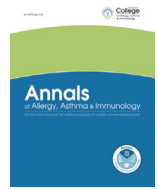




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Review

Children with reported penicillin allergy

Public health impact and safety of delabeling

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Key Messages

- Most allergies in pediatric patients are self-reported and often inconsistent with true allergy. Most of these supposed allergic reactions are attributed to β -lactam antibiotics.
- Traditional penicillin allergy testing has involved a 3-tier approach; however, mounting evidence indicates that a direct oral challenge in children with low-risk allergy symptoms may be the optimal approach to delabel a child with reported β -lactam allergy.
- Children with reported penicillin or drug allergies are often found to have an increase in alternative prescriptions for their bacterial illness.
- Prescription costs are 30% to 40% higher in patients with suspected penicillin allergy.
- With the evidence indicating the safety of delabeling and the accumulating evidence for the negative economic, individual, and public health burden of a penicillin allergy diagnosis, there is a need to establish strategies and programs to develop feasible, scalable, and effective approaches.

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ABSTRACT

Objectives: To review the relevant literature related to children with reported penicillin allergy and highlight the different ways in which children could be delabeled and to evaluate the public health impact that a penicillin allergy has for children.

Data Sources: Data for this review were obtained via PubMed searches and then retrieval of articles from their respective journals for further review.

Study Selection: Studies regarding the safety of different ways to evaluate penicillin allergy in children were identified via PubMed searches. Any study that reported different ways of testing (3-tier, direct oral challenge, 5-day oral challenges) were included. This same format was used when selecting relevant articles related to the costs, prescription patterns, and stewardship trends associated with a penicillin allergy label.

Results: This review found that penicillin allergy testing is a safe and effective way to delabel those with reported allergy. In children with low-risk allergy symptoms, a direct oral challenge approach may be

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optimal. In those children with a history of high-risk allergy symptoms, a 3-tiered approach is ideal. The review also found that there is a significant cost associated with reported penicillin allergy and that there are increased negative health benefits to those children with reported allergy.

Conclusion: Penicillin allergy is overdiagnosed, often incorrectly, and the label is frequently first applied during childhood. Targeting children for the removal of the incorrect penicillin allergy label provides a mechanism to reduce the use of broader-spectrum and less effective antibiotics.

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Introduction

Allergy to a medication in the penicillin class is reported to occur in approximately 10% of patients internationally.^{1–3} Most patients report low-risk symptoms of allergy, such as delayed rash, at a very young age, which is unlikely to recur with subsequent exposures.^{4–6} When a penicillin allergy is reported in a child, there are increased costs to families and health care systems.^{7–9} In addition, the presence of a reported penicillin allergy also leads to adverse health outcomes, such as increases in hospital-acquired infections, hospital length of stay, resistance due to alternative antibiotics, and morbidity and mortality.^{9,10} Previously, penicillin allergy was typically evaluated using a 3-tier testing method that involved sequential prick testing, skin testing, and oral challenge. In select lower-risk patient populations and particularly in children based on observational evidence, there has been a trend toward direct oral amoxicillin challenges to delabel reported allergy, without preceding skin testing.^{11,12} Regardless of diagnostic approach, penicillin allergy testing has proved to be a safe and effective way to delabel allergy in countless studies. Removal of a penicillin allergy label has positive health implications for the lifespan of the individual and the general population.

Prevalence of Adverse Drug Reactions

Most allergies in pediatric patients are self-reported and often inconsistent with a true allergy. The rate of parent-reported adverse drug reactions ranges from 6% to 10%.^{13–15} Most of these supposed allergic reactions are attributed to β -lactams, followed by anti-inflammatory drugs and other non- β -lactam antibiotics.¹³ The most frequently reported antibiotic allergy symptoms with children are nonimmediate dermatologic symptoms that often occurred in young age, in the first week or early in the second week of treatment, and via the oral route.^{14,13–16} However, when the history was reviewed in these parent-reported allergies, the clinical history was only suggestive of drug allergy in 1.16% of patients, and 76% of children were found to have low-risk symptoms of allergy inconsistent with a true IgE-mediated reaction.^{4,14} It is also important to note that antibiotics can cause adverse reactions in 4% to 10% of patients, and these reactions often lead to the self-diagnosis or self-report in children continuing into adulthood.^{13,17} These adverse reactions include dose-dependent development of maculopapular rashes and diarrhea,¹⁷ which are commonly seen as penicillin allergy symptoms to families with children. Ultimately, most children who report penicillin allergy can tolerate the medication without adverse reactions, and testing for allergy via a variety of different mechanisms has been proved to be safe and effective.

Evaluation and Management of Penicillin Allergy

With the emergence of increased antibiotic resistance and the increased use of broad-spectrum antibiotics, testing for penicillin allergy has emerged as an essential pillar of antimicrobial stewardship.¹² Traditional penicillin allergy testing, which is the gold standard, involves 3-sequential steps: (1) skin prick testing, (2) intradermal testing, and (3) oral challenge with penicillin (ie,

penicillin VK or amoxicillin).¹¹ The skin testing is performed with the major determinant penicilloyl polylysine and commercially available penicillin G. The negative predictive value (NPV) of skin testing with the major and minor determinants is more than 95% but approaches 100% when followed by an oral challenge, which is the last but necessary step to remove a label of penicillin allergy.¹⁸ Current testing strategies beyond the 3-tier testing include direct single-dose oral challenges and 5-day oral challenges (Fig 1). These strategies have evolved over time, with the oral-challenge-only approach coming into favor in select populations during the past few years. There is increasing evidence that different types of oral challenge options in adults and children are a safe and effective way to delabel patients with reported antibiotic allergy and low-risk allergy symptoms.

Safety of Skin Testing in Penicillin Allergy

In children with reported allergy to β -lactam antibiotics, skin testing followed by drug challenge is an effective process to delabel those with reported allergy (Table 1). Importantly, skin testing with a complete set of validated reagents that includes the implicated penicillin, major and minor determinants (including benzyl penicillin), is currently only validated to have a near 100% NPV for penicillins and not for other β -lactams.

Ponvert et al¹⁹ studied 1865 children aged from 4 months to 18 years with suspected β -lactam allergy and completed skin prick, intradermal, and patch testing (on selected patients) followed by oral challenge. A total of 869 children were examined 1 year or less from their reaction compared with 562 children who underwent testing more than 1 year from their reaction. Patients with anaphylaxis or urticaria were more often examined in the earlier time frame. Those patients with unidentified rashes or severe skin reactions were examined nearly evenly between the 2 time frames. Oral challenge was completed only if all skin test results were negative. The investigators found that after examination of 1431 children, 227 (15.9%) were diagnosed as allergic to β -lactams. A total of 103 (45%) were diagnosed by skin testing, 111 (48.9%) by oral challenge, and 13 (5.7%) by convincing clinical history without allergy testing. With data suggesting that only 50% of patients with positive penicillin skin test results will develop an immediate reaction on reexposure to the drug, it is likely that the 227 children with positive test results may overestimate the rate of reactivity.^{5,20} In the patients who were diagnosed as allergic, 50 (22%) had immediate reactions and 177 (77.9%) had nonimmediate reactions. A total of 43 of 50 immediate reactions were found via skin testing, and of these children, 6 had adverse reactions, including 1 immediate reaction (urticaria and asthma) and 5 nonimmediate reactions (urticaria). In children who received oral challenges with results deemed positive, all reactions were mild to moderately severe and resolved rapidly with oral antihistamines and/or corticosteroids. Overall, for most patients, penicillin allergy label was removed with no serious events occurring. In addition, with the movement toward an oral-challenge-only approach in patients with low-risk allergy symptoms, many of the patients with nonimmediate reactions within this study may have been candidates to bypass skin testing.

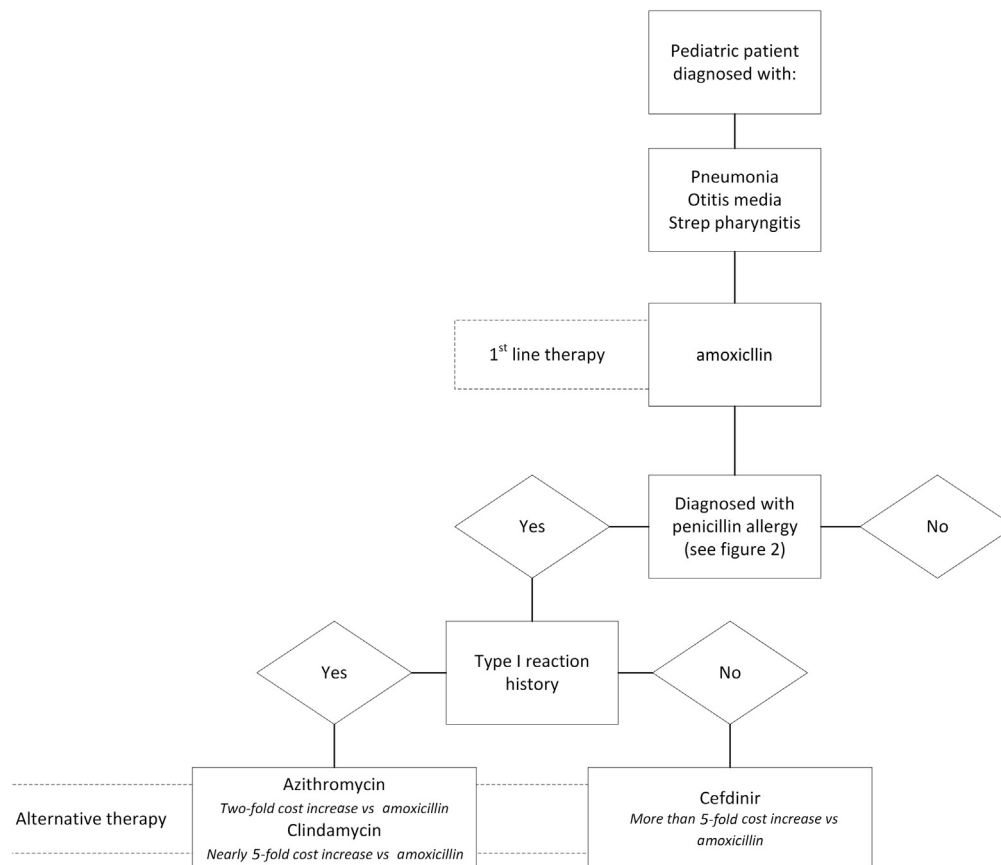


Figure 1. Antibiotic pathway in children with penicillin allergy. Pediatric patients commonly present for a range of bacterial illnesses. The most common pediatric illnesses include pneumonia, otitis media, and streptococcal pharyngitis. The first-line antibiotic therapy for children with these illnesses is amoxicillin. However, in patients reporting penicillin allergy, practitioners are reluctant to prescribe and often alter their prescribing practices based on the reported allergy. If a type 1 reaction is suspected, then alternative therapy often includes azithromycin or clindamycin, both of which are 2- to 5-fold cost increases over amoxicillin. If the patient is not suspected of having had a type 1 reaction, then cefdinir is often the second-line agent, which is approximately a 5-fold increase over amoxicillin.

A large study completed by Zambonino et al²¹ also used the combination of skin testing and oral challenge testing in a cohort of 783 patients aged 1 to 14 years. With this testing, 721 (93.08%) were able to be delabeled, and only 62 patients (7.92%) were confirmed to be allergic, with 9 (14.52%) immediate and 53 (85.48%) non-immediate reactions. The interval from reaction to testing in both the allergic and nonallergic groups was 9 months. In those who had immediate reactions, 2 were diagnosed via in vitro testing, 2 via skin testing, and 5 via direct provocation challenge. In those with nonimmediate reactions, 2 were diagnosed via skin testing and 51 via direct provocation challenge. In the 4 patients who had a positive skin test result, 1 developed symptoms consistent with anaphylaxis; however, no signs of shock developed. In the 56 patients who underwent a drug provocation challenge and were then deemed allergic, symptoms primarily consisted of exanthema, urticaria, and 1 serum sickness-like reaction. The skin testing proved to be safe, but the researchers concluded that direct provocation testing was an essential tool for diagnosis of β -lactam allergy. Ultimately, delabeling was possible in more than 90% of the children.

Caubet et al²² also used a skin testing approach in children aged 0 to 16 years with reported β -lactam allergy who had been diagnosed because of delayed-onset urticarial or maculopapular rash. The interval from reaction to testing in this study was 2 months. The investigators conducted intradermal and patch skin testing followed by an oral challenge and viral screening on all 88 children. Intradermal skin test results were positive in 11 patients. Reassuringly, the investigators ultimately found that only 6 patients (6.8%) had reproducible rash with drug rechallenge, no reaction was

worse than the index visit, and 4 of the 6 had a positive intradermal test result. The reactions consisted of urticaria (4 patients) and maculopapular rash (2 patients).

Alternative methods of skin testing have also been explored and proved to be an effective way to address reported penicillin allergy in children. Picard et al²³ evaluated the safety and NPV of skin testing with only penicillin G followed by a 3-dose graded challenge to the incriminated penicillin. In a 3-year period, they skin tested 563 patients aged 7 months to 21 years with penicillin G, and 185 (33%) had a positive skin result. The patients who had a positive skin test result were found to have a shorter interval between the initial reaction (1.7 years) compared with those patients who had a negative skin test result (3.1 years). Of the 185 who had a positive skin test result, 1 had a positive scratch test result and 184 had a positive intradermal test result. A total of 375 of 378 patients (99%) with a negative skin test result were challenged, and 18 (4.8%) had reactions. The reactions were all mild and consisted of skin findings ($n = 18$), throat symptoms ($n = 2$), and irritability ($n = 1$). These findings all resolved quickly with treatment. This method of skin testing and oral challenge translated to an NPV of 95.2%.

These studies reinforce the overall safety of skin testing followed by oral challenge in children with reported β -lactam allergy. This approach is undoubtedly the safest way to identify true allergy in children with high-risk allergy symptoms that may produce a serious reaction on reexposure to the medication. However, it may not be the optimal approach toward patient populations whose reaction history stratifies as being lower risk. The concept of risk stratification and direct oral challenge of low-risk patients has been

Table 1
Summary of Safety of Penicillin Allergy Testing

Study	Study type	No. of study participants	Positive ST results, n (%)	Positive OC result, n (%)	OC protocol	Diagnoses removed, n (%)
Vyles et al ³⁹	Prospective	37	NA	1/37	Single-dose OC, 500 mg to all patients	36 (97.2)
Labrosse et al ²⁹	Prospective	130	NA	3/130 (2.3) immediate, 3/127 (2.3) 5-day OC, 2/127 (1.6) 5-day, OC equivocal results	Single-dose OC, amoxicillin (45 mg/kg per dose), 1/100 dose (step 1), 1/10 dose (step 2), full dose (step 3), doses given at 30-min intervals, patients with negative initial OC result were sent home with a therapeutic 4-day ambulatory course of amoxicillin (45 mg/kg per day) for a total challenge duration of 5 days	122 (93.8)
Vyles et al ²⁷	Prospective	100	3/100 (3.0)	0/100 (0.0)	Single-dose OC, 500 mg to all patients	100 (100.0)
Mill et al ²⁵	Prospective	818	NA	48/818 (5.9)	Two-step OC 10% therapeutic dose (step 1), 90% therapeutic dose (step 2)	770 (94.1)
Mori et al ³⁰	Prospective	200	9/200 (4.5)	17/177 (9.6)	5-day OC in ST-positive or ST-negative patients with nonimmediate reactions, 1/10-2/10-7/10 of amoxicillin therapeutic dose Every 30 min until therapeutic dose reached (day 1), if day 1 negative, daily therapeutic doses of amoxicillin for 5 days (days 2-5)	160 (90.3)
Zambonino et al ²¹	Prospective	783	4/783 (0.05) 2/783 (0.025) in vitro test	56/783 (7.1)	Escalating dose OC, escalating doses of the drug at intervals of 30 to 90 min up to the full therapeutic dose	721 (92.0)
Caubet et al ²²	Prospective	88	11/88 (12.5)	6/88 (6.8)	ST positive 50% of therapeutic dose (step 1), 100% of remaining therapeutic dose (step 2), ST negative 150% therapeutic dose (single step)	82 (93.1)
Moral et al ²⁶	Prospective	67	0/17 (0.0)	1 (1.4) 50 OC only, 17 OC after ST	OC with culprit drug 1/50 the usual single dose (step 1), 1/5 the usual single dose (step 2), usual single dose (step 3), doses were given 1 h apart	66 (98.5)
Chambel et al ²⁴	Prospective	159	8/47 (17.0)	12/112 (10.7)	OC with culprit drug, increasing doses of the antibiotic, every 30 min	140 (88.0)

Abbreviations: NA, not applicable; OC, oral challenge; ST, skin test.

explored in many recent studies but was also explored by Chambel et al²⁴ in 2010. In their study, they evaluated 161 children younger than 15 years with immediate or delayed reactions who were consecutively referred to an allergy department for a history compatible with allergy to β -lactams. In this study, 114 patients with a history of low-grade severity reactions were given a direct provocation challenge without prior skin testing. In these patients, 68 were challenged with the culprit drug, 32 with an alternative drug, and 14 with both drugs. They found that in this population 11 of 82 patients (13.4%) who did not undergo a skin test had a positive challenge result. Skin eruption was the manifestation of reaction in all challenges with positive results, with symptoms occurring within 1 hour of exposure. They ultimately concluded that in select populations in patients with nonsevere allergy history, a direct oral challenge may be the optimal pediatric testing approach.

Safety of Oral Challenge Only in Penicillin Testing

Traditionally, skin testing has often been performed in patients with β -lactam allergy before completing an ingestion challenge. Recent studies and reviews of the management of reported penicillin allergy have highlighted the safety of direct ingestion challenge options (Table 1). A recent review article completed by Shenoy et al¹² highlighted that in terms of access and scalability, direct oral amoxicillin challenge in patients with low-risk allergy histories may be the optimal approach to delabeling allergy. Their review provides a toolkit that highlights who these patients are and offers additional information on when to challenge with this method vs skin testing before challenge. Nonetheless, when skin testing is unvalidated, oral challenge is necessary to confirm or delabel allergy.

Oral challenges to address penicillin allergy have taken the forms of graded provocation challenges, single-dose oral challenges, and multiday oral challenges to address penicillin allergy. One of the largest studies to be completed in children was completed by Mill et al.²⁵ They completed an observational study in children with a history of penicillin allergy in which they gave a graded oral amoxicillin challenge (10% of dose followed by 90% of the dose 20 minutes later) with a 1-hour postchallenge observation period. They assessed 818 children and found that 770 (94.1%) tolerated the challenge without any sign of reaction. In this study, 17 patients (2.1%) patients had an immediate reaction, all of which were mild and consistent with hives. Mild, nonimmediate reactions occurred in 31 patients (3.8%). The study concluded that graded challenges may be the optimal way to test for penicillin allergy in children because skin tests often have a high false-negative or false-positive result. Moral et al²⁶ also evaluated the safety of direct oral provocation testing in low-risk patients via a short clinic-based protocol. They found that in 67 patients who underwent challenge, only 1 patient had a reaction, and it was delayed and mild in nature. Both studies highlighted graded provocation challenges in allergy clinic settings. Additional novel settings for evaluating low-risk patients who report penicillin allergy have been performed in the past several years as well.^{27,28}

Although an allergy clinic is an ideal location to evaluate penicillin allergy, exclusively doing so may miss a significant portion of pediatric patients with lower-risk reactions who may otherwise not have access to specialty services and never present for diagnosis. Additional locations for allergy evaluation could include a variety of different clinic settings, especially in children with low-risk symptoms of penicillin allergy. Vyles et al²⁷ have explored this mechanism of testing in 2 different ways. First, they completed an allergy questionnaire in the pediatric emergency department to identify patients with low-risk symptoms of allergy to penicillin. After the administration of this questionnaire, they invited 100 of these low-risk patients to an outside hospital-associated clinic and

found that all tested negative for penicillin allergy after a 3-tier testing process. After obtaining the results of this study, they completed a pediatric emergency-based randomized controlled study in which they gave single-dose oral challenges to children presenting for reasons that would or would not require antimicrobial therapy.²⁸ Ultimately, 37 children were given an oral challenge, and 36 (97%) tolerated it in the emergency department without an allergic reaction. One child had a minor rash that resolved with administration of an antihistamine. This challenge was a single dose (500 mg of amoxicillin) independent of weight; however, multiple-day challenges have also proved to be effective.

There has been some debate on whether extended oral challenges to delabel penicillin allergy should occur compared with single-dose or single-day challenges. Several research studies have found that extended 5-day challenges are safe and effective. Labrosse et al²⁹ completed a study in which 130 children underwent a graded drug provocation test. Their study included an initial evaluation at the outpatient allergy clinic, and if the challenge result was negative, the patient was then sent home with a 4-day ambulatory course of amoxicillin. After 2 years, a telephone call follow-up was completed. In the initial challenge, all patients underwent a single-dose graded challenge with amoxicillin (45 mg/kg per dose) in 3 steps: 1/100, 1/10, and full dose at 30-minute intervals. If the initial challenge result was negative, patients were sent home with a therapeutic 4-day ambulatory course of amoxicillin (45 mg/kg per day). Of these patients tested, 122 (93.8%) had negative results, and this cohort of patients then underwent a 5-day challenge to rule out nonimmediate reactions. They were called 2 years after this challenge, and 114 (93.4%) were contacted for assessment of amoxicillin use since their initial allergy workup. Of these, 67 (89.3%) had used penicillin antibiotics. Most children who were reexposed to penicillin antibiotics tolerated it well; however, 3 patients (4.5%) developed mild delayed cutaneous symptoms.

Mori et al³⁰ completed a similar study and evaluated the safety and effectiveness of a 5-day challenge. Their study evaluated 200 patients with penicillin allergy, and 177 (88.5%) underwent the 5-day challenge. On day 1 of the protocol, a challenge with amoxicillin (1/10-2/10-7/10 of the therapeutic dose [50/mg/kg daily in 2 doses] administered every 30 minutes) was performed. If the challenge result was negative, amoxicillin was administered the day after in a single dose, and if this result was negative, a therapeutic daily dose was prescribed for 5 days. Of these patients who were challenged through this extended process, 17 patients were found to have confirmed allergy, 14 of the 17 had a nonimmediate reaction, and 4 of the 14 reacted on day 5. All reactions were mild, and all patients were treated at home with antihistamines and/or oral corticosteroids. They concluded that their methods were safe and may be the ideal way to delabel reported penicillin allergy in children with nonimmediate reactions. Overall multiple-day challenges appear to be safe and effective in demonstrating tolerance to penicillins when a child is well; however, a single-dose ingestion challenge is sufficient to rule out any risk of an immediate reaction. In addition, for multiple-day challenges, it is a risk-benefit ratio of whether they constitute unnecessary exposure to antibiotics and, in the case of a history of a mild delayed reaction, whether it makes sense in the absence of a single-dose reaction simply to challenge the child with multiple doses when they next have a need for a penicillin antibiotic.

Effectiveness of Allergy Delabeling

The prevalence of reported penicillin allergy is high, and it has been shown that delabeling patients either by 3-tier testing or direct oral challenge only can be safe. However, even though we have safe practices to delabel patients of penicillin allergy, we must

also have a way to evaluate the effectiveness of our current approaches. When we look at the literature, we can see that reported penicillin allergy has a significant effect on prescription patterns for common pediatric illnesses, which results in increased use of more expensive second-line or inappropriate antibiotics.³¹⁻³³ In addition, even patients for whom penicillin allergy label has been removed can later be relabeled and continue to carry their diagnosis because of incomplete understanding of their testing results or continued parental fear of an allergic reaction despite negative ingestion challenge results.^{8,34} Ultimately, to effectively delabel patients with drug allergy, we must have sustained educational and antimicrobial stewardship programs as well as decision support in the electronic health record to address these other concerns and increase the effectiveness of the initial intervention.

Outpatient Prescription Patterns in Children With Drug Allergy

Children with reported penicillin or drug allergies are often found to have an increase in alternative prescriptions for their

bacterial illness. McGrath et al³¹ evaluated the trends in antibiotic treatment in children with acute otitis media. During this review, they found that the use of broad-spectrum antibiotics to treat otitis media during an 11-year period increased, although there was a high rate of treatment failure. This increased use can be attributed to the rate of reported penicillin allergy and the high utilization of cephalosporins as the first-line alternative. Ultimately, they concluded that this would likely lead to the development of antibiotic-resistant infections. Stille et al³² assessed trends in second-generation macrolide use from 1996 to 2000 in children treated as outpatients in 9 US health plans. They first found that there was a 5.5-fold increase over time in dispensing these antibiotics to children with otitis media, despite literature that called for the use of penicillin to treat these infections. They cited that the prevalence of allergy likely contributed to the use of these second-line agents.

In addition to increased broad-spectrum antibiotic use for otitis media, pediatric patients with pneumonia have also experienced a similar effect. Stille et al³² also found that there was an increase in the use of broad-spectrum antibiotics as initial treatment for

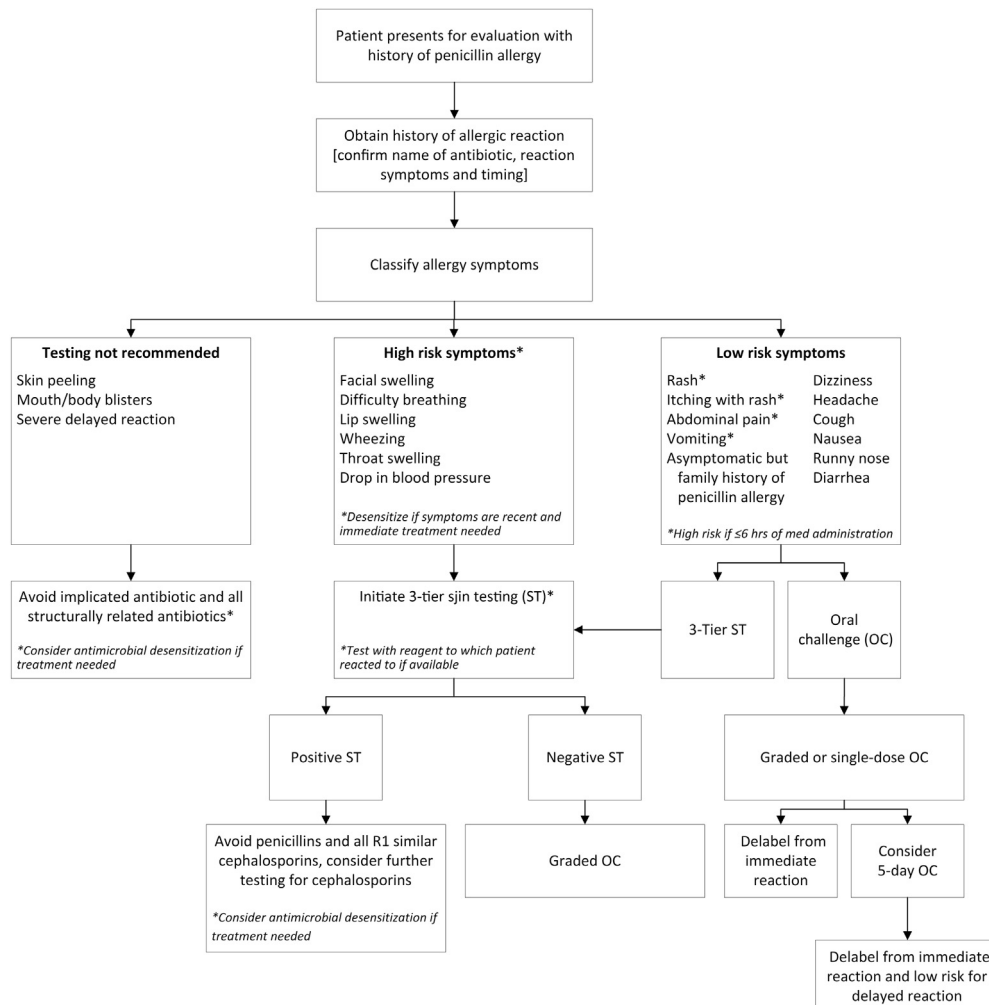


Figure 2. Risk-stratified pathway for penicillin allergy evaluation. Different strategies of evaluation for penicillin allergy are effective in removing the diagnosis of penicillin allergy in children. The first step in a penicillin allergy evaluation is to obtain the history of the allergic reaction, including name of drug, reaction symptoms, and timing. Once a comprehensive history is taken, one can progress down different pathways, including a high- and low-risk pathway along with a pathway in which testing is not recommended. If a patient has low-risk symptoms, then based on the patient's comfort level, a practitioner could perform a 3-tier skin test (ST) or direct oral challenge (OC). The OC options would include a graded, single-dose, or extended-day OC. If a patient has high-risk symptoms (or underwent a skin test for low-risk symptoms), proceeding with an OC depends on the result of the ST and practitioner comfort. In those with negative ST results, a practitioner should move forward with a graded OC. If a positive ST result is obtained, then it is best to avoid penicillins and all R1 similar cephalosporins and consider further testing for cephalosporins. Testing is not recommended in children who have had skin peeling, mouth or body blisters, and severe delayed reactions.

pneumonia among children aged between 3 months and 6 years. Again, the reports of allergy to penicillin likely affected these prescription patterns as well. Desai et al³⁵ found that in a cohort of 47 children with pneumonia, only 10.6% were prescribed amoxicillin at discharge, and the rest were all prescribed second-line alternative agents. Otitis media and pneumonia are common pediatric illnesses for which penicillins are the most appropriate treating agents. Another common bacterial infection in children is urinary tract infections, and much like other previously mentioned illnesses, antibiotic allergy likely has an effect on physician prescribing patterns.^{36,37} Copp et al³⁸ reviewed the ambulatory prescribing patterns for pediatric urinary tract infections and found that physicians commonly prescribed broad-spectrum antibiotics. Factors such as age and height of fever likely contributed to this choice, but antibiotic allergy reporting also had an effect as well.

Another recent study evaluated the prescription patterns in children with reported penicillin allergy from a primary care and pediatric emergency department perspective. Vyles et al³⁹ found that when both of these groups of practitioners were surveyed, pediatric emergency department physicians reported that they would choose a cephalosporin 81.3% of the time when treating a child with reported penicillin allergy.⁴⁰ A group of primary care providers in the same study³⁹ reported they would use a cephalosporin in the same circumstances 98.1% of the time. Puchner et al⁴¹ also found similar findings in their study. They found that physicians were more likely to prescribe cephalosporins in the setting of a history of rash with exposure to penicillin. They also found marked variation in prescribing cephalosporins and in requesting penicillin skin testing in patients with varied histories of penicillin allergy. Both studies ultimately concluded that there is an increased need for penicillin allergy education that may decrease the use of broad-spectrum alternative antibiotics (eg, clindamycin and quinolones) associated with increased drug costs, further adverse events, and generation of antimicrobial resistance.

The Cost of Broad-Spectrum Prescriptions

Multiple studies have found an increased use of broad-spectrum antibiotics in the presence of a penicillin allergy, but what is the actual cost of this to patients and health care systems? Prescription costs are 30% to 40% higher in patients with suspected penicillin allergy.^{7,34,40} If half of the children with reported penicillin allergy who presented with otitis media received amoxicillin instead of cefdinir, the estimated annual savings would exceed \$34 million. Vyles et al⁸ completed a similar analysis and found that the cost savings of removing penicillin allergy label in patients was \$1368.13, the cost avoidance was \$1812.00, and the total potential cost savings for the pediatric emergency department population was \$192,223.00. Macy⁴² found that in 236 patients who underwent penicillin allergy testing, the total cost for antibiotics dispensed decreased 32% from \$17,211.88 to \$11,648.27 along with a reduction of 5.5% in the mean cost per antibiotic.

Antibiotic Use After Removal of Penicillin Allergy Label

With the increased cost (patient and health care network) and potential generation of antibiotic resistance in those who report a penicillin allergy, it is important to also evaluate the effect that allergy delabeling may have on prescription patterns (Fig 2). Picard and Galvão³⁵ reported that both parents and their respective physicians were reluctant to use penicillin-class antibiotics after the penicillin allergy label was removed. In their study of 170 children who had received antibiotics since allergy delabeling, they found that 24 parents (18%) refused these penicillin-class antibiotics because fear of a subsequent allergic reaction. Vyles et al⁸ found a similar trend as well in which 22 of 81 parents surveyed after oral amoxicillin challenge reported that they were only “somewhat

comfortable or not comfortable” in potentially receiving a penicillin antibiotic. The reason often cited was the fear of a subsequent reaction with exposure to the drug. Gerace and Phillips⁴³ also reviewed and characterized this problem as well and noted that one-third of patients retained their penicillin allergy label despite negative test results. They also highlighted that many patients were relabeled as having penicillin allergy after testing despite no new history of adverse event. The examples of these studies and others highlights the real need for sustained antimicrobial stewardship programs.

Antimicrobial Stewardship Programs

With the evidence showing the safety of delabeling and the accumulating evidence of the negative economic, individual, and public health burden of a penicillin allergy label, there is a need to establish strategies and programs to develop feasible, scalable, and effective approaches. The development of an antimicrobial stewardship and decision support program has already been shown to have an impact at select centers.^{44–46} Reported penicillin allergy is a global threat to public health because 8% to 25% of most studied populations report allergy.^{47,48} Across the globe, most reported reactions are similar in that they are often cutaneous reactions unrelated to drug hypersensitivity. Trubiano et al^{49,50} highlighted that antimicrobial stewardship programs increase guideline-concordant antibiotic therapies and that with these programs antibiotic prescribing patterns would likely be improved. Ultimately, there is a great need for these programs, and the use of well-established delabeling strategies could increase the availability and provide scalable penicillin allergy testing approaches. A future area of study through such programs would need to evaluate parental perception of penicillin allergy in children and the best ways to keep a delabeled allergy from returning to the child's medical record and certainly to address this before adulthood, when true antibiotic needs may again be higher. This goal may be achieved through targeted patient interventions that focus on education on allergy along with a better understanding of the low likelihood of any additional reactions on reexposure to medications. However, if we can couple safe testing and targeted patient-practitioner education, we can have a significant effect on reported penicillin allergy.

Conclusion

Penicillin allergy is overdiagnosed, often incorrectly, and the label is frequently first applied during childhood. Targeting children for the removal of penicillin allergy label removal provides a mechanism to reduce a lifelong use of broader-spectrum and less effective antibiotics. It also provides an opportunity to counsel parents in an attempt to reduce unnecessary antibiotic use overall. The 3-tiered approach to penicillin testing has been proved to be safe and effective. It also has an NPV approaching 100% when the appropriate major, minor, and specific (eg, ampicillin) reagents are used. However, there is mounting evidence to support the safety and cost-effectiveness of a direct oral challenge approach in children with low-risk symptoms of allergy. Current and future efforts should focus on (1) targeting children and young adults in delabeling efforts to prevent penicillin allergy labels carrying over into adulthood, (2) maximizing the effectiveness of penicillin allergy strategies by follow-up patient and practitioner education and decision support in the electronic medical record, (3) testing and application of low-risk strategies, such as amoxicillin oral challenge, in low-risk patients, (4) integrating penicillin allergy management into outpatient and inpatient stewardship efforts, and (5) providing government and third-party payer incentives for penicillin allergy delabeling at a population level.

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