Bridts CH, et al. Cefazolin Hypersensitivity: Toward Optimized Diagnosis. J Allergy Clin Immunol Pract 2016;4(6):1232–6.
101. Groups AE. Therapeutic guidelines: antibiotic. Version 16 edition. Melbourne: Therapeutic Guidelines Limited; 2019.