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Review

Reevaluating Pediatric Penicillin Allergy: Diagnosis, Clinical Impact, and De-labeling Strategies

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ABSTRACT

Penicillin allergy is the most commonly reported drug allergy in children, yet the vast majority of these labels are incorrect. Approximately 5-10% of pediatric patients are reported to be penicillin-allergic, but over 90% are found to tolerate penicillins after thorough evaluation. Overdiagnosis of penicillin allergy in children leads to significant clinical and public health consequences, including the unnecessary use of broad-spectrum antibiotics, higher rates of antimicrobial resistance (e.g., *Clostridioides difficile* and methicillin-resistant *Staphylococcus aureus* infections), and increased healthcare costs. This narrative review examines the discrepancy between reported and true penicillin allergy prevalence in pediatrics and discusses the immunopathology of hypersensitivity reactions (Types I-IV). We outline current strategies for diagnosing penicillin allergy, from detailed history-taking and risk stratification to skin testing using non-irritating concentrations and drug provocation test, which remains the gold standard. We also review the evidence on β-lactam cross-reactivity, clarifying that cross-allergy with cephalosporins and carbapenems is lower than historically thought and largely related to side-chain structures. The clinical impact of mislabeling children as penicillin-allergic is explored, highlighting the benefits of penicillin "de-labeling" programs and antibiotic stewardship interventions. Ongoing trials aim to demonstrate improved outcomes when incorrect allergy labels are removed. Finally, we address the challenges and practice gaps in low-resource settings, particularly in Asia, where limited access to allergy testing and specialist care complicates penicillin allergy management. By improving the accurate diagnosis of penicillin allergy in children, we can optimize antibiotic use, enhance patient safety, and combat antibiotic resistance.

Keywords: Pediatric allergy, drug hypersensitivity, beta-lactam allergy, allergy de-labeling, drug provocation test

Introduction

Penicillin, first discovered by Alexander Fleming in 1928 and widely used since the 1940s, remains a cornerstone antibiotic for pediatric infections. However, penicillin allergy is commonly reported and often overdiagnosed in children. Approximately 10% of all patients, including 5-10% of children, are labeled "penicillin-allergic," making it the most documented drug allergy in the medical records. In reality, true immunoglobulin E (IgE) mediated penicillin allergy is uncommon: fewer than 1-2% of the population is truly allergic upon formal evaluation (1) (Centers for Disease Control and Prevention website, "Clinical features of penicillin allergy," accessed June 24th, 2025). Studies

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have shown that 80-90% of individuals with a reported penicillin allergy can actually tolerate penicillin upon testing or re-exposure [British Society for Antimicrobial Chemotherapy website, "The risk of being risk-averse: penicillin allergy labels (PALs)," accessed June 25th, 2025]. Many pediatric patients lose their penicillin sensitivity over time or were never allergic to begin with. Mislabeling often stems from misinterpreting benign rashes or viral exanthems as allergic reactions (1). For example, common childhood viral infections frequently cause rashes which coincide with antibiotic treatment, leading caregivers and clinicians to mistakenly attribute the rash to a drug allergy.

Overdiagnosis of penicillin allergy in children has important consequences for both individual patients and public health. Once a PAL is attached to a child's medical record, it tends to persist into adulthood. This label can lead to an avoidance of all β-lactam antibiotics, resulting in the use of alternative broad-spectrum agents which may be less effective, more toxic, and more expensive. The downstream effects include longer illness durations, higher rates of treatment failure, antibiotic resistance, and increased healthcare costs (2). Growing awareness of these issues has prompted efforts to "de-label" patients who are not truly allergic and encourage more accurate diagnostic workups for reported penicillin allergies (1). In this review, we examine the epidemiology of reported versus confirmed penicillin allergies in pediatric populations, discuss the immunologic mechanisms and types of hypersensitivity reactions, and describe current best practices for testing and management. We also explore the clinical impact of penicillin mislabeling, including antibiotic stewardship considerations and emerging de-labeling programs, with special attention to challenges in low-resource settings.

Epidemiology of Reported vs True Penicillin Allergies

Penicillin allergy is vastly over-reported relative to its true prevalence. In pediatric populations, an estimated 5-10% of children are believed to have a penicillin allergy based on their history. However, comprehensive allergy evaluations reveal that over 90% of these children are not truly allergic. In other words, only about 1 in 20 children with a PAL have a confirmed immunologic hypersensitivity. This disparity is consistent with findings in adults: around 10% of the general population reports penicillin allergy, but fewer than 1% are truly allergic when formally tested (Centers for Disease Control and Prevention website, "Clinical features of penicillin allergy," accessed June 24th, 2025).

Large cohort studies and meta-analyses have established that the vast majority of PALs are inaccurate. For example, Macy and Contreras (3) examined a large healthcare database and found that 94% of patients with listed penicillin allergy were able to tolerate penicillin upon further evaluation or testing. Similarly, a UK study reported that while 6% of patients in primary care carried PAL, only about 0.6% (1 in 10 of those labeled) had a true allergy on comprehensive testing. Pediatric-specific studies also confirm that over 9 out of 10 children with reported penicillin allergy can be safely de-labeled. Vyles et al. (4), for instance, showed that among children with low-risk histories (e.g., only mild rash without features of anaphylaxis), direct oral amoxicillin challenges were negative in over 95% of cases, indicating no allergy in those children. Moreover, penicillin allergy can be transient; it is well documented that IgE-mediated penicillin sensitivity wanes over time. Approximately 50% of patients lose their penicillin-specific IgE antibodies within 5 years, and about 80% may lose sensitivity after 10 years. Many children "outgrow" their penicillin allergy, especially if their initial reaction was mild (5).

Why is Penicillin Allergy Over Diagnosed?

A major reason is the misattribution of symptoms. Children frequently develop rashes due to viral infections or due to benign drug side effects (e.g., transient gastrointestinal upset or diarrhea), which can be misconstrued as allergic reactions. For example, amoxicillin is often prescribed for viral infections (such as Epstein-Barr virus) which cause rashes. When a rash appears, penicillin is blamed. In one study, viral rashes accounted for a large portion of suspected antibiotic "allergies" in children (1). Another contributor is that detailed allergy evaluations are seldom performed at the time of the reaction. Understandably, if a child has any suggestive reaction during antibiotic therapy, families and physicians may choose to err on the side of caution and avoid penicillins thereafter, without pursuing confirmatory testing (6). Over time, the PAL remains in the chart unchallenged. This highlights a critical epidemiologic point: while PALs are present in up to 10% of pediatric charts, the true prevalence of confirmed penicillin allergy in children is of the order of 1% or less. Most labeled children could safely receive penicillins. Recognizing this gap has led to initiatives to better diagnose and, when appropriate, to remove inaccurate PALs in pediatric practice.

Pathophysiology and Types of Hypersensitivity Reactions

Adverse reactions to penicillins can be broadly categorized as either immune-mediated (allergic) or non-immune in nature. Non-immune reactions (previously

called "Type A" reactions) are predictable from the drug's pharmacology and are not due to the immune system, such as diarrhea from amoxicillin or yeast diaper rash after antibiotics. In contrast, true penicillin allergies are immune-mediated ("Type B" reactions) and involve drug-specific immunologic mechanisms. Penicillin and other β-lactam antibiotics can elicit all four types of hypersensitivity described by the Gell-Coombs classification (Types I-IV), though Type I (immediate IgE-mediated) and Type IV (delayed T-cell-mediated) reactions are the most common in clinical practice.

Type I (Immediate, IgE-mediated) Hypersensitivity

These reactions are classically what physicians think of as "true penicillin allergy." Type I reactions occur when a patient has drug-specific IgE antibodies which trigger an immediate allergic response upon penicillin exposure. Onset is usually within minutes to an hour after administration. Clinical manifestations range from urticaria (hives), flushing, angioedema (swelling of the face/lips), and bronchospasm, to anaphylaxis with hypotension and shock. Anaphylaxis to penicillin, while rare, can be life-threatening. Epidemiological data indicate that the incidence of anaphylactic reactions to penicillin is approximately 0.01% or less (in the order of 1-4 per 10,000 courses). The risk of fatal penicillin anaphylaxis is even rarer, estimated to be around 1 in 50,000 to 100,000 courses. Risk factors for IgE-mediated penicillin allergy include repeated high-dose exposures, parenteral (injectable) administration, and a history of atopy or other drug allergies. Notably, children may be less likely to experience severe IgE-mediated reactions than young adults–for example, epidemiologic studies have noted the highest incidence of serious penicillin anaphylaxis in adults aged 20-49 years, possibly because younger children have fewer cumulative exposures or differences in immune response. Nonetheless, immediate allergic reactions can occur at any age, and penicillin is a leading cause of anaphylaxis in children (7,8).

Type I reactions result from penicillin (a hapten) binding to proteins and forming antigenic complexes which IgE antibodies recognize. The classic allergenic determinant is the penicilloyl moiety (the "major determinant"), but minor determinants and side-chain antigenic determinants also contribute. Upon re-exposure, IgE on mast cells and basophils triggers the release of histamine and other mediators, causing the allergic symptoms. Importantly, IgE-mediated penicillin allergy tends to wane over time. IgE levels decline if the patient avoids penicillin for years, which is why many individuals "lose" their penicillin allergy with time. This transient nature underpins the concept of "impermanent allergy" in children, reinforcing the need to periodically re-evaluate PALs.

Type IV (Delayed, T Cell-mediated) Hypersensitivity

Delayed reactions to penicillins, mediated by T lymphocytes, account for many cutaneous "allergic" reactions which occur more than 1-2 hours after drug administration. These typically manifest as maculopapular rashes, which can arise days into a course of penicillin or even days after completion. The majority of benign amoxicillin or ampicillin rashes in children (often seen in the setting of viral infections) are considered delayed T-cell mediated exanthems. These rashes are generally self-limited and not life-threatening, though they lead to an allergy label if misinterpreted. More severe Type IV syndromes include contact dermatitis, drug fever, and certain severe cutaneous adverse reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), although SJS/TEN due to penicillins is exceedingly rare. Delayed hypersensitivity can also manifest as organ-specific reactions (e.g., interstitial nephritis from methicillin) or as part of multiorgan immune reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). These severe T-cell mediated reactions (SJS, TEN, DRESS) are medical emergencies and contraindications to future penicillin use. Fortunately, they are extremely uncommon in pediatrics (Centers for Disease Control and Prevention website, "Clinical features of penicillin allergy," accessed June 24th, 2025).

Other Hypersensitivity Types

Penicillins can, less commonly, cause Type II (cytotoxic antibody-mediated) and Type III (immune complex-mediated) reactions. An example of a Type II reaction is immune-mediated hemolytic anemia: high-dose penicillin can bind to red blood cell membranes and induce IgG antibodies which leads to red blood cell destruction. Type III reactions involve circulating immune complexes; an example is serum sickness-like syndrome, featuring fever, rash, arthralgias, and lymphadenopathy, which can occur days after starting therapy. These are relatively rare and usually associated with high-dose, prolonged penicillin therapy (Centers for Disease Control and Prevention website, "Clinical features of penicillin allergy," accessed June 24th, 2025).

In summary, penicillin hypersensitivity in children can range from acute IgE-mediated anaphylaxis to benign delayed rashes. When evaluating a child with a history of "penicillin allergy," it is critical to characterize the reaction's timing, symptoms, and severity. Many reported

"allergies" in children are actually non-allergic adverse reactions or viral rashes rather than true immune-mediated events. Understanding the type of hypersensitivity not only guides risk assessment (e.g., an isolated delayed rash vs. an immediate anaphylaxis history) but also informs the approach to allergy testing and future antibiotic choices.

Diagnostic Testing Strategies for Penicillin Allergy

Accurately diagnosing penicillin allergy in children is essential in order to distinguish true hypersensitivity from minor reactions or other causes. A comprehensive approach includes a careful clinical history, risk stratification, skin testing (when indicated), and drug provocation (challenge) testing as the gold standard. Recent guidelines also emphasize using validated non-irritating concentrations (NICs) for skin tests to improve specificity.

1. Clinical history and risk assessment: The first step is a detailed history of the reaction. Key details include: the specific drug and dose, timing of symptom onset relative to drug administration, the nature of the symptoms (e.g., hives vs. flat rash vs. respiratory distress), severity, need for hospitalization, and how the reaction was managed. One should also note how long ago the reaction occurred and whether the child has tolerated related antibiotics since then. Historical features help stratify the allergy label as high-risk or low-risk. For example, a child who developed immediate urticaria and wheezing within 30 minutes of a penicillin dose likely had an IgE-mediated reaction and is higher-risk. In contrast, a child who had only a mild rash one day into therapy, or whose reaction was many years ago in infancy, may be low-risk for true allergy. Several risk stratification tools have been developed for penicillin allergies. One example for adults is the Penicillin Allergy Network formula score, which assigns points based on time since reaction, features, and the need for treatment, to predict the likelihood of true allergy. A score <3 suggests low-risk (under 5% chance of true allergy). In pediatrics, simplified approaches often identify children with only benign rashes or remote histories as candidates for direct challenge without extensive skin testing (9). Ultimately, risk assessment guides whether to proceed with immediate challenge or perform skin testing first.

2. Skin prick and intradermal testing: Skin testing for penicillin allergy has been a standard diagnostic tool for decades. Traditional protocols use the major penicillin determinant (penicilloyl-polylysine) and a mixture of minor determinants, as well as the suspect penicillin (e.g., amoxicillin) itself, to increase sensitivity. In skin prick testing, a drop of reagent is placed on the skin, and the skin is superficially pricked; in intradermal testing, a small amount is injected into the dermis. A positive test is a wheal-and-flare reaction at the site, indicating the presence of drug-specific IgE on the patient's mast cells. Modern practice employs NICs of antibiotics for skin testing. NIC refers to the highest concentration of a drug which does not cause non-specific irritation. Using too high a concentration can cause false-positive skin irritation unrelated to IgE; thus, guidelines define appropriate dilutions for skin tests. For penicillins, for example, the recommended NIC for amoxicillin or ampicillin in skin testing is 20 mg/mL, and for benzylpenicillin (penicillin G), it is 10,000 IU/mL. Commercially available penicillin skin test kits (e.g., Pre-Pen, which contains the major determinant) are widely used in North America and Europe, but such reagents may be unavailable in low-resource settings. A positive skin test indicates penicillin-specific IgE and confirms an immediate allergy, and so the patient should avoid penicillin-class drugs. A negative skin test greatly reduces the likelihood of an IgE-mediated allergy, but it does not completely rule it out, especially if only the major determinant was tested and not the full spectrum of metabolites. In practice, when skin tests are negative, an oral challenge is usually performed to conclusively confirm tolerance.

3. Drug provocation test (oral challenge): The drug provocation test, also called an oral challenge, is the gold standard for diagnosing penicillin allergy. In a supervised medical setting, the patient is given a test dose of penicillin (typically an age-appropriate dose of amoxicillin) and observed for any reaction. A stepwise graded challenge may be used–for instance, administering 10% of the dose, then the remaining 90% if no reaction occurs after a set interval. If the patient tolerates the full dose without symptoms, penicillin allergy is effectively ruled out, and the label can be removed. If a reaction does occur, it is managed, and the allergy is confirmed. Drug challenges carry a small risk of inducing an allergic reaction, so they are generally reserved for patients deemed unlikely to react (e.g., those with negative skin tests or very low-risk histories). In children, direct oral challenges without preceding skin tests have been successfully employed for low-risk cases, given the relatively low likelihood of serious reactions (10,11). Several studies have demonstrated the safety of direct amoxicillin challenges in children who have only vague rash histories. For higher-risk histories or where skin testing is available, a negative skin test before challenge adds an extra layer of safety.

4. *In vitro* testing: Blood tests play a more limited role. Serum specific IgE assays for penicillin (radioallergosorbent

tests or newer fluorescence immunoassays) are available, but they have suboptimal sensitivity, often failing to detect many true allergies, and they only address IgE-mediated allergy. A negative IgE test does not rule out penicillin allergy, and a positive test must be interpreted with caution due to false positives. More advanced tests, such as the basophil activation test (BAT), have shown promise in research settings, where a patient's basophils are exposed to the drug *in vitro* and activation markers are measured. BAT can help detect IgE-mediated allergy and may be useful for cases where skin testing is inconclusive or contraindicated. However, BAT and other T-cell assays (for delayed allergy, such as the lymphocyte transformation test or enzyme-linked immunospot for interferon-gamma) are not routinely available in clinical practice and remain research tools.

5. Special considerations: If a patient has a history suggestive of a severe non-IgE reaction (e.g., SJS/TEN or DRESS from penicillin), neither skin testing nor challenge should be carried out due to the risk and the label in these cases should generally be considered permanent, and alternative antibiotics should be used. Desensitization is another procedure used in certain scenarios. If a patient has a confirmed penicillin allergy but absolutely needs a penicillin (for example, a child with neurosyphilis or endocarditis with no good alternatives), an allergist can perform a temporary desensitization. This involves administering gradually increasing doses of the antibiotic under close monitoring, which can induce a temporary state of tolerance. Desensitization carries significant risk and is only performed in hospital settings; once the antibiotic course is finished, the patient will revert to being allergic.

A structured approach to penicillin allergy testing in children involves: (a) identifying those at such low-risk that they can undergo direct oral challenge, (b) performing skin prick/intradermal tests for those with moderate risk or uncertain history (using appropriate NICs to avoid false positives), and (c) confirmatory oral challenge for those with negative or equivocal skin tests (Table I).

When implemented, this approach can safely clarify allergy status in the majority of children and allow those without true allergy to safely receive penicillins again.

Cross-reactivity of Penicillins with Other β-Lactams

A common concern is whether a child with penicillin allergy can safely take other β-lactam antibiotics, such as cephalosporins, carbapenems, or monobactams. Early studies from decades ago suggested up to 8-10% cross-reactivity between penicillins and cephalosporins, leading to a cautious approach where cephalosporins were often avoided in penicillin-allergic patients. However, more recent research has clarified that cross-reactivity risk is generally much lower and is largely related to similarities in chemical structure (specifically, the R1 side chain) rather than the β-lactam ring itself (1).

Penicillins: Within the penicillin class, cross-reactivity is effectively assumed if a patient is truly allergic to one penicillin (e.g., amoxicillin), and so they are usually presumed to be allergic to all penicillin-type antibiotics (ampicillin,

Table I. Risk-stratified diagnostic approach for evaluating pediatric penicillin allergy

Risk category	Typical history features	Recommended evaluation pathway	Outcome
Low-risk	• Benign maculopapular rash only • No mucosal involvement • >12 months since reaction • No features of anaphylaxis	Direct oral amoxicillin challenge (single-or two-step) under supervision	If tolerated → remove allergy label; resume penicillins
Intermediate risk	• Urticaria without respiratory compromise • Reaction within first hour of dose • Unclear medication history	Skin prick±intradermal testing using non-irritating concentrations, followed by oral challenge if negative	Negative tests → safe use; positive → avoid penicillins
High risk	• Anaphylaxis signs: wheeze, angioedema, hypotension • Hospitalization for reaction • Immediate onset of symptoms within minutes	Skin testing plus graded oral challenge in specialist setting; consider avoidance until reviewed by allergist	Confirmed IgE-mediated allergy → avoid penicillins; consider desensitization if no alternative available
Severe cutaneous or organ involvement	• Stevens-Johnson syndrome (SJS) • Toxic epidermal necrolysis (TEN) • DRESS • Serum sickness-like syndrome	Do not perform skin test or oral challenge; permanent avoidance recommended	Avoid all penicillins; document clearly in the patient's record

DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

penicillin G, piperacillin, etc.) due to the shared core penicilloyl determinant. There are exceptions; for instance, some patients have selective allergies to amoxicillin or ampicillin (often manifesting as a delayed maculopapular rash), yet they can tolerate penicillin G. These cases are often due to unique side-chain sensitivities. Overall though, a positive skin test to one penicillin indicates avoidance of all penicillins is prudent. The good news is that 80-90% of those labeled allergic to penicillin are not actually allergic and they can be de-labeled, regaining access to all penicillins.

Cephalosporins: Cephalosporins share the β-lactam ring with penicillins but have a different adjacent ring (dihydrothiazine) and distinct side chains. The historical teaching of a 10% cross-reactivity between penicillins and cephalosporins is an overestimate. The overall risk that a penicillin-allergic patient will have an allergic reaction to a cephalosporin is around 1-3% or even lower. A 2012 literature review by Campagna et al. (12) found the cross-reactivity rate to be approximately 2% between penicillins and first-generation cephalosporins, and negligible for later-generation cephalosporins. Critical to this risk is whether the cephalosporin shares a similar side chain to the culprit penicillin. Immunologic cross-reactivity occurs when the immune system recognizes chemical similarities. For example, amoxicillin and certain early cephalosporins (such as cefadroxil, cefatrizine, and cephalexin) share an identical R1 side chain; hence, an individual allergic to amoxicillin is at higher risk of reacting to those cephalosporins. European studies have documented cross-reactivity rates as high as 30-40% between amino-penicillins (amoxicillin, ampicillin) and amino-cephalosporins (such as cefaclor, cephalexin) which have similar side chains. On the other hand, cephalosporins with dissimilar side chains may be tolerated. For instance, cefazolin (a first-generation cephalosporin often used for surgical prophylaxis) has a unique side chain and exhibits essentially no cross-reactivity with penicillins, and so it can be safely used in most penicillin-allergic patients (13). Clinically, the approach is to avoid cephalosporins which share identical or very similar side chains with the culprit penicillin. Allergy specialists have developed side-chain cross-reactivity charts in order to guide safe antibiotic choices. If a penicillin-allergic child needs a cephalosporin, one strategy is to choose a cephalosporin from a later-generation with a dissimilar structure or perform cephalosporin skin testing if the allergy history was severe. It is worth noting that most data on cross-reactivity pertain to IgE-mediated (immediate) allergies; much less is known about cross-reactivity in delayed T-cell mediated reactions. In severe delayed reactions such as SJS/TEN, some experts recommend avoiding all structurally similar β-lactams entirely due to the life-threatening nature of recurrence.

Carbapenems: Carbapenems (e.g., meropenem, imipenem) also contain a β-lactam ring and initially were thought to pose a high cross-allergy risk in penicillin-allergic patients. Newer studies have dispelled this to a large extent. Reported cross-reactivity between penicillins and carbapenems is under 1% in most recent series. For example, a 2014 multicenter study found that >98% of penicillin skin test-positive patients tolerated meropenem. Therefore, the vast majority of penicillin-allergic individuals can receive carbapenems without incident, especially if their penicillin allergy is not recent or severe. Skin testing protocols for carbapenems have been proposed, and some allergists will perform a test dose or graded challenge to a carbapenem in a penicillin-allergic patient if use is necessary. Overall, current evidence supports that cross-reactivity is low, and carbapenems can be considered with caution or testing, rather than automatically avoided.

Monobactams: Aztreonam is the sole monobactam antibiotic in common use and has a monocyclic β-lactam ring distinct from penicillins. Aztreonam has virtually no cross-reactivity with penicillin allergy at the IgE level. However, an important exception is its side chain, which is identical to that of ceftazidime (a third-generation cephalosporin). Patients allergic to ceftazidime may react to aztreonam due to this shared side chain epitope, but penicillin-allergic patients without ceftazidime allergy are not at an increased risk of reacting to aztreonam. Thus, aztreonam is often a safe alternative in a penicillin-allergic patient if a gram-negative β-lactam is needed (assuming no ceftazidime allergy).

In summary, the fear of cross-reactivity has historically led to overly broad restrictions of β-lactams in penicillin-allergic patients. We now appreciate that, especially for non-critical allergies, many β-lactams can be used safely with appropriate caution. For pediatricians, this means that an allergy to penicillin does not necessarily preclude using all cephalosporins or carbapenems. A careful review of the allergy and possibly consultation with an allergist can identify safe options. For mild penicillin allergies, a cephalosporin with a dissimilar side chain (or even a test dose in a controlled setting) can be reasonable. Avoidance of all β-lactams should be reserved for those with severe, high-risk allergies until they can be formally evaluated. This nuanced understanding helps prevent the unnecessary use

of second-line antibiotics when a safe β-lactam alternative might exist.

Clinical Consequences of Mislabeling Penicillin Allergy

Labeling a child as penicillin-allergic when they are not truly allergic carries significant clinical repercussions. Avoidance of first-line therapy: penicillins (and other β-lactams) are often the preferred treatment for many pediatric infections due to their effectiveness and narrow spectrum. If a child is labeled as allergic, clinicians must resort to second-line or broad-spectrum antibiotics. For example, instead of amoxicillin for an acute otitis media, a "penicillin-allergic" child might receive a macrolide such as azithromycin (which may be less effective against *Streptococcus pneumoniae*). Instead of penicillin for streptococcal pharyngitis, they might receive clindamycin or a cephalosporin. In hospitalized patients, PALs lead to the use of fluoroquinolones, vancomycin, or extended-spectrum agents in place of β-lactams. These substitutes can be suboptimal as they can be broader-spectrum than necessary, potentially more toxic, and sometimes inferior in efficacy. A well-documented example is surgical prophylaxis: patients with a PAL often receive vancomycin or clindamycin instead of a first-generation cephalosporin such as cefazolin, and this has been associated with higher rates of postoperative surgical site infection. In a cohort of over 8,000 surgical patients, those labeled penicillin-allergic had a 50% higher risk of surgical site infection, likely due to less effective prophylactic antibiotics (e.g., vancomycin) being used in place of cefazolin. Mislabeling thus directly impacts patient outcomes.

Higher risk of antibiotic resistance and infections: Perhaps the most concerning consequence is the increased risk of developing infections with resistant organisms. PALs have been linked to greater incidences of *Clostridioides difficile (C. difficile)* infection and methicillin-resistant *Staphylococcus aureus* (MRSA), among others. A landmark population-based study published in 2018 (UK) followed over 300,000 patients and found that those with a documented penicillin allergy had a 69% higher incidence of MRSA and a 26% higher incidence of *C. difficile* infection compared to matched patients without a PAL (14). The primary driver was the use of broader-spectrum, non-penicillin antibiotics in the allergy-labeled group–for instance, an increased use of fluoroquinolones and clindamycin, which are known risk factors for *C. difficile*, and the use of vancomycin or sulfonamides which exert selective pressure for MRSA. The U.S. Centers for Disease Control and Prevention similarly reported significantly higher *C. difficile* rates among hospitalized patients labeled as penicillin-allergic. Thus, carrying a PAL can tangibly harm patients by predisposing them to difficult infections. From a public health perspective, this contributes to the broader problem of antimicrobial resistance. An allergy label leads to more use of broad-spectrum agents, which in turn fosters resistant bacteria– a ripple effect caused by an inaccurate label.

Increased healthcare utilization and cost: Multiple studies have demonstrated that PALs are associated with longer hospital stays and higher healthcare costs. Sousa-Pinto et al. (15) analyzed hospital records and found that patients labeled as penicillin-allergic had significantly longer admissions (on average) and greater hospital expenses than similar patients without such a label, after eliminating confounders. Another study by Mattingly et al. (16) showed that antibiotic costs were higher for penicillin-allergic inpatients, since alternative drugs such as daptomycin or linezolid (for MRSA) and aztreonam (for gram-negatives) are far more expensive than standard β-lactams. In children, if an alternative antibiotic is less effective, it might lead to treatment failures or complications which require additional clinical visits or hospitalizations. All of these add to the healthcare burden (16).

Impact on patient experience and outcomes: Children labeled as penicillin-allergic often face more complex medication regimens. They may receive intravenous antibiotics instead of oral ones (e.g., IV vancomycin for an infection which could have been treated with oral amoxicillin), which can be painful, require hospital stays, and disrupt family life. Broad-spectrum antibiotics such as quinolones can have more side effects (e.g., gastrointestinal upset, musculoskeletal effects) which children must endure unnecessarily. There is also a psychological aspect: families might worry excessively about medication safety due to the label, potentially leading to avoidance of necessary medications or vaccine components (though penicillin allergy does not equate to vaccine allergy, some may misunderstand the risk).

Special cases–rheumatic fever prophylaxis: In some parts of the world, notably low-resource settings with higher rates of rheumatic fever, penicillin (benzathine penicillin G injections) is critical for prophylaxis against recurrent *Streptococcus* infections. If a child is labeled as being allergic, doctors may avoid penicillin prophylaxis, potentially leading to recurrent rheumatic fever and progression of rheumatic heart disease. Unfortunately, false PALs can deprive patients of this life-saving, inexpensive

preventive therapy and necessitate the use of much less established alternatives.

In summary, a PAL is not benign as it can set off a "cascade of consequences." Overdiagnosis negatively impacts individual patient care (through use of suboptimal antibiotics and increased side effects) and contributes to larger issues of antimicrobial resistance and healthcare costs. Recognizing these consequences has been a major driver in improving penicillin allergy evaluation and de-labeling efforts, which we discuss next.

Education of both families and clinicians plays a key role in preventing overdiagnosis. Many reported allergies stem from misinterpretations of benign rashes or viral symptoms, and counseling families about true vs. false allergies reduces avoidance of first-line therapies. Pediatricians who receive focused training in allergy history-taking and direct oral challenge protocols report higher de-labeling success rates.

De-labeling and Antibiotic Stewardship Programs

Given the high frequency of false PALs and their deleterious effects, healthcare systems are increasingly implementing penicillin "de-labeling" programs. De-labeling refers to the process of identifying patients who are not truly allergic and removing the allergy label from their medical record, thereby restoring penicillins as a treatment option. This process aligns closely with antibiotic stewardship goals, as it enables the use of first-line narrow spectrum agents and reduces unnecessary broad-spectrum antibiotic use.

Antibiotic stewardship guidelines: The Infectious Diseases Society of America stewardship guidelines highlight allergy assessment as a key component of optimizing antibiotic use. Hospitals are encouraged to implement protocols whereby patients with reported penicillin allergy, especially those needing antibiotics, are evaluated by allergy or infectious disease specialists. By confirming or refuting the allergy, clinicians can avoid second-line therapies when penicillin (or a cephalosporin) would be more appropriate (17). Many institutions have created penicillin allergy assessment pathways (PAAPs) as part of their routine care, sometimes led by pharmacists, infectious disease physicians, or allergists. For example, some stewardship programs use questionnaires in order to identify low-risk allergy histories and then perform direct oral amoxicillin challenges on the ward or in clinic. Others have developed rapid de-labeling protocols in postoperative patients, intensive care units, or general pediatric wards in order to ensure that patients receive optimal prophylaxis or therapy during their hospital stay (18).

Outcomes of penicillin allergy testing and de-labeling: The benefits of penicillin allergy testing (skin tests and/or challenges) in hospitalized patients are well documented. A 2017 systematic review and meta-analysis by Sacco et al. (19) looked at outcomes following inpatient penicillin allergy. They found that after a negative penicillin allergy evaluation, 80-100% of patients went on to receive penicillin or cephalosporin safely, indicating successful de-labeling. Importantly, such testing was associated with reduced lengths of hospital stay in some studies, fewer readmissions, and no serious adverse reactions from the testing itself in the vast majority of cases (19). Another analysis noted that penicillin allergy evaluation led to changes in antibiotic therapy in over 90% of tested patients, commonly de-escalating to a β-lactam, with resultant cost savings (20). In pediatric patients, a recent systematic review (2021) found that penicillin de-labeling programs in children increased the subsequent use of penicillins for infections and did not lead to increased adverse outcomes (21). Essentially, once cleared, children can reap the benefits of effective β-lactam therapy without harm.

Outpatient de-labeling and special programs: In addition to hospital-based programs, outpatient penicillin allergy clinics have emerged. Blumenthal et al. (22) described a risk-based outpatient pathway in which low-risk patients (e.g., benign rash history) went straight to amoxicillin challenge, while moderate-risk cases underwent skin testing first; this approach was safe and efficient in removing allergy labels. Some centers have even piloted penicillin allergy testing in primary care offices or emergency departments for children, which could provide opportunities when children present for unrelated issues. Education is key, both healthcare providers and families need awareness that penicillin allergies can and should be reevaluated. A notable commentary titled "de-labelling penicillin allergy is not rocket science" Turner (23) underscored that with proper protocols, general pediatricians can identify candidates for de-labeling safely. That said, having allergy specialist support is valuable for higher-risk cases.

The Allergy Antibiotics and Microbial Resistance trial: One of the most significant ongoing efforts to rigorously evaluate penicillin allergy de-labeling is the Allergy Antibiotics and Microbial Resistance (ALABAMA) trial. ALABAMA is a multicenter, parallel-arm randomized controlled trial in the UK designed to measure the impact of a PAAP in primary care. Adults with penicillin allergy records are randomized to either undergo a comprehensive allergy evaluation (including history, skin testing, and/

or direct challenge as appropriate) or to usual care (no testing). The trial's outcomes include the proportion of patients successfully de-labeled, changes in antibiotic prescribing patterns, incidences of infections such as MRSA/*C. difficile*, and cost-effectiveness. While focused on adults, the trial's results (expected in the next couple of years) will provide high-quality evidence on the benefits of penicillin allergy de-labeling on a large scale. The inclusion of "microbial resistance" in its title highlights that a major hypothesis is that removing incorrect allergy labels will lead to more penicillin use and consequently lower rates of resistant infections and overall broad-spectrum antibiotic consumption. Early phases of this work have already shown that integrating allergy assessments into primary care is feasible by using electronic health record prompts and pharmacy support. If ALABAMA demonstrates significant benefits, it could pave the way for broader policy changes encouraging routine penicillin allergy verification as part of standard care in the national health service and beyond (24).

Other Trials and Studies: Another noteworthy initiative is the U.S. based Penicillin Allergy Delabeling Program by the Pediatric Asthma and Allergy community, which tested direct amoxicillin challenges in low-risk children in a community setting with success rates >95% (10). This underscores a growing trend to undo the legacy of penicillin overdiagnosis.

Penicillin allergy de-labeling and stewardship programs have emerged as win-win interventions. They improve patient care by enabling the use of optimal antibiotics and concurrently help combat antimicrobial resistance. The key components for success include education, a standardized pathway (risk assessment, skin testing, challenge), and support from multidisciplinary teams. Even in the absence of an allergist, many centers have shown that trained hospitalists or pharmacists can implement screening and direct challenge protocols safely for low-risk cases. Moving forward, expanding these programs, including to outpatient and resource-limited settings, will be crucial to fully address the penicillin allergy overdiagnosis problem.

Practice Gaps in Low-resource Settings (Indian/Asian Context)

While penicillin allergy de-labeling has gained traction in many high-income countries, significant challenges remain in low-resource settings such as parts of Asia. The epidemiology of PALs differs somewhat in these regions. A recent review on penicillin allergy in India and Sri Lanka noted that the reported prevalence of PALs in those populations (around 1-4% in secondary care) is lower than the 10-20% reported in Western countries. This may be due to under-recognition or under-reporting; however, even a "small" percentage in South Asia translates to millions of individuals because of the large population base. Moreover, once labeled, the impact on care may be even more pronounced given the reliance on penicillin for endemic infections (9).

Limited access to allergy evaluation: Low-resource settings often lack trained allergists and the infrastructure for formal allergy testing. Allergy/immunology as a specialty is still developing in countries such as India. There is a "huge unmet need for allergy specialists" in these regions. For instance, India, with over a billion people, has only a handful of centers which routinely perform drug allergy testing. Consequently, most PALs are assigned (and maintained) based solely on history without verification. The unavailability of standardized skin test reagents is a major barrier. The penicillin skin test kits (major/minor determinants) used in Western countries are often not available or even licensed in South Asian markets. Physicians might attempt ad-hoc testing with the drug itself, but without validated NICs and proper technique, this can yield false positives or even provoke reactions (9).

Non-standard practices: In the absence of guidelines and trained personnel, some practitioners engage in "pre-emptive, non-standardized and unregulated skin testing by untrained operators." For example, a common practice in some Indian hospitals is to administer a small test dose of penicillin (either intradermal or subcutaneous) before giving the full dose, as a crude allergy check. This practice is not standardized, and so concentrations and interpretation vary widely, and it may itself sensitize patients or give misleading results. Without clear protocols, a patient can be mislabeled as allergic due to an irritant reaction from an overly concentrated test dose. The Biswas et al. (25) review highlighted the need for establishing validated NICs and protocols tailored to the local setting in order to avoid false diagnoses. Additionally, in many Asian countries, drug allergy history is not systematically documented; patients may not even be aware of the specifics of a past reaction. This makes subsequent evaluation very difficult (9).

Antimicrobial stewardship challenges: The implications of a PAL in low-resource settings can be especially problematic for diseases such as rheumatic fever, rheumatic heart disease, and syphilis, which are managed with long-acting penicillin injections. As noted, if someone who has been labeled as allergic foregoes penicillin prophylaxis, they risk recurrent disease.

Unfortunately, alternative prophylactic regimens (such as sulfadiazine for rheumatic fever) are less effective. Another example is pediatric sepsis management: in settings where third-generation cephalosporins (e.g., ceftriaxone) are standard for severe infections, a penicillin/cephalosporin allergy label might lead to the use of chloramphenicol or fluoroquinolones (older or more toxic drugs) due to the lack of availability of newer alternatives such as carbapenems. This can adversely affect outcomes.

The weak health system framework in some areas means that there is limited oversight on how drug allergies are recorded or acted upon. Patients might self-report an allergy and have it accepted at face value without further inquiry. Conversely, true allergies may be missed due to a lack of awareness, leading to serious reactions. Global pushes for antibiotic stewardship, such as the World Health Organization's Access, Watch, Reserve (AWaRe) classification to guide antibiotic use, must take these local limitations into account (World Health Organization website, "The WHO AWaRe antibiotic book – Infographics," accessed June 25th, 2025). The 2025 review by Moitra et al. (9) advocates for a "pragmatic, cautious and staged approach" to penicillin allergy mitigation in India and Sri Lanka. This could include measures such as: focusing on identifying low-risk patients who could safely receive penicillin under observation (direct oral challenge), improving physician training in allergy history-taking, lobbying for access to penicillin skin testing reagents, and creating local guidelines for allergy management which align with international best practices but are feasible in resource-limited contexts (9).

Awareness and education: There is also a gap in public and provider awareness. In many Asian countries, the concept of drug allergy is not well understood by patients, some of whom may not differentiate between an adverse effect and an allergy. Educational initiatives are needed to inform healthcare workers about the high false-positive rates of penicillin allergy histories and to encourage referrals or cautious test doses under proper conditions rather than blanket avoidance. Encouragingly, some large tertiary hospitals in India (e.g., in Vellore, Chandigarh) have started antibiotic allergy testing clinics as part of research collaborations. Regional allergy societies (such as the Allergy and Immunology Society of Sri Lanka and the Indian College of Allergy, Asthma and Applied Immunology) are now discussing penicillin allergy in their meetings, indicating a growing recognition (9).

In summary, low-resource settings face unique challenges such as fewer specialists, a lack of testing reagents, and often a greater burden of infections where penicillin is vital. Penicillin allergy overdiagnosis is a global issue but it needs local solutions. Bridging this gap will require international support in order to improve access to diagnostics, local guideline development, and the integration of penicillin allergy assessments into broader antimicrobial resistance strategies. Without addressing penicillin allergy mislabeling, efforts to optimize antibiotic use in these countries will be incomplete.

Conclusion

Penicillin allergy in children is often overdiagnosed, with the vast majority of pediatric patients labeled as "allergic" ultimately found to tolerate penicillins upon proper evaluation. Rethinking our approach to pediatric penicillin allergy is imperative–both to improve individual patient care and to advance public health goals such as antimicrobial stewardship. Clinicians should maintain a healthy skepticism regarding historical penicillin allergy reports and consider formal allergy assessments for children, especially when β-lactam antibiotics are the best therapy. By understanding the immunologic basis of reactions (Types I-IV) and employing available diagnostic tools, such as careful history, skin testing with NICs, and drug challenges, we can accurately identify the rare truly allergic child and, just as importantly, de-label the many who are not allergic. The benefits of penicillin allergy de-labeling are clear: children gain access to optimal antibiotic therapy, experience fewer side effects and complications, and healthcare systems see a reduced emergence of resistant infections and lower costs. Programs around the world are demonstrating that penicillin de-labeling is feasible and safe, and ongoing research, such as the ALABAMA trial, will further quantify its impact.

Penicillin, a drug which has saved countless lives, should not be needlessly avoided due to an unwarranted allergy label. For pediatricians, an important practice point is to revisit allergy histories periodically; a child labeled in infancy may not be allergic a few years later. Incorporating penicillin allergy assessments into routine pediatric care and stewardship protocols will ensure that our young patients receive the most effective treatments. In low-resource settings, tackling penicillin allergy overdiagnosis will require innovative strategies and support in order to overcome resource gaps. Across all contexts, the message is consistent: it is time to replace cautionary avoidance with evidence-based evaluation. By doing so, we can safely "reclaim" penicillin for the majority of children who need it, improving health outcomes and preserving the utility of this invaluable class of antibiotics.

Footnotes

Authorship Contributions

Surgical and Medical Practices: I.V., S.M., P.B., V.S.P., S.T.K., Concept: I.V., S.M., P.B., V.S.P., S.T.K., Design: I.V., S.M., P.B., V.S.P., S.T.K., Data Collection or Processing: I.V., S.M., P.B., V.S.P., S.T.K., Analysis or Interpretation: I.V., S.M., P.B., V.S.P., S.T.K., Literature Search: I.V., S.M., P.B., V.S.P., S.T.K., Writing: I.V., S.M., P.B., V.S.P., S.T.K.

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