

REVIEW ARTICLE

The challenge of de-labeling penicillin allergy

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Abstract

Background: Even though 8%-25% of most populations studied globally are labeled as penicillin allergic, most diagnoses of penicillin allergy are made in childhood and relate to events that are either not allergic in nature, are low risk for immediate hypersensitivity, or are a potential true allergy that has waned over time. Penicillin allergy labels directly impact antimicrobial stewardship by leading to use of less effective and broader spectrum antimicrobials and are associated with antimicrobial resistance. They may also delay appropriate antimicrobial therapy and lead to increased risk of specific adverse healthcare outcomes. Operationalizing penicillin allergy de-labeling into a new arm of antimicrobial stewardship programs (ASPs) has become an increasing global focus.

Methods: We performed an evidence-based narrative review of the literature of penicillin allergy label carriage, the adverse effects of penicillin allergy labels, and current approaches and barriers to penicillin allergy de-labeling. Over the period 1928-2018 in Pubmed and Medline, search terms used included "penicillin allergy" or "penicillin hypersensitivity" alone or in combination with "adverse events," "testing," "evaluation," "effects," "label," "de-labeling," "prick or epicutaneous," and "intradermal" skin testing, "oral challenge or provocation," "cross-reactivity," and "antimicrobial stewardship".

Results: Penicillin allergy labels are highly prevalent, largely inaccurate and their carriage may lead to unnecessary treatment and inferior outcomes with alternative agents as well as adverse public health outcomes such as antibiotic resistance.

Conclusions: Operationalizing penicillin allergy de-labeling as an aspect of ASP has become an increasing global focus. There is a need for validated approaches that optimally combine the use of history and ingestion challenge with or without proceeding formal skin testing to tackle penicillin allergy efficiently within complex healthcare systems. At the same time, there is great promise for penicillin allergy evaluation and de-labeling as an individual and public health strategy to reduce adverse healthcare outcomes, improve antimicrobial stewardship, and decrease healthcare costs.

KEYWORDS

allergy, de-labeling, label, penicillin, testing

1 | BACKGROUND

Carriage of a label of penicillin allergy in the medical record is a common clinical entity; studies in the United Kingdom (UK), United States (US), and Australia estimate the prevalence to be between 8% and 25%.^{45–47} In contemporary clinical practice where the patient population has a lower overall historical risk of penicillin allergy, skin prick and intradermal skin testing to validated reagents followed by ingestion challenge to a penicillin such as amoxicillin demonstrates that only between 1% and 10% of those carrying a label of penicillin allergy are allergic, and in many recent studies, this is 4% or less.^{17,48–50} It is clear that penicillin allergy labels should no longer be considered passive entities within the medical record and that systematic approaches need to be developed to manage the large global burden of over-labeled patients.^{46,51} Recent research has highlighted that 75% of children are labeled as penicillin allergic by age 3 and furthermore that there are specific risks that appear to be associated with an unverified penicillin allergy label.^{42,52–54} The potential negative sequelae associated with a penicillin allergy label include risk of antimicrobial treatment failure, antimicrobial resistance, adverse drug reactions from use of a broader spectrum or alternative antibiotic, and increased healthcare costs.^{32,33,55–64} Thus, there is a great need to understand the circumstances surrounding the acquisition of penicillin allergy labels; to differentiate those with a true immunological basis from those which have an alternative etiology; and to determine the best strategies to safely de-label unnecessary penicillin allergy labels at an individual and population level. This paper will critically review the current state of science and evidence surrounding “penicillin allergy labels” including their origin, consequences, and it will provide a roadmap to strategically address penicillin allergy labels at both an individual and population levels.

2 | ACQUISITION OF PENICILLIN ALLERGY LABELS

The allergy section of a medical record is meant as a safeguard against patients being harmed by administration of a drug or exposure that they have failed to tolerate. Traditionally, the “allergy box” in the

Major Milestone Discoveries

- 1928—Discovery of penicillin¹
- 1940—Usage of penicillin in military²
- 1941—Widespread usage of penicillin²
- 1941–1947—Unusual cutaneous and systemic reactions to penicillin described^{3,4}
- 1944–1946—First cases of skin test positive against penicillin described^{4,5}
- 1948–1949—First cases of penicillin anaphylaxis⁸
- 1950s—Early use of penicillin reagents in skin testing⁹
- 1960s—Implication of serologic factors in penicillin allergy¹⁰
- 1960s—First cases suggesting cross-reactivity between penicillins and cephalosporins.^{11,12}
- 1967—Discovery of Immunoglobulin E (IgE)^{14,15}
- 1972—Amoxicillin introduced in widespread usage
- 1960s–1990s—Early and established use of penicillin reagents in skin testing¹⁶; several papers established the high negative predictive value of skin testing when combined with oral challenge¹⁷
- 1990—Side chain reactions associated with amino penicillins described and more prevalent in Southern Europe^{18,19}
- 1990—Reports of beta-lactam cross-reactivity^{21,22}
- 1990—Reports of waning skin test reactivity to penicillin and other reagents over time^{21,22}
- 1995—First description of selective allergic reaction to clavulanic acid in Southern Europe.²⁴
- 2005—Penicillin reagents (Allergopharma) removed from market leaving void of commercially available and validated penicillin major and minor determinants: This necessitated use of alternative skin testing strategies²⁵
- 2008—Penicillin major and minor determinant reagent (Diater®) available for testing in Europe and special access in some other countries (eg, Australia)²⁶
- 2010—Benzylpenicilloyl-polylysine (Pre-Pen®) (Allerquest) available as commercial reagent on US market²⁷
- 2010—Early reports of the burden of over-labeling of penicillin allergy.²⁸

- 2010—First direct challenges of children with benign non-immediate reactions to penicillin without preceding skin testing²⁸
- 2012—Early reports of the impact of penicillin labels on antimicrobial stewardship^{29,30}
- 2013—First reports of term “penicillin allergy de-labeling”³¹
- 2014-2018—Impact of penicillin labels on *Clostridioides difficile*^{32,33}
- 2016—Recognition of the need to address penicillin allergy by Centers for Disease Control, Infectious Disease Society of America antimicrobial stewardship guidelines³⁴
- 2016-2018—More recent articles on penicillin and cephalosporin cross-reactivity highlight specific R1 cross-reactivity patterns and very low rate of cross-reactivity based on beta-lactam ring (<2%)^{35,36}
- 2016-2018—Impact of penicillin labels on time to antibiotic administration^{37,38}
- 2017—Impact of penicillin over-labeling on antibiotic resistance⁴⁰
- 2017-2018—Oral challenge data in low-risk children^{41,42}
- 2018—Impact of penicillin labels on surgical site infections⁴⁴

Future Research Perspectives

Areas of Greatest Need:

- Development of large collaborative drug allergy research networks
- Standardized clinical phenotyping of penicillin reactions.
- Standardization of skin testing protocols for determination of immediate and delayed hypersensitivity phenotypes and beta-lactam cross-reactivity pattern.
- Development and standardization of sensitive and specific in vitro testing tools for penicillin allergy
- Validation and implementation of point-of-care tools to identify “low-risk” penicillin allergy
- Evidence base for de-labeling penicillin allergy patients, using risk stratification to direct patients for allergy label removal using direct oral challenge versus skin testing followed by challenge.
- Long-term outcomes from controlled intervention studies of penicillin allergy label removal.
- Development of “toolkit” for routine integration of penicillin and antibiotic allergy management into antimicrobial steward programs.
- Understanding the immunopathogenesis of and mechanisms of sensitization, cross-reactivity and waning of immunity to penicillins and other beta-lactam antimicrobials and differences in regional epidemiology
- Qualitative studies to examine behavioral factors that drive differences in the effectiveness of penicillin allergy de-labeling.

patient's health record has been the place that all adverse reactions to drugs, foods, and other substances are documented to help mitigate future harm from inadvertent re-exposure.⁶⁵ A major challenge to realizing the utility of the allergy box is that the use of the term “allergy” largely ends up being both vague and unreconciled to both patients and healthcare providers. This undifferentiated approach also promotes misunderstanding about whether any individual drug adverse event was a true immune-mediated allergic reaction with a hard stop for future avoidance, versus a potentially manageable side effect which does not preclude future use of the drug. Experts note that when record takers note the name of a drug in the allergy section of the chart, they frequently omit details⁶⁵ or provide incomplete, incorrect, or misleading details.⁶⁶ Such data leaves future prescribers either at risk to make further erroneous conclusions or incapable of making reasonable conclusions, especially if patients can no longer recall the details of the associated event. It is not surprising that by adulthood, almost one-third of penicillin allergy labels in the patient's record lack specific details. Unfortunately, the label's presence is enough to create uncertainty and to have negative consequences on the prescribing habits of healthcare providers.^{46,51}

Most penicillin allergy labels are acquired in childhood, and many are acquired within the context of children being administered unnecessary antibiotics for viral infections. Studies suggest that 75% of penicillin allergy labels are obtained by the age of three years, and the prevalence of penicillin allergy is only slightly less in children compared to adults.^{42,52-54} In a retrospective US cohort, adverse drug events were reported in children at a rate of 1.6% per year over a 10-year study period; of these adverse drug events, 16% were found to correlate with administration of a penicillin or cephalosporin.⁵³

When a patient suffers an adverse outcome while taking penicillin in childhood, there is frequently uncertainty in both the underlying diagnosis and in causal attribution, leading to false labeling of a patient as “allergic.”⁶⁷ Many times, the index reaction is clearly inconsistent with true allergy, such as nausea, vomiting, or diarrhea in isolation, or the documented reason for avoidance is a “family history of penicillin allergy” which has no relation to risk of true penicillin allergy.⁴² Cutaneous rashes are the most common pathway to an allergy label in childhood. Viral infections are the most common cause of cutaneous rashes in childhood, and virally-induced rashes or drug-virus interactions can be mistakenly diagnosed as penicillin allergy.^{28,68} Vyles *et al* queried parents on the symptoms which led to a penicillin allergy diagnosis and noted 75% of the symptoms were low risk for an immunoglobulin E (IgE)-mediated allergy with the most frequent description of the event being a nonspecific rash and/or pruritis.⁴² When evaluating the frequency and quality of penicillin-associated rash, Ibia *et al* found that penicillin administration temporally correlated with a rash 2.72% of the time in children; of these, only one-third of the rashes were clinically consistent with urticaria accompanied by itching and the remainder were not consistent with IgE-mediated hypersensitivity.⁶⁹ Thus, while a concomitant rash with penicillin administration is common in childhood, clinical features consistent with IgE-mediated hypersensitivity occur in only a minority

Events that lead to application of a penicillin allergy label

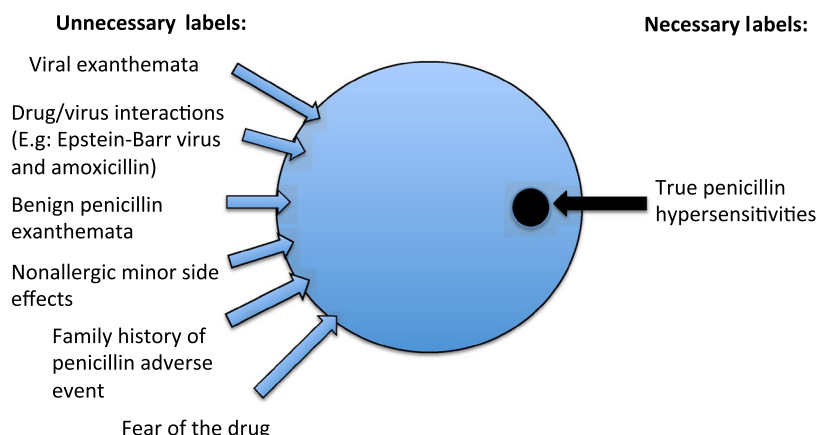


FIGURE 1 Events that Lead to Application of a Penicillin Allergy Label. The application of penicillin allergy labels results from events that are low risk for allergy in the vast majority of cases.^{42,52-54,67,69,70}

of these cases. Commonly, a penicillin allergy label is acquired due to an associated rash regardless of its true etiology or severity.⁷⁰ (Figure 1).

A small subset of patients with penicillin allergy labels have a history consistent with a high-risk reaction, such as anaphylaxis, severe cutaneous adverse reactions, or immune-mediated organ injuries (eg, acute interstitial nephritis [AIN], drug-induced liver injury [DILI]). Depending on the specific type of reaction, older age, penicillin dose received, duration of treatment, route of drug administration, underlying genetic or metabolic factors, and the chemical properties of the drug (largely its protein reactivity), have all been reported as risk factors for true drug hypersensitivity.⁷¹ Yet, in the absence of clear comprehensive documentation of the primary penicillin adverse event in the medical record, it is frequently difficult to tell which labels must be taken seriously.^{65,66}

3 | IMPORTANT NEGATIVE CONSEQUENCES OF PENICILLIN ALLERGY LABELS

In patients labeled as penicillin allergic, clinicians must weigh the benefits of prescribing penicillin or related beta-lactam antibiotics against the risk of an adverse reaction (Figure 2). In the setting of busy and demanding clinical practices, many times, the penicillin allergy label is inadequately reconciled and prescribers choose an alternative antimicrobial with potentially lesser efficacy, greater unintended adverse effects, and increased costs during treatment.^{46,51} A conscious choice to avoid penicillin also leads to prescriber avoidance of other beta-lactam antimicrobials, especially cephalosporins.⁷²

Alternative antimicrobials often have decreased efficacy compared to penicillin class antibiotics; hence, carriage of a penicillin allergy label is not a passive or benign state. Patients with penicillin

allergy labels have been shown to have an increased mortality risk from coexisting hematologic malignancies⁵⁸ and infections from penicillin susceptible organisms such as methicillin-susceptible *Staphylococcus aureus* (MSSA).⁵⁹ Blumenthal et al⁷³ have identified that penicillin allergy labels put patients at greater risk of post-operative surgical site infections, mediated by use of alternative antibiotics. Preoperative evaluation of penicillin allergy leads to increased utilization of appropriate antimicrobials, theoretically lowering surgical site infection risk.^{60,61} Multiple investigators have shown that patients with penicillin allergy labels demonstrate increased length of hospital stay compared to the general population.^{33,55-58} Prolongation of hospitalizations appears to be mediated by increased treatment failures from less effective alternative antimicrobials.^{74,75} Additionally, MacFadden et al⁵⁵ demonstrated that patients who did not receive preferred beta-lactam therapy as a consequence of a beta-lactam allergy had a greater risk for a composite outcome of future adverse events in an adjusted model (aOR 3.1 95% CI 1.28-7.89). Increases in readmissions and reactions to alternative antimicrobials were the main drivers of this composite outcome.⁵⁵ These treatment failures, adverse events, and prolongations of care have been shown to be modifiable by removal of the penicillin allergy label.^{60,61}

Patients with penicillin allergy labels are also at greater risk for multidrug-resistant infections and use of inappropriate antimicrobials during treatment. It has been shown across several countries and healthcare systems that patients with penicillin allergy labels experience increased rates of infection with multidrug-resistant organisms such as *Clostridioides difficile*,^{32,33,55,58,62} methicillin-resistant *Staphylococcus aureus* (MRSA),^{32,33} and vancomycin-resistant *Enterococcus* species.^{33,62} This increase is likely mediated by use of alternative broad-spectrum antimicrobials that favor selection of these organisms.⁷⁶ In the US, pregnant patients with penicillin allergy labels are more likely to receive antibiotics during labor which are ineffective for treatment of group B *Streptococcus* carriage.⁷⁷

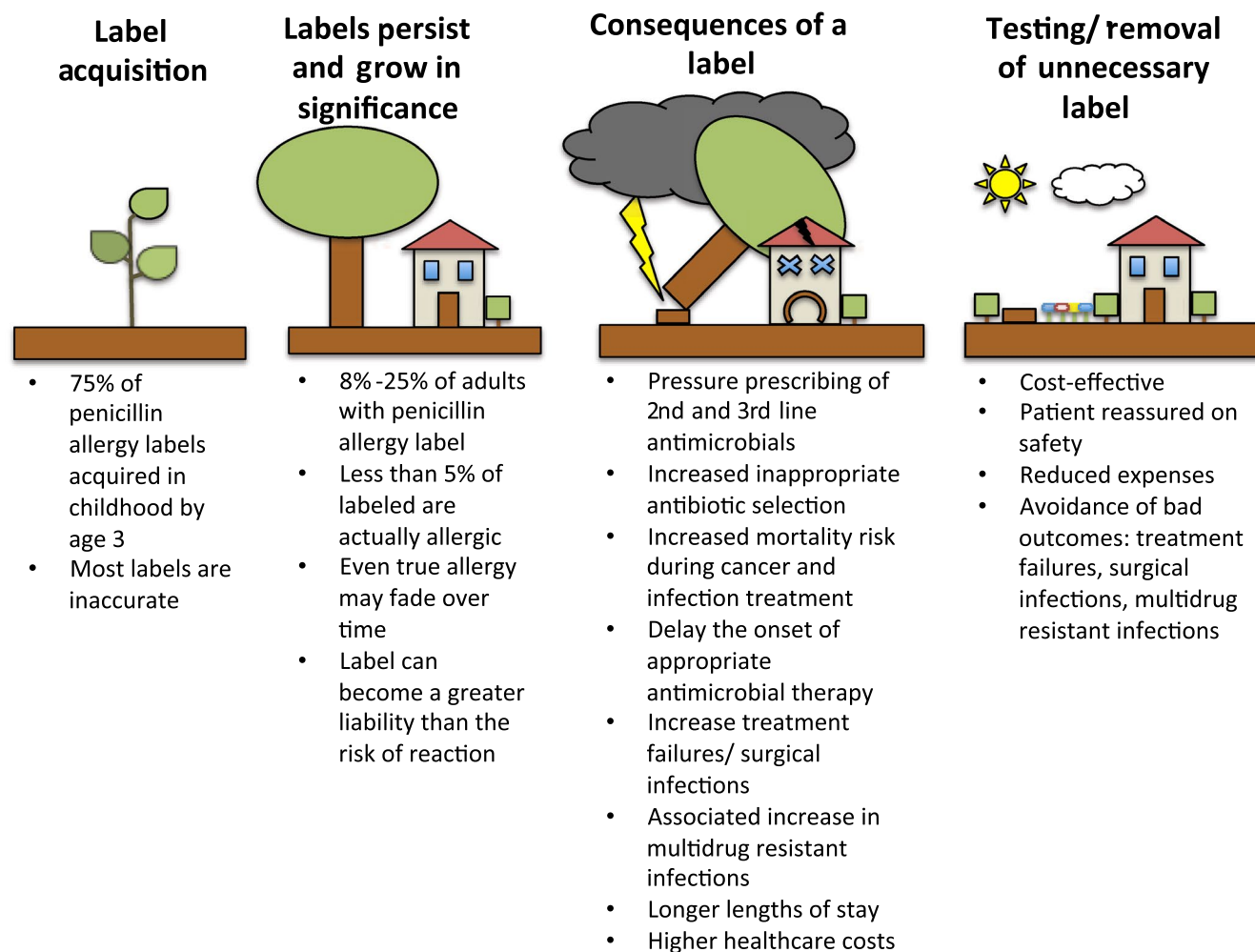


FIGURE 2 A Penicillin Allergy Label is like a Tree Planted Too Close to Your House in Childhood. Most penicillin allergy labels are applied in childhood, like a seed that grows up into a tree too close to the house (Label Acquisition). In adulthood, the justification for leaving such a tree next to the house is shaky (Labels Persist and Grow in Significance), as they can contribute to worsened outcomes during the storm of a healthcare encounter requiring antimicrobial treatment (Consequences of a Label). Removal of unnecessary penicillin allergy labels is likely to provide protection against adverse outcomes associated with its carriage (Testing/Removal of Unnecessary Labels)

Decreased efficacy, treatment failures, and unintended adverse effects of alternative antimicrobials lead inexorably to increased costs during the delivery of healthcare. Li *et al*⁶³ have shown cost estimates from the UK indicating that use of alternative antimicrobials is more expensive than if patients were able to tolerate a penicillin. A retrospective study from a Canadian tertiary center by Picard *et al*⁶⁴ demonstrated greater expenditures per penicillin allergy patient during a one-year period due to the use of non- β -lactam antibiotics. Prolongations of hospitalizations,^{33,55-58} surgical site infections,⁷³ and treatment failures^{74,75} are costly outcomes that are increased in the context of a penicillin allergy label. Huang *et al* report that patients with penicillin allergy labels and hematologic malignancies incur around \$50,000 USD in additional costs during their hospitalizations.⁵⁸

On the other hand, formal evaluation of penicillin allergy with skin testing has been estimated by Blumenthal *et al* and Rimawi *et al* to cost less per patient⁷⁸ than it may save annually³⁰ especially if a 2nd or 3rd line antibiotic is avoided.⁷⁹ Vyles *et al* estimated

the hospital savings of removing inaccurate penicillin allergy diagnosis for a pediatric emergency room with 67 000 annual visits at \$192 223 USD.^{41,42} Penicillin allergy label removal has been found to be cost effective, even in more expensive inpatient care settings.⁸⁰ Thus, de-labeling of unnecessary penicillin allergies could be an important cost-effective strategy which simultaneously protects patients from adverse outcomes and reduces healthcare costs.

4 | PENICILLIN ALLERGY DE-LABELING AS A CRUCIAL ELEMENT OF ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship programs (ASPs) aim to improve treatment outcomes while simultaneously reducing the creation and spread of multidrug-resistant infections. Operationalizing penicillin allergy de-labeling into a new arm of ASP has therefore become an

TABLE 1 Approaches to immediate hypersensitivity penicillin allergy labels in an individual patient

Approach	De-labeling approach	Strengths	Limitations	Level of recommendation and evidence
Select an alternative antibiotic ^{50,61,66,80-86}	No	No risk of provoking penicillin reaction in the individual patient	- Alternative antibiotic may be less effective than penicillin - Adverse effects from 2nd and 3rd line antimicrobials - May promote drug resistance over time - Does not provide any information on whether the patient can actually take the drug safely. - Increased cost to patient and healthcare system	2c, benefits of using alternative agents are unclear, and there are clearly known adverse effects reported across high-quality clinical studies. Would suggest use of other approaches
Desensitization at point of care ^{52,58,87-91}	No	Patient can typically receive the drug that is needed at the point of care safely	- Expensive, time, and resource intensive, especially for patients with frequent antibiotic utilization (cystic fibrosis, cancer, immune suppressed) - Does not provide any information on whether the patient can actually take the drug safely - The majority of patients were not allergic to begin with and there are limited data examining postdesensitization testing to validate need for desensitization	2c for selected patient populations (see text) but not recommended for general population
De-label using history alone ⁹²⁻⁹⁴	Yes	Many histories are easily identified as incompatible with true allergy	- The risk of many histories has not yet been validated - Possibility for faulty memories or mistakes - Patients may still be fearful to take the drug without objective testing - Nonzero probability of immediate reaction when challenged in the future	2c, randomized clinical trials of this approach are lacking, but observational clinical studies have been performed showing benefit. Currently limited by unclear knowledge of when to use this approach
De-label using direct ingestion challenge ^{36,46,95-99}	Yes	- Safe testing approach in patients who are at low risk of immediate hypersensitivity - Most patients are low risk of true allergy - Provides definitive answer on whether the patient is at risk of immediate reaction - Least resources used to provide an answer	- Least conservative approach - Some patients may have reactions during testing	2c, observational studies have been performed particularly in children showing benefit. Currently limited by unclear knowledge of when to use this approach and lack of large studies in adults
De-label using skin testing alone ^{14,80,100-105}	Yes	Negative skin testing using appropriate protocols reduces the pretest probability that a patient will react when challenged	- No skin testing strategy has 100% negative predictive value - Epidemiology of penicillin allergy has changed with changing patterns of parenteral beta-lactam use - Inadequate to determine true cross-reactivity patterns - Future challenge might not be performed in a controlled setting	2c, randomized clinical trials of this approach are lacking, but clinical studies have been performed showing benefit
De-label using skin testing followed by ingestion challenge ^{14,80,100-105}	Yes	- Most conservative testing approach - Greatest reduction in probability of reaction prior to oral challenge - Provides definitive answer on whether the patient is at risk of immediate reaction	- Greatest testing costs (still cost effective compared to maintaining penicillin allergy label) - Time and resource intensive - Shortage of resources to perform the volume of penicillin skin testing that is currently needed	1b, absence of randomized double-blind clinical trials of this approach, but a large body of historical evidence including large prospective cohort studies for its use as the current gold standard approach

(Continues)

TABLE 1 (Continued)

Approach	De-labeling approach	Strengths	Limitations	Level of recommendation and evidence
Risk stratifying approach ^{3,6,62,92,106-109}	Yes	- Assesses individual patient's history to determine penicillin allergy testing strategy - Low-risk patients targeted for direct oral challenge - Higher risk patients for preceding skin testing - Provides definitive answer on whether the patient is at risk of immediate reaction - Appropriate allocation of scarce testing resources	- Most complex - Need for validated risk assessment tools and decision support that have generalizability to different populations	2c, randomized clinical trials of this combination approach are lacking, but clinical and quasi-experimental design studies have been performed showing benefit. Possibility for this approach to become a new gold standard

Level of evidence evaluated using the GRADE scoring system⁷⁹: A "1" represents a strong recommendation, while a "2" represents weak recommendations/suggestions. "a, b, c" represent the levels of available evidence, with "a" representing consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. "b" represents evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate. "c" represents evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.

increasing global focus.^{31,81,82} Inappropriate prescribing,⁵¹ broad-spectrum antimicrobial utilization,^{45,51,55,64,83,84} delayed time to appropriate antibiotic therapy,⁸⁵ and surgical site infections⁴⁴ are ASP foci and modified by penicillin allergy labels. A recent meta-analysis by Wu et al demonstrated that an "antimicrobial allergy label" was associated with significant reductions in antibiotic guideline concordance, antibiotic appropriateness, and beta-lactam utilization, in conjunction with inferior hospital outcomes (increased readmissions, length of stay, and antibiotic costs).⁸⁶ Further, Blumenthal et al recently demonstrated that the presence of a penicillin allergy in a large UK population was associated with a 1.69 fold increase risk of MRSA and 1.26 fold risk of *Clostridioides difficile* infection.³² The paradox is that a penicillin allergy label attached to a patient's record with the intent of improving patient safety, harm minimization, and reducing adverse events is now recognized to adversely impact key ASP targets—antimicrobial appropriateness, antimicrobial resistance, and medication safety.

Any intervention that aligns antibiotic choice with guidelines should be able to significantly reduce antimicrobial resistance.^{40,87} Hence, the impacts of penicillin allergy label removal on antibiotic utilization and antimicrobial resistance are avoidable, as over 90% of patients can have their penicillin allergy label removed by formal testing.^{52,88} Compounding the patient-level impacts of penicillin labels is the healthcare burden, where over 20% of all hospitalized patients in some studies report an antibiotic allergy, highest among cancer and hematology patients.^{51,58} Therefore, the focus of ASPs should rightfully include penicillin de-labeling, in particular in the most vulnerable populations.⁸⁹ Identification of patients that are low risk (eg, childhood benign rashes) that are potentially amenable to direct oral challenge without preceding skin testing is vital to future ASPs. Benign childhood rashes are typically defined to include urticaria without pruritus and flushing with onset typically greater than 6 hours after the first dose of a penicillin and nonsevere delayed onset exanthema without mucosal, systemic symptoms, or organ involvement.⁶⁸ The assessment of penicillin allergy and incorporation of testing into clinical practice is therefore supported by international ASP guidelines,³⁴ even if the optimal approach remains to be determined.

5 | CURRENT APPROACHES TO PENICILLIN ALLERGY LABELS AND PENICILLIN TREATMENT

Multiple strategies exist to approach a patient labeled as penicillin allergic. (Table 1) In a practical real world setting, utilization of each approach may be driven by availability of specialty services. Patients with a historically high pretest probability of previous penicillin anaphylaxis (see Severe Immediate Symptoms, Table 2) who have an immediate need for a penicillin benefit most from either desensitization, validated prick, and intradermal skin testing followed by oral challenge if negative, or from use of a comparably efficacious but structurally distinct antibiotic.

Current approaches to the diagnosis of delayed reactions associated with penicillins and other beta-lactams require standardization with regards to specific procedures and concentrations used and include delayed intradermal skin testing and patch testing.⁹⁰ These procedures have had highest diagnostic utility for maculopapular exanthema, acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESSs). When testing is performed on DRESS patients, it is recommended that it be done off steroids and a minimum of 6 months from the acute episode.⁹⁰ Currently, *in vitro* and *ex vivo* testing such as ELISpot and lymphocyte transformation test have shown some diagnostic utility for delayed beta-lactam allergy but are subject to false positives and negatives, require widespread validation, and are only available in specialized research centers.⁹¹ Patients whose histories are consistent with severe delayed cutaneous adverse reactions with systemic or mucosal involvement such as DRESS or Stevens-Johnson Syndrome/toxic epidermal necrolysis (SJS/TEN) should avoid direct challenges and desensitization with the implicated and structurally related drugs and use the most efficacious structurally unrelated alternative antibiotic. (see Severe Delayed Symptoms, Table 2).

Patients with a low-risk history or a history inconsistent with allergy can be challenged directly (see Favors Low Risk, Table 2) There are strengths, limitations, and differing levels of evidence to support the use of each approach.⁹²

5.1 | De-labeling approaches to penicillin allergy

Penicillin allergy de-labeling can take one of many interventional forms—including (a) assessment by history only, (b) formal skin testing in combination with single or graded two dose ingestion challenge; (c) single or graded two dose ingestion challenge without preceding skin testing. The most definitive test for de-labeling a penicillin allergy is tolerance of the drug on ingestion challenge. Tolerance of a graded two dose or single dose ingestion challenge is the gold standard to evaluate immediate hypersensitivity drug reactions.

Penicillin allergy assessment by history alone utilizing validated point-of-care assessment tools^{93,94} can risk stratify patients and potentially directly de-label those with clearly non-immune-mediated reactions (20% of all reported penicillin allergies).⁴⁶ These approaches currently target inaccurate penicillin allergy labels placed for reasons such as nausea, vomiting, diarrhea alone, or a family history of allergy. They also target labeled patients where previous tolerance of penicillin can be readily demonstrated by chart review. It needs to be shown whether such approaches are convincing enough to have patients and physicians let go of penicillin allergy labels without a subsequent intentional drug ingestion. Devchand et al recently validated an antibiotic allergy assessment tool that enables risk stratification based upon reported phenotype,⁹³ which may aid in the identification of patients with low-risk phenotypes amenable to direct rechallenge.

Penicillin or aminopenicillin direct ingestion challenge has been employed successfully to definitively remove immediate hypersensitivity penicillin allergy labels.⁹⁵⁻⁹⁸ At present, direct ingestion has been done in carefully selected cohorts, predominantly healthy children or healthy adults, whose historical symptoms were at lower risk of true penicillin allergy.^{39,43,95,99} (Table 2) Direct provocation of a penicillin-labeled patient without preceding skin testing appears to be an important tool in the de-labeling toolkit, as tolerance demonstrates the absence of immediate hypersensitivity. This approach has been particularly relevant in children where the pretest risk of true anaphylaxis was very low.³⁹ A rational approach for future studies would be to combine direct ingestion challenges with screening criteria validated on previous skin testing or challenge studies, to identify patients at low risk of an immediate hypersensitivity reaction *a priori*.⁹³

Skin testing for penicillin allergy has long been known to add additional predictive utility for immediate hypersensitivity over clinical history alone.^{17,100} In those with a history of high-risk reactions (eg, widespread immediate urticaria upon first dose, anaphylaxis), skin testing has been successfully deployed to improve point-of-care prescribing, including in the intensive

TABLE 2 Risk stratification of penicillin allergy labels by history

History Elements that Favor Higher Risk of Penicillin Hypersensitivity		
Severe Delayed Symptoms at any point in the past	Severe Immediate Symptoms (particularly within the last 5 y)	History Elements that Favor Low Risk of Penicillin Hypersensitivity
• Mouth or eye ulcerations • Skin or mucosal sloughing • Serum sickness • Immune-mediated kidney Injury • Immune-mediated liver Injury • Stevens-Johnson syndrome (SJS) • Toxic epidermal necrolysis (TEN) • Drug reaction with eosinophilia and systemic symptoms (DRESSs) • Acute generalized exanthematous pustulosis (AGEP)	After administration of the first dose of a new treatment course with a penicillin, patient developed any of the following severe symptoms within one hour. Pretest probability is highest when two or more occur together: • Disseminated hives/urticaria • Angioedema/Swelling of face/throat • Shortness of breath, wheezing, coughing • Shock • Weak pulse • Loss of consciousness/confusion • Severe gastrointestinal symptoms (diarrhea, vomiting)	Low risk for allergy: • Remote history of symptoms not suggestive of severe reaction, >5-10 y ago • Delayed onset urticaria (>6 h following dosing) • Urticaria only, >5-10 y ago • Self-limited mild exanthem Incompatible with allergy: • Gastrointestinal symptoms only • Family history of penicillin allergy only • Avoidant from fear of allergy only

care unit (ICU),¹⁰¹ emergency department (ED),¹⁰² and inpatient wards.^{103,104} Sacco et al performed a recent systematic review and meta-analysis of inpatient penicillin allergy testing (n = 24 studies) that demonstrated an increase in penicillin utilization (9.9%-49%) and decrease in vancomycin and fluoroquinolone usage after skin testing.⁸⁰ Heil et al demonstrated that an infectious disease led testing service facilitated narrow-spectrum antibiotic selection in an additional 63% of patients.¹⁰⁵

The limitation of skin testing is that the pretest probability for positive penicillin allergy skin testing remains low, and allergy resources are typically scarce. In a large, prospective, inner-city cohort of consecutive adult patients being treated for sexually transmitted diseases, those reporting penicillin allergy had negative skin testing 93% of the time, and skin testing had a 97%-99% negative predictive value for tolerating an oral challenge with penicillin.¹⁷ The likelihood of a positive challenge to a beta-lactam after negative skin testing has been observed by Goldberg et al to be <4%, with around 5% still at risk for mild delayed onset rashes.¹⁰⁶

Romano et al have shown that among patients who have demonstrable beta-lactam allergy, 10% demonstrate loss of skin test reactivity every year,^{21,22} and once skin test reactivity to beta-lactams disappears, <1% of previously allergic patients will ever reacquire a true immune-mediated beta-lactam allergy even when exposed to multiple courses of oral antibiotics.^{107,108} Similarly, among children with benign beta-lactam exanthema which are reproducible by direct provocation challenge, 89% will not react to the same challenge after 3 years.¹⁰⁹

A future model of successful penicillin allergy evaluation will therefore need a collaborative, multimodal approach to de-labeling which incorporates decision support and risk stratification. Once risk is assessed, pathways will lead toward direct provocation challenges in low-risk patients or skin testing in higher risk patients. One inpatient multi-center ASP-led beta-lactam allergy testing service has already been shown to improve beta-lactam usage.¹¹⁰ A multi-disciplinary ASP-led approach in Australia was able to remove a penicillin allergy label in 83% of patients and increase narrow-spectrum beta-lactam (aOR, 3.54; 95% CI, 1.98-6.33) and appropriate antibiotic usage (aOR, 12.27; 95% CI, 5.00-30.09) up to 90-day post-testing.¹¹¹ Such a multimodal "all of the above" approach has been used successfully in the US by Blumenthal et al to reduce the effect of penicillin allergy labels in quasi-experimental study designs.^{75,112-114}

5.2 | Role of desensitization and alternative antibiotics

In some instances, such as treatment of a patient with an acute life-threatening infection, direct de-labeling of the penicillin allergy may not be feasible or practical and favored approaches might be: (a) utilization of a nonpenicillin (structurally dissimilar beta-lactam or non-beta-lactam) or (b) desensitization. At the point of care, if an allergy label is present and an alternative antimicrobial is available with no drop in treatment efficacy, use of that alternative agent may be an acceptable practice,¹¹⁵ but this is

not true for all infections.^{114,116} An avoidance of penicillin leading to use of bacteriostatic, overly broad-spectrum antimicrobials or less effective antibiotic, rather than a similar spectrum cephalosporin, is of higher concern. There is now sufficient evidence to conclude that use of alternative antimicrobials is likely the primary pathway by which the associated harm and expense of a penicillin allergy label is mediated to patients.^{32,73,78,114,117} Therefore, the current practice of using alternative antimicrobials to work around penicillin allergy labels needs to be critically reassessed and modified to include risk stratification. When appropriate and available, a referral to an allergy specialist for testing and de-labeling, if appropriate, should be utilized, especially in cases where future use of antimicrobials is anticipated.^{29,118,119}

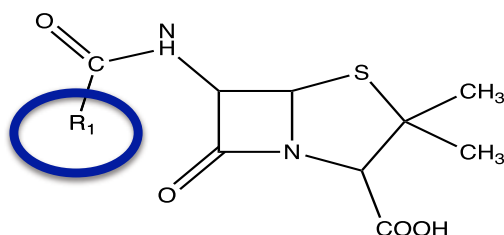
Desensitization is another established procedure in which a patient who is allergic to a penicillin receives tolerable subtherapeutic doses (usually 1/10 000th of effective dose)¹²⁰ of the drug delivered initially, with increasing doses at set intervals of time, until effective treatment doses are achieved and temporary tolerance is induced.^{121,122} Desensitization is currently used in an expanding variety of drug hypersensitivity reactions as a method to induce a temporary drug tolerance which diminishes once the treatment is stopped.¹²¹ A desensitized patient can take the drug safely for a prescribed course, provided that the interval between any two doses does not exceed four drug half-lives.¹²³ Very rarely, patients will react during desensitization and the protocol will need modification. This can also be an important clue that the reaction was real. Desensitization is a temporary strategy to induce tolerance rather than a test; therefore, it cannot be expected to provide any information about whether the patient has a true immunologically mediated adverse drug reaction or if the patient could tolerate the medication in the future. Routine postdesensitization care of the "penicillin allergic" patient should therefore include subsequent formal drug allergy evaluation and appropriate testing >6 weeks following last receipt of the drug to clarify the need for the label.^{122,124}

Desensitization of a penicillin labeled patient is most useful under three scenarios:¹²²

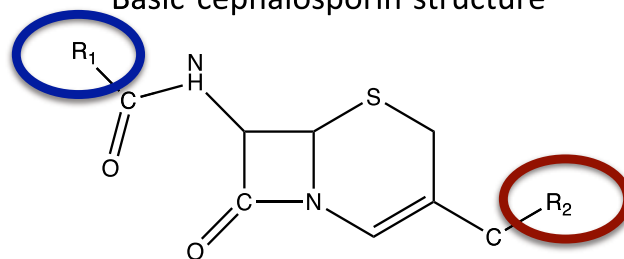
(a) When the patient's skin test status to a penicillin is known to be positive; (b) A clear, recent reaction concerning for an IgE-mediated reaction has been identified, the drug is indicated for a susceptible infection, and testing cannot be immediately performed.¹²⁵; and/or (c) When a patient's underlying medical conditions predispose them to instability or fragility, but penicillin is required for immediate treatment. Many physicians cite syphilis infection either during pregnancy or recalcitrant to alternative therapies¹²⁴ and treatment of susceptible and deep-seated staphylococcal or enterococcal infections^{126,127} as examples of indications for desensitization.

The main arguments against using routine desensitization for every penicillin allergy label are the time and resources used without having gained any information on the validity of the label or whether the patient is truly penicillin allergic. In penicillin allergy, the vast majority of labeled patients are unlikely to have true hypersensitivity reactions.^{17,106} Hence, frequent desensitizations in a patient who

Basic penicillin structure



Basic cephalosporin structure



Penicillin G	Penicillin VK	Cefoxitin Cephalothin (R1) Cefuroxime (R2)	Cefdinir Cefixime (R1 similar, R2 identical)	Cephalothin Cefoxitin (R1) Cefotaxime (R2)
Amoxicillin Cefadroxil, Cefprozil, Ampicillin*, Cefaclor*, Cephalexin*	Ampicillin Cefaclor, Cephalexin, Amoxicillin*, Cefadroxil*, Cefprozil*	Ceftriaxone Cefotaxime, Cefpodoxime, Cefepime Ceftriaxone Cefuroxime, Cefepime Cefotaxime	Ceftazidime Aztreonam	Cefotetan Cefamandole (R2)

FIGURE 3 Understanding Cross-Reactivity Among Beta-Lactams Based Upon R1, R2 Side Chains, or Shared Methoxyimino (MI) Grouping is Important to De-labeling Efforts. For example, consider a patient with two allergy labels, one to penicillin and the other to ceftriaxone. Tolerance of an oral challenge with amoxicillin would prove the safety of all penicillins in this patient by challenging the patient with both the basic penicillin structure and the aminopenicillin side chain. This challenge would not effectively determine the safety of ceftriaxone in a patient labeled allergic to ceftriaxone, however, due to differing side chains and basic structure. Hence, the penicillin allergy label could be removed, but additional basic cephalosporin and ceftriaxone-specific side chain-specific testing would be needed to determine the safety of ceftriaxone prior to ceftriaxone label removal^{18,35,142,146}

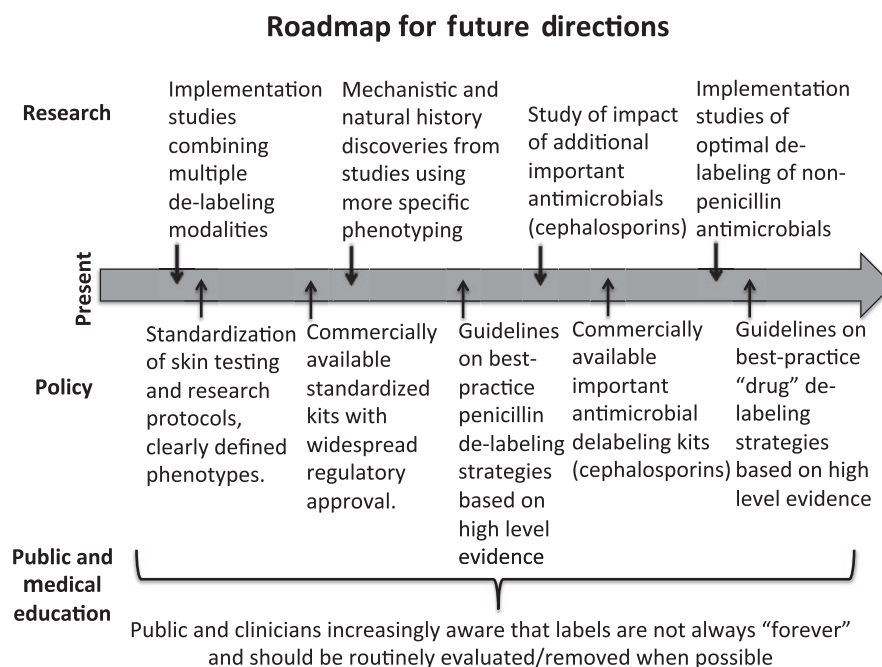
has never been skin tested or challenged represent a suboptimal approach that is unlikely to be cost effective.

6 | SPECIFIC CHALLENGES TO ALLERGY DE-LABELING

Currently, there are important barriers and limitations that must be considered to address the large burden of patients carrying a penicillin allergy label. Access to penicillin skin testing is not universally available.¹²⁸ Internationally, not all allergists offer penicillin skin testing as part of their routine practice.¹²⁹ Allergy and Immunology training programs do not universally offer drug and antibiotic allergy training that can be implemented into routine clinical practice.¹³⁰

The burden of proof to convince a patient that a penicillin allergy label is no longer needed may vary between childhood and adulthood. Tonson de la Tour et al demonstrated that a 2-day challenge and de-labeling in children led to a 69% utilization of subsequent penicillin treatment within the next three years.¹⁰⁹ Vyles et al demonstrated that 73% of parents felt comfortable giving penicillin derivatives to their children after skin testing and single dose oral challenge de-labeling.^{41,43} Labrosse et al demonstrated that parents were convinced of penicillin safety at high rates by negative direct provocation testing, and to a greater degree by a multiple day challenge compared to a single dose challenge.¹³¹ Labels that are removed in adulthood may require greater effort to assuage a patient's desire to avoid that drug. Adult patients have previously received negative conditioning and reinforcement about avoidance of penicillin. They can be fearful of label removal and reluctant to

FIGURE 4 Roadmap for Future Directions in Penicillin De-labeling Research. An additional important milestone includes research to identify factors that lead to reintroduction of penicillin allergy labels into a patient's chart



take penicillin despite being told it is safe after a negative evaluation, which would suggest that earlier intervention is needed. In a study by Gerace et al, 41% of patients who underwent outpatient penicillin

allergy testing with or without challenge continued to avoid all penicillins in the absence of post-testing physician counseling.¹³² Using a more intensive program, Bourke et al found that an inpatient drug

TABLE 3 Characteristics that favor or impede penicillin allergy de-labeling: a SWOT analysis

	Helpful to achieving the objective	Harmful to achieving the objective
Internal Origin (Attributes of the Institution/Organization)	Strengths - Dedicated antimicrobial stewardship program, allergy testing/specialty allergy services, and implementation sciences - Strong institutional commitment to quality improvement and collaboration - Widely utilized electronic health record systems	Weaknesses - Siloed or absent expertise - Lack of access to specialty services in a timely fashion - Lack of institutional support - Poorly integrated electronic health record or clinical communication systems
External Origin (Attributes of the Environment)	Opportunities - Clinicians and patients can be trained to reduce unnecessary label application and will seek best practices - Public is aware of need to utilize antimicrobials more effectively - Public is interested and eager for improvements in allergy care - Messaging can be simple and clear	Threats - Lack of awareness that penicillin allergy labels should be re-evaluated - Need for reeducation around low-risk events and labels - Stigma of fear around penicillin labels may lead to their reapplication despite de-labeling

allergy de-labeling service resulted in 75% of patients following allergy label modifications.⁸⁸ Ratzon et al found that adult patients were more convinced by a multiple day challenge than by a single dose challenge for de-labeling.¹³³

Unfortunately, while most penicillin allergies are currently acquired in childhood, decisions about whether to test a child's antibiotic allergy label are often deferred, as antibiotic alternatives may appear to be readily available and parents see testing as uncomfortable or painful for their child.^{57,68} However, Lucas et al have recently shown that penicillin labels are associated with adverse outcomes such as longer hospital stay even in childhood.⁵⁷ Deferral of penicillin allergy testing may also lead to the acquisition of additional drug labels as alternatives are utilized over time, leading to the scenario of a multidrug allergy labeled patient who has run out of treatment options.^{29,118,119} Overcoming any reluctance or inertia to testing penicillin allergy earlier in childhood or adolescence will likely be crucial in reducing the "stickiness" of labels that have been reinforced for decades.

There is also still some debate as to the length of provocation challenge needed for allergy label removal. Both single step and graded same day drug challenges are utilized for de-labeling in current practice, but graded challenges may not provide much additional utility over single dose challenges in exchange for the increased resources required.¹³⁴ Multiple day challenges may provide additional diagnostic utility for delayed rashes compared to a single dose with prolonged patient follow-up, but published series suggest this benefit is also small.¹³⁵ Immediate clinical use of a penicillin following de-labeling is beneficial to future patient confidence for use. Multi-day challenges also have the potential to decrease patient anxiety and penicillin avoidance, but this will need to be weighed against the downside of increased antimicrobial exposure.^{131,133}

There are no validated blood testing strategies or biomarkers to aid in penicillin allergy de-labeling that are sufficiently sensitive or specific enough to use alone in clinical practice. It is known that IgE specific for drugs are mechanistically involved in Type I immediate hypersensitivity reactions. Unfortunately, testing for penicillin-specific IgE currently lacks both sensitivity and specificity to detect true drug allergy, does not cover the penicillin minor determinants, and has a negative predictive value significantly <100%.^{122,136,137} Partially, this may reflect a limited window in which penicillin-specific IgE is detectable after a reaction, followed by a rapid decrease in circulating antibody concentrations.^{138,139} Similarly, the basophil activation test, a flow cytometry-based test that measures drug-induced activation of basophils by examining alterations in the expression of basophil markers such as CD63 and CD203c, is not available at many centers and does not have the negative predictive value needed for use in clinical practice.¹⁴⁰ Because of these limitations, current commercial versions of specific IgE tests and investigational tests such as the basophil activation test do not provide sufficient clinical utility to support their use in de-labeling.¹⁴¹

Current skin testing and oral challenge protocols to de-label penicillin are not standardized across practices within countries,

much less internationally, and do not always account for the new knowledge of beta-lactam cross-reactivity. Oral tolerance of amoxicillin is sufficient to remove all penicillin allergy labels. However, in an amoxicillin-labeled patient, skin testing using major and minor penicillin determinants may miss some patients with selective side chain-specific aminopenicillin allergies who will react to amoxicillin- and ampicillin-based compounds upon provocation, and this is particularly true in Europe and other countries such as Australia where one-third or more of patients may demonstrate selective aminopenicillin skin test reactivity.^{18,142} Selective reactions to clavulanic acid have been described for which an intradermal skin testing strategy exists in Europe and Australia but not in North America, which may reflect differing sensitization patterns.^{24,143} While parenteral amoxicillin/clavulanic acid is used in many countries around the world, including Europe and Australia, only oral administration is approved by the FDA for use in the US.¹⁴⁴ When skin testing to amoxicillin and/or ampicillin is negative in the setting of an immediate reaction to amoxicillin-clavulanate within the last 5 years in particular, a selective reaction to clavulanate should be considered.^{24,143} Simultaneous sensitization to both amoxicillin and clavulanic acid have been reported in Spain.¹⁴⁵ Cephalosporin labels must be considered separately from penicillin labels, using knowledge of cross reactive families, as side chain cross-reactivity patterns are likely to be a primary driver in cephalosporin reactions and are particularly relevant to cross-reactivity between aminopenicillin and aminoccephalosporins.^{35,146} (Figure 3) Selective aminopenicillin reactions and cross-reactivity between aminopenicillins and cephalosporins appear to be more prevalent in Europe and Australia than in the US although because of lack of widespread use of multiple penicillin and cephalosporin reagents and cephalosporin ingestion challenge in the US, this has not been fully examined.^{31,35,128,143,146} A recent prospective multicenter open-label investigation of penicillin skin testing in 455 patients with histories of immediate reactions to penicillin was conducted across 13 allergy centers in the US using a penicillin skin testing kit containing penicilloyl-polylysine, tripartite minor determinant mixture (penicillin G, penicilloate, and penilloate), and amoxicillin. In this study, 4 of 63 (6.3%) of skin test-positive patients reacted to amoxicillin alone with negative skin tests to the other reagents.¹⁴⁷

7 | FUTURE DIRECTIONS/OPPORTUNITIES FOR IMPROVEMENT

Despite these limitations, energy and enthusiasm to tackle the problem of inappropriate penicillin allergy labeling is currently high, given the demonstrable effects of penicillin allergy labels on antimicrobial stewardship and healthcare outcomes. Within this window of opportunity, there are multiple ways in which we can improve upon our testing, research, and implementation (Figure 4; Table 3).

In light of the emerging knowledge of beta-lactam allergy cross-reactivity patterns,^{18,35} there is a need for easier access to skin

testing reagents, standardized international skin testing protocols and research protocols. Results from this standardization will lead to more precise phenotyping in routine clinical practice. Since true beta-lactam allergy with a positive skin test is somewhat rare, collaborative research networks aimed at a deeper understanding of penicillin allergy epidemiology and mechanisms are needed once standardized testing is implemented.

On the implementation side, the awareness that most patients carry unnecessary penicillin allergy labels highlights the need to further validate clinical tools to correctly risk stratify patients with low-risk penicillin allergy history who may be appropriate for direct ingestion challenge.

Finally, there is a growing need for insight into factors from both a patient and healthcare provider perspective that impede the effectiveness of penicillin allergy de-labeling strategies and lead to reintroduction of penicillin allergy labels into a patient's chart. The work, resources, and effort of de-labeling are in vain if the results are unconvincing to patients and treating clinicians during future healthcare encounters.

8 | CONCLUSIONS

Penicillin allergy labels are highly prevalent, largely inaccurate and their carriage may lead to unnecessary treatment and inferior outcomes with alternative agents as well as adverse public health outcomes such as antibiotic resistance. Operationalizing penicillin allergy de-labeling as an aspect of ASP has become an increasing global focus. There is a need for validated approaches that optimally combine the use of history and risk stratification with validated allergy testing approaches such as ingestion challenge with or without preceding formal skin testing to tackle penicillin allergy efficiently across disparate healthcare systems. At the same time, there is great promise for penicillin allergy evaluation and de-labeling as an individual and public health strategy to reduce adverse healthcare outcomes, improve antimicrobial stewardship, and decrease healthcare costs.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests to disclose.

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REFERENCES

1. Fleming A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzae* 1929. *Bull World Health Org*. 2001;79(8):780-790.
2. du Vigneaud V, Carpenter F, Holley R, Livermore A, Rachele J. Synthetic penicillin. *Science*. 1946;104(2706):431-450.
3. Keefer C, Blake F, Marshall E, et al. Penicillin in the treatment of infections: A report of 500 cases. *J Am Med Assoc*. 1943;122(18):1217-1224.
4. Welch H, Rostenberg A Jr. Hypersensitivity of the tuberculin type to crystalline penicillin sodium. *J Am Med Assoc*. 1944;126(1):10-12.
5. Kolodny MH, Denhoff E. Reactions in penicillin therapy. *J Am Med Assoc*. 1946;130(16):1058-1061.
6. Jaslowitz H. Reaction to penicillin. *Br Med J*. 1945;2(4430):767-767.
7. Farrington J, Riley K, Olansky S. Untoward reactions and cutaneous testing in penicillin therapy. *South Med J*. 1948;41(7):614-620.
8. Waldbott G. Anaphylactic death from penicillin. *J Am Med Assoc*. 1949;139(8):526-527.
9. Berger A, Eisen B. Feasibility of skin testing for penicillin sensitivity: A study of one thousand cases. *J Am Med Assoc*. 1955;159(3):191-193.
10. Schwartz R, Vaughan J. Immunologic responsiveness of man to Penicillin. *JAMA*. 1963;186:1151-1157.
11. Scholand J, Tennenbaum J, Cerilli G. Anaphylaxis to cephalothin in a patient allergic to penicillin. *JAMA*. 1968;206(1):130-132.
12. Crieo M. Cross-allergenicity of the penicillins and the cephalosporins. *Archiv Int Med*. 1967;119(2):141-145.
13. Rothschild P, Doty D. Cephalothin reaction after penicillin sensitization. *JAMA*. 1966;196(4):372-373.
14. Johansson S, Bennich H, Wide L. A new class of immunoglobulin in human serum. *Immunology* 1968;14(2):265-272.
15. Ishizaka K, Ishizaka T. Physicochemical properties of reaginic antibody. 1. Association of reaginic activity with an immunoglobulin other than gammaA- or gammaG-globulin. *J Allergy*. 1966;37(3):169-185.
16. Levine B, Redmond A. Minor haptenic determinant-specific reagents of penicillin hypersensitivity in man. *Int Archiv Aller Appl Immunol*. 1969;35(5):445-455.
17. Gadde J, Spence M, Wheeler B, Adkinson N Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA* 1993;270(20):2456-2463.
18. Romano A, Torres MJ, Fernandez J, et al. Allergic reactions to ampicillin. Studies on the specificity and selectivity in subjects with immediate reactions. *Clin Exp Allergy*. 1997;27(12):1425-1431.
19. Blanca M, Fernandez J, Miranda A, et al. Cross-reactivity between penicillins and cephalosporins: clinical and immunologic studies. *J Allergy Clin Immunol*. 1989;83(2 Pt 1):381-385.
20. Torres MJ, Gonzalez FJ, Mayorga C, et al. IgG and IgE antibodies in subjects allergic to penicillins recognize different parts of the penicillin molecule. *Int Arch Allergy Immunol*. 1997;113(1-3):342-344.
21. Blanca M, Torres M, Garcia J, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. *J Allergy Clin Immunol*. 1999;103(5 Pt 1):918-924.
22. Romano A, Gaeta F, Valluzzi R, Zaffiro A, Caruso C, Quarantino D. Natural evolution of skin-test sensitivity in patients with IgE-mediated hypersensitivity to cephalosporins. *Allergy*. 2014;69(6):806-809.
23. Linares T, Marcos C, Gavilan M, Arenas L. Hypersensitivity to penicillin V with good tolerance to other beta-lactams. *J Investig Allergol Clin Immunol*. 2007;17(1):50-51.
24. Fernandez-Rivas M, Perez Carral C, Cuevas M, Marti C, Moral A, Senent C. Selective allergic reactions to clavulanic acid. *J Allergy Clin Immunol* 1995;95(3):748-750.
25. Rodriguez-Bada JL, Montanez MI, Torres MJ, et al. Skin testing for immediate hypersensitivity to betalactams: comparison between two commercial kits. *Allergy*. 2006;61(8):947-951.
26. Nolan R, Puy R, Deckert K, O'Hehir R, Douglass J. Experience with a new commercial skin testing kit to identify IgE-mediated penicillin allergy. *Intern Med J*. 2008;38(5):357-361.
27. FDA. FDA Approved Drug Products. *Drugs@FDA: FDA Approved Drug Products* 2018; 2018. <https://www.accessdata.fda.gov/>

- drugsatfda_docs/applletter/2009/050114s008ltr.pdf. Accessed November 20, 2018.
28. Caubet J, Kaiser L, Lemaitre B, Fellay B, Gervais A, Eigenmann P. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol*. 2011;127(1):218-222.
 29. Caimmi S, Sanfiorenzo C, Caimmi D, Bousquet P, Chiron R, Demoly P. Comprehensive allergy work-up is mandatory in cystic fibrosis patients who report a history suggestive of drug allergy to beta-lactam antibiotics. *Clin Transl Allergy*. 2012;2(1):10.
 30. Rimawi RH, Cook PP, Gooch M, et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. *J Hosp Med*. 2013;8(6):341-345.
 31. 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):526-537.
 32. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of methicillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study. *BMJ*. 2018;361:k2400.
 33. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. *J Allergy Clin Immunol*. 2014;133(3):790-796.
 34. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect*. 2016;62(10):e51-77.
 35. Romano A, Gaeta F, Arribas Poves M, Valluzzi R. Cross-reactivity among Beta-Lactams. *Curr Allergy Asthma Rep*. 2016;16(3):24.
 36. Romano A, Valluzzi RL, Caruso C, Maggioletti M, Quarantino D, Gaeta F. Cross-Reactivity and Tolerability of Cephalosporins in Patients with IgE-Mediated Hypersensitivity to Penicillins. *J Allergy Clin Immunol*. 2018;6(5):1662-1672.
 37. Moussa Y, Shuster J, Matte G, et al. De-labeling of beta-lactam allergy reduces intraoperative time and optimizes choice in antibiotic prophylaxis. *Surgery*. 2018 [Epub ahead of print].
 38. Conway EL, Lin K, Sellick JA, et al. Impact of penicillin allergy on time to first dose of antimicrobial therapy and clinical outcomes. *Clin Ther*. 2017;39(11):2276-2283.
 39. Mill C, Primeau M-N, Medoff E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. *JAMA Pediatr*. 2016;170(6):e160033.
 40. Baur D, Gladstone BP, Burkert F, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2017;17(9):990-1001.
 41. Vyles D, Chiu A, Routes J, et al. Antibiotic use after removal of penicillin allergy label. *Pediatrics*. 2018;141(5):990-1001.
 42. Vyles D, Chiu A, Simpson P, Nimmer M, Adams J, Brousseau D. Parent-reported penicillin allergy symptoms in the pediatric emergency department. *Academic Pediatrics*. 2017;17(3):251-255.
 43. Vyles D, Adams J, Chiu A, Simpson P, Nimmer M, Brousseau D. Allergy testing in children with low-risk penicillin allergy symptoms. *Pediatrics*. 2017;140(2):e20170471.
 44. Blumenthal KG, Ryan EE, Li Y, Lee H, Kahlen JL, Shenoy ES. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis*. 2018;66(3):329-336.
 45. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Curr Allergy Asthma Rep*. 2014;14(11):476.
 46. Trubiano JA, Cairns KA, Evans JA, et al. The prevalence and impact of antimicrobial allergies and adverse drug reactions at an Australian tertiary centre. *BMC Infect Dis*. 2015;15:572.
 47. Kerr J. Penicillin allergy: a study of incidence as reported by patients. *Br J Clin Pract*. 1994;48(1):5-7.
 48. Sogn D, Evans R III, Shepherd G, et al. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. *Arch Intern Med*. 1992;152(5):1025-1032.
 49. Borch J, Andersen K, Bindeslev-Jensen C. The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. *Basic Clin Pharmacol Toxicol*. 2006;98(4):357-362.
 50. Blanca M, Romano A, Torres MJ, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy*. 2009;64(2):183-193.
 51. Trubiano JA, Chen C, Cheng AC, Grayson ML, Slavin MA, Thursky KA. Antimicrobial allergy 'labels' drive inappropriate antimicrobial prescribing: lessons for stewardship. *J Antimicrob Chemother*. 2016;71(6):1715-1722.
 52. Trubiano J, Adkinson N, Phillips E. Penicillin allergy is not necessarily forever. *JAMA*. 2017;318(1):82-83.
 53. Le J, Nguyen T, Law A, Hodding J. Adverse drug reactions among children over a 10-year period. *Pediatrics*. 2006;118(2):555-562.
 54. Romano A, Caubet J. Antibiotic allergies in children and adults: from clinical symptoms to skin testing diagnosis. *J Allergy Clin Immunol*. 2014;2(1):3-12.
 55. 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):904-910.
 56. Macy E, Contreras R. Adverse reactions associated with oral and parenteral use of cephalosporins: A retrospective population-based analysis. *J Allergy Clin Immunol*. 2015;135(3):745-752.
 57. Lucas M, Arnold A, Sommerfield A, et al. Antibiotic allergy labels in children are associated with adverse clinical outcomes. *J Allergy Clin Immunol*. 2018;7(3):975-982.
 58. Huang K, Cluzet V, Hamilton K, Fadugba O. The impact of reported beta-lactam allergy in hospitalized patients with hematologic malignancies requiring antibiotics. *Clin Infect Dis*. 2018;67(1):27-33.
 59. Kim S-H, Kim K-H, Kim H-B, et al. Outcome of vancomycin treatment in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2008;52(1):192-197.
 60. McDanel DL, Azar AE, Dowden AM, et al. Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplast*. 2017;32(9S):S101-S108.
 61. Park M, Markus P, Matesic D, Li J. 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):681-687.
 62. Krishna MT, Huissoon AP, Li M, et al. Enhancing antibiotic stewardship by tackling "spurious" penicillin allergy. *Clin Exp Allergy*. 2017;47(11):1362-1373.
 63. Li M, Krishna M, Razaq S, Pillay D. A real-time prospective evaluation of clinical pharmaco-economic impact of diagnostic label of 'penicillin allergy' in a UK teaching hospital. *J Clin Pathol*. 2014;67(12):1088-1092.
 64. Picard M, Begin P, Bouchard H, et al. Treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital. *J Allergy Clin Immunol*. 2013;1(3):252-257.
 65. Nebeker J, Barach P, Samore M. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med*. 2004;140(10):795-801.
 66. Inglis J, Caughey G, Smith W, Shakib S. Documentation of penicillin adverse drug reactions in electronic health records: inconsistent use of allergy and intolerance labels. *Intern Med J*. 2017;47(11):1292-1297.
 67. Edwards I, Aronson J. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356(9237):1255-1259.
 68. Norton A, Konvinse K, Phillips E, Broyles A. Antibiotic Allergy in Pediatrics. *Pediatrics*. 2018;141:5.

69. Ibia E, Schwartz R, Wiedermann B. Antibiotic rashes in children: a survey in a private practice setting. *Arch Dermatol*. 2000;136(7):849-854.
70. National Clinical Guideline Centre (UK). *Drug Allergy: Diagnosis and Management of Drug Allergy in Adults, Children and Young People*. London: National Clinical Guideline Centre; 2014.
71. Adkinson N Jr. Risk factors for drug allergy. *J Allergy Clin Immunol*. 1984;74(4 Pt 2):567-572.
72. Macy E, Blumenthal K. Are cephalosporins safe for use in penicillin allergy without prior allergy evaluation? *J Allergy Clin Immunol*. 2018;6(1):82-89.
73. Blumenthal K, Ryan E, Li Y, Lee H, Kuhlen J, Shenoy E. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis*. 2018;66(3):329-336.
74. Jeffres M, Narayanan P, Shuster J, Schramm G. Consequences of avoiding beta-lactams in patients with beta-lactam allergies. *J Allergy Clin Immunol*. 2016;137(4):1148-1153.
75. Blumenthal KG, Wickner PG, Hurwitz S, et al. Tackling inpatient penicillin allergies: Assessing tools for antimicrobial stewardship. *J Allergy Clin Immunol*. 2017;140(1):154-161.
76. Su T, Broekhuizen B, Verheij T, Rockmann H. The impact of penicillin allergy labels on antibiotic and health care use in primary care: a retrospective cohort study. *Clin Transl Allergy*. 2017;7:18.
77. Briody V, Albright C, Has P, Hughes B. Use of cefazolin for group B streptococci prophylaxis in women reporting a penicillin allergy without anaphylaxis. *Obstet Gynecol*. 2016;127(3):577-583.
78. Blumenthal K, Li Y, Banerji A, Yun B, Long A, Walensky R. The cost of penicillin allergy evaluation. *J Allergy Clin Immunol*. 2017;6(3):1019-1027.e2.
79. Jones B, Bland C. Penicillin skin testing as an antimicrobial stewardship initiative. *Am J Health-Syst Pharm*. 2017;74(4):232-237.
80. Sacco K, Bates A, Brigham T, Imam J, Burton M. Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis. *Allergy*. 2017;72(9):1288-1296.
81. Ressler RA, Gada SM, Banks TA. Antimicrobial stewardship and the allergist: reclaiming our antibiotic armamentarium. *Clin Infect Dis*. 2016;62(3):400-401.
82. Blumenthal KG, Wickner PG, Hurwitz S, et al. Tackling inpatient penicillin allergies: tools for antimicrobial stewardship. *J Allergy Clin Immunol*. 2017;140(1):154-161.e6.
83. 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):2819-2822.
84. van Dijk SM, Gardarsdottir H, Wassenberg MW, Oosterheert JJ, de Groot MC, Rockmann H. The high impact of penicillin allergy registration in hospitalized patients. *J Allergy Clin Immunol*. 2016;4(5):926-931.
85. Mattingly TJ II, Fulton A, Lumish RA, et al. The cost of self-reported penicillin allergy: a systematic review. *J Allergy Clin Immunol*. 2018;6(5):1649-1654.e4.
86. Wu JH, Langford BJ, Schwartz KL, et al. Potential negative effects of antimicrobial allergy labelling on patient care: a systematic review. *Can J Hosp Pharm*. 2018;71(1):29-35.
87. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*. 2017;2:CD003543.
88. Bourke J, Pavlos R, James I, Phillips E. Improving the effectiveness of penicillin allergy de-labeling. *J Allergy Clin Immunol*. 2015;3(3):365-374.
89. Trubiano JA, Grayson ML, Thursky KA, Phillips EJ, Slavin MA. How antibiotic allergy labels may be harming our most vulnerable patients. *Med J Australia*. 2018;208(11):469-470.
90. Phillips EJ, Bigliardi P, Bircher AJ, et al. Controversies in drug allergy: Testing for delayed reactions. *J Allergy Clin Immunol*. 2019;143(1):66-73.
91. Mayorga C, Ebo DG, Lang DM, et al. Controversies in drug allergy: In vitro testing. *J Allergy Clin Immunol*. 2019;143(1):56-65.
92. Kavanagh B. The GRADE system for rating clinical guidelines. *PLoS Medicine*. 2009;6(9):e1000094.
93. 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*. 2019;7(3):1063-1065.
94. 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.
95. Tucker MH, Lomas CM, Ramchandrar N, Waldram JD. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. *J Allergy Clin Immunol*. 2017;5(3):813-815.
96. Vezir E, Dibek Misirlioglu E, Civelek E, et al. Direct oral provocation tests in non-immediate mild cutaneous reactions related to beta-lactam antibiotics. *Pediatr Allergy Immunol*. 2016;27(1):50-54.
97. Iammatteo M, Alvarez-Arango S, Ferastraoaru DE, et al. Safety and outcomes of oral graded challenges to amoxicillin without prior skin testing. *J All Clin Immunol*. 2018;141(2):AB34.
98. Confino-Cohen R, Rosman Y, Meir-Shafir K, et al. Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. *J Allergy Clin Immunol*. 2017;5(3):669-675.
99. Confino-Cohen R, Rosman Y, Meir-Shafir K, et al. Challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. *J Allergy Clin Immunol*. 2017;5(3):669-675.
100. Tannert L, Mortz C, Skov P, Bindslev-Jensen C. Positive skin test or specific IgE to penicillin does not reliably predict penicillin allergy. *J Allergy Clin Immunol*. 2017;5(3):676-683.
101. Arroliga ME, Vazquez-Sandoval A, Dvoracek J, Arroliga AC. Penicillin skin testing is a safe method to guide beta-lactam administration in the intensive care unit. *Ann Allergy Asthma Immunol*. 2016;116(1):86-87.
102. Marwood J, Aguirrebarrena G, Kerr S, Welch SA, Rimmer J. De-labelling self-reported penicillin allergy within the emergency department through the use of skin tests and oral drug provocation testing. *Emerg Med Australas*. 2017;29(5):509-515.
103. Macy E, Roppe LB, Schatz M. Routine penicillin skin testing in hospitalized patients with a history of penicillin allergy. *Permanente J*. 2004;8(3):20-24.
104. King EA, Challa S, Curtin P, Bielory L. Penicillin skin testing in hospitalized patients with beta-lactam allergies: Effect on antibiotic selection and cost. *Ann Allergy Asthma Immunol*. 2016;117(1):67-71.
105. Heil EL, Bork JT, Schmalzle SA, et al. Implementation of an infectious disease fellow-managed penicillin allergy skin testing service. *Open Forum Infectious Diseases*. 2016;3(3):ofw155.
106. Goldberg A, Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol*. 2008;100(1):37-43.
107. Ponvert C, Weilenmann C, Wassenberg J, et al. Allergy to beta-lactam antibiotics in children: a prospective follow-up study in retreated children after negative responses in skin and challenge tests. *Allergy*. 2007;62(1):42-46.
108. Solensky R, Earl H, Gruchalla R. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med*. 2002;162(7):822-826.
109. Tonson la Tour A, Michelet M, Eigenmann P, Caubet J. Natural history of benign nonimmediate allergy to beta-lactams in children: a prospective study in retreated patients after a positive and a negative provocation test. *J Allergy Clin Immunol*. 2018;6(4):1321-1326.
110. 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):1059-1065.

111. 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):166-174.
112. Blumenthal K, Shenoy E, Varughese C, Hurwitz S, Hooper D, Banerji A. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. *Ann Allergy Asthma Immunol*. 2015;115(4):294-300.
113. Blumenthal K, Shenoy E, Hurwitz S, Varughese C, Hooper D, Banerji A. Effect of a drug allergy educational program and antibiotic prescribing guideline on inpatient clinical providers' antibiotic prescribing knowledge. *J Allergy Clin Immunol*. 2014;2(4):407-413.
114. Blumenthal K, Parker R, Shenoy E, Walensky R. Improving clinical outcomes in patients with methicillin-sensitive *Staphylococcus aureus* bacteremia and reported penicillin allergy. *Clin Infect Dis*. 2015;61(5):741-749.
115. Miller MA, Fish DN, Barber GR, et al. A comparison of safety and outcomes with cefazolin versus nafcillin for methicillin-susceptible *Staphylococcus aureus* bloodstream infections. *J Microbiol Immunol Infect*. 2018. S1684-1182(18)30304-9.
116. Vogler S, Pavich E. Pyelonephritis treatment in the community emergency department: Cephalosporins vs. first-line agents. *Am J Emerg Med*. 2018;36(11):2054-2057.
117. Blumenthal KG, Shenoy ES, Huang M, et al. The impact of reporting a prior penicillin allergy on the treatment of methicillin-sensitive *Staphylococcus aureus* bacteremia. *PLoS ONE*. 2016;11(7):e0159406.
118. Phillips E, Mallal S. Drug hypersensitivity in HIV. *Curr Opin Allergy Clin Immunol*. 2007;7(4):324-330.
119. Petroni DH, Aitken ML, Ham E, et al. Approach to the evaluation of adverse antibiotic reactions in patients with cystic fibrosis. *Ann Allergy Asthma Immunol*. 2016;117(4):378-381.
120. Khan D, Solensky R. Drug allergy. *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S126-137.
121. Castells MC. A new Era for drug desensitizations. *J Allergy Clin Immunol*. 2015;3(4):639-640.
122. Joint Task Force on Practice Parameters. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105(4):259-273.
123. Legendre D, Muzny C, Marshall G, Swiatlo E. Antibiotic hypersensitivity reactions and approaches to desensitization. *Clin Infect Dis*. 2014;58(8):1140-1148.
124. Pham M, Ho H, Desai M. Penicillin desensitization: Treatment of syphilis in pregnancy in penicillin-allergic patients. *Ann Allergy Asthma Immunol*. 2017;118(5):537-541.
125. Wendel G Jr, Stark B, Jamison R, Molina R, Sullivan T. Penicillin allergy and desensitization in serious infections during pregnancy. *N Engl J Med*. 1985;312(19):1229-1232.
126. Kwong J, Urbancic K, Trubiano J. Beyond penicillin - rapid desensitization for specific flucloxacillin hypersensitivity. *Antimicrob Agents Chemother*. 2018;62(12):e01371-18.
127. Sullivan T. Antigen-specific desensitization of patients allergic to penicillin. *J Allergy Clin Immunol*. 1982;69(6):500-508.
128. Trubiano JA, Beekmann SE, Worth LJ, et al. Improving antimicrobial stewardship by antibiotic allergy delabeling: evaluation of knowledge, attitude, and practices throughout the emerging infections network. *Open Forum Infectious Diseases*. 2016;3(3):ofw153.
129. Gerace K, Karlin E, McKinnon E, Phillips E. Varying penicillin allergy testing practices in the United States: A time for consensus. *J Allergy Clin Immunol*. 2015;3(5):791-793.
130. Derrick M, Williams K, Shade L, Phillips E. A survey of drug allergy training opportunities in the United States. *J Allergy Clin Immunol*. 2018;6(1):302-304.
131. Labrosse R, Paradis L, Lacombe-Barrios J, et al. Efficacy and safety of 5-day challenge for the evaluation of nonsevere amoxicillin allergy in children. *J Allergy Clin Immunol*. 2018;6(5):1673-1680.
132. Gerace K, Phillips E. Penicillin allergy label persists despite negative testing. *J Allergy Clin Immunol*. 2015;3(5):815-816.
133. Ratzon R, Reshef A, Efrati O, et al. Impact of an extended challenge on the effectiveness of beta-lactam hypersensitivity investigation. *Ann Allergy Asthma Immunol*. 2016;116(4):329-333.
134. Mawhirt S, Fonacier L, Calixte R, Davis-Lorton M, Aquino M. Skin testing and drug challenge outcomes in antibiotic-allergic patients with immediate-type hypersensitivity. *Ann Allergy Asthma Immunol*. 2017;118(1):73-79.
135. Garcia Rodriguez R, Moreno Lozano L, Extremera Ortega A, Borja Segade J, Galindo Bonilla P, Gomez TE. Provocation tests in non-immediate hypersensitivity reactions to beta-lactam antibiotics in children: are extended challenges needed? *J Allergy Clin Immunol*. 2018;7(1):265-269.
136. Blanca M, Mayorga C, Torres M, et al. Clinical evaluation of Pharmacia CAP System RAST FEIA amoxicilloyl and benzylpenicilloyl in patients with penicillin allergy. *Allergy*. 2001;56(9):862-870.
137. Fontaine C, Mayorga C, Bousquet P, et al. Relevance of the determination of serum-specific IgE antibodies in the diagnosis of immediate beta-lactam allergy. *Allergy*. 2007;62(1):47-52.
138. Hjortlund J, Mortz C, Stage T, Skov P, Dahl R, Bindslev-Jensen C. Positive serum specific IgE has a short half-life in patients with penicillin allergy and reversal does not always indicate tolerance. *Clinical and translational allergy*. 2014;4:34.
139. Opstrup M, Poulsen L, Malling H, Jensen B, Garvey L. Dynamics of plasma levels of specific IgE in chlorhexidine allergic patients with and without accidental re-exposure. *Clin Exp Allergy*. 2016;46(8):1090-1098.
140. Rive C, Bourke J, Phillips E. Testing for drug hypersensitivity syndromes. *Clin Biochem Rev*. 2013;34(1):15-38.
141. Macy E, Goldberg B, Poon K. Use of commercial anti-penicillin IgE fluorometric enzyme immunoassays to diagnose penicillin allergy. *Ann Allergy Asthma Immunol*. 2010;105(2):136-141.
142. Macy E, Ngor E. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. *J Allergy Clin Immunol*. 2013;1(3):258-263.
143. Blanca-Lopez N, Perez-Alzate D, Ruano F, et al. Selective immediate responders to amoxicillin and clavulanic acid tolerate penicillin derivative administration after confirming the diagnosis. *Allergy*. 2015;70(8):1013-1019.
144. Food and Drug Administration. AUGMENTIN 2011; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/050564s052,050720s0251bl.pdf. Accessed February 28 2019.
145. Salas M, Laguna J, Dona I, et al. Patients taking amoxicillin-clavulanic can become simultaneously sensitized to both drugs. *J Allergy Clin Immunol*. 2017;5(3):694-702.
146. Trubiano J, Stone C, Grayson M, et al. The 3 Cs of antibiotic allergy-classification, cross-reactivity, and collaboration. *J Allergy Clin Immunol*. 2017;5(6):1532-1542.
147. Solensky R, Jacobs J, Lester M, et al. Penicillin allergy evaluation: A prospective, multicenter, open label evaluation of a comprehensive penicillin skin test kit. *J Allergy Clin Immunol*. 2019. S2213-2198(19)30262-4.

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