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Evaluating Penicillin Allergies Without Skin Testing

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Abstract

Purpose of Review An unconfirmed penicillin allergy is known to confer significant risk to patients. Only a small minority of patients labeled with penicillin allergy will be confirmed to be hypersensitive with the current reference standard test, an oral amoxicillin therapeutic dose challenge. Skin testing has been recommended prior to oral challenges to reduce the risk of severe acute challenge reactions. The rate of severe acute anaphylactic reactions with oral amoxicillin is currently extremely low. Unfortunately, penicillin skin testing, as commonly performed, has a high rate of false positive results.

Recent Findings Encouraging skin testing in all individuals with an unconfirmed penicillin allergy, prior to a confirmatory oral challenge, would be technically difficult, make testing all individuals with an unconfirmed penicillin allergy very unlikely, and ultimately increase the risk to patients because of suboptimal antibiotic use. Most patients, who are appropriate candidates for a direct oral amoxicillin challenge, to confirm current penicillin tolerance, can be safely identified by their clinical histories. Higher risk individuals, those with a history of anaphylaxis or other acute onset potentially IgE-mediated reaction such as hives within 6 h of the first dose of the last course of a penicillin, may benefit from properly performed puncture and intradermal skin testing, using commercially available penicilloyl-polylysine, prior to an oral challenge, if skin test negative.

Summary Direct oral amoxicillin challenges in low-risk individuals are well accepted by patients and a safe and effective part of penicillin allergy delabeling.

Keywords Adverse drug reaction · Antibiotic stewardship program · Amoxicillin · Delabeling · Oral challenge · Drug allergy · Penicillin · Hypersensitivity · Skin testing

Abbreviations

ABIM	American Board of Internal Medicine
ASP	Antibiotic stewardship program
Cdiff	*Clostridiodes difficile*
ED	Emergency Department
FDA	US Food and Drug Administration
KPSC	Kaiser Permanente Southern California
MSSA	Methicillin-sensitive *Staphylococcus aureus*
OC	Oral challenge
SCAR	Serious cutaneous adverse reaction
ST	Skin testing
VRE	Vancomycin-resistant *Enterococcus*

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Introduction

Penicillins are first-line therapy for a wide variety of common bacterial infections, and among the most commonly prescribed and unfortunately overprescribed antibiotic family [1]. An adverse reaction is noted after at least 0.5% of all penicillin administrations and many subsequently will be reported as a penicillin "allergy" in the medical record [2]. Because penicillins were one of the first widely used antibiotics, and drug allergy labels are rarely confirmed or removed, about 7% of the US population, with a higher prevalence in hospitalized populations, women, and the elderly, currently carry an unconfirmed penicillin allergy [3••, 4]. When appropriately tested, more than 95% are shown to be currently tolerant [4]. The reference standard test to confirm current

penicillin tolerance is an oral challenge with a therapeutic dose [5]. Delabeling patients of their reported penicillin allergy benefits the individual patient and public health at large [6•]. An unconfirmed penicillin allergy is associated with an increased incidence of *Clostridioides difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* in both outpatient and hospitalized populations [7, 8•]. Although there is some controversy as to exactly what constitutes a low-risk history, there is currently an international consensus that the history associated with the index reaction should guide the selection of the method used to confirm current penicillin tolerance [9]. The use of oral challenges, without prior skin tests, in children with a history of a non-severe penicillin allergy is safe and effective and becoming the standard of care [10]. The authors now feel that in all low-risk individuals, those without a convincing history of anaphylaxis or a recent acute, potentially IgE-mediated, reaction, direct oral amoxicillin challenges are a safe way to confirm current penicillin tolerance [11]. This review critically evaluates the available literature regarding direct oral challenges to evaluate reported penicillin allergy.

The History of Penicillin Allergy Delabeling Using Primarily Penicillin Skin Testing

In 1942, the first dose of penicillin was administered in the USA [12]. Penicillin's use rapidly expanded in caring for the armed forces during World War II and civilians soon after [4]. Suchecki was able to provide a review of nearly 47 cases of life-threatening allergic reactions to penicillins by 1946 [13]. Since that time, the manufacture and preparation of antibiotic agents, preferred routes and forms of administration, and availability of validated methods for testing and assessing reported allergy have evolved considerably.

The reference standard test to confirm current penicillin tolerance remains a challenge with a therapeutic dose [5]. Penicillin skin testing has been widely performed since relevant antigenic determinants, such as penicilloyl-polylysine (PPL), became commercially available in the 1970s [14]. Descriptions of the use of PPL, native penicillin G, and minor determinant mixes (MDM) in skin prick and intradermal testing were prevalent in the 1990s [15, 16]. The use of in vitro anti-penicillin IgE assays have been promoted, particularly by European investigators, though false positives are common with high total IgE levels, and when tested against reference standard oral challenges, were not found to be clinically useful in screening average risk patients [17–19].

In 1997, we stressed the importance of pre-test probability in the context of performing and interpreting penicillin test results [16]. This highlights the importance of remaining mindful of the difference between adverse drug reactions (ADRs) and potential immunologically mediated hypersensitivity reactions. Over 95% of penicillin-associated ADRs are predictable reactions based on the known pharmacologic or toxic properties of penicillins, or a manifestation of the illness being treated, or mistreated [4]. Less than 5% can be confirmed to be potentially immunologically mediated [4]. Unfortunately, accurate and precise documentation of ADRs is often lacking in the electronic health record (EHR), significantly contributing to the mislabeling of ADRs as penicillin allergies [20].

Even though penicillins are the antibiotic family most associated with anaphylaxis, severe, potentially life-threatening, reactions are extremely rare. Less than 1 in 1000 reported penicillin allergies are due to anaphylaxis when audited. Delayed onset severe cutaneous adverse reactions (SCAR) such as Stevens–Johnson are rarer still with less than 1 in 10,000 reported penicillin allergies even tangentially associated with a SCAR [17, 20]. Fatal reactions after oral penicillin exposures are also extremely uncommon, as evidenced by a review from Great Britain, which identified only one fatality associated with oral amoxicillin use in review of more than 100,000,000 amoxicillin courses administered over 35 years [21].

Drawbacks and Limitations of Skin Testing

While a well-established means of assessing potential IgE-mediated penicillin allergy, penicillin skin testing does have associated limitations that may diminish its role in some or even most patients. We have noted a falling rate of properly performed positive penicillin skin test results from 1995 to 2007, using a complete panel of reagents at appropriate concentrations, penicilloyl-polylysine, penilloate, penicilloate, native penicillin, and amoxicillin, and 5 mm of wheal, with flare greater than wheal, as the criteria for a positive result from 1995 to 2007 [16, 22].

Compounding this issue are changes in the broader literature and clinical practice regarding the interpretation of positive skin result. In Sogn and coworkers landmark paper from 1992, the lowest level positive result, a Class I reaction, was defined as a 4–6 mm wheal, with flare greater than wheal [15]. The FDA-approved packaging from commercially available penicilloyl-polylysine (Pre-Pen®) notes, "A positive reaction consists of the development within 10 minutes of a pale wheal, sometimes with pseudopods, surrounding the puncture site and varying in diameter from 5 to 15mm (or more)." [23] There has been a trend over time to call smaller and smaller wheal sizes positive, including a threshold of as low as 3 mm in some reports [24, 25]. This has led to effects such as the erroneous report that women have positive penicillin allergy test results at 5–6 times the rate observed in males, a finding that disappeared when using 5 mm wheal, with flare greater then wheal, as the criteria for a positive result [22, 24]. Oral

challenge of patients with a remote history of non-life-threatening reactions to penicillins, with a low threshold "positive" penicillin skin test result, was not associated with a greater prevalence of adverse reactions compared to oral challenges in patients with completely negative results [25].

Recent studies have identified alternate mechanisms for both apparent immediate penicillin hypersensitivity reactions and false positive penicillin skin test results. In a murine study, Han et al. elucidated a novel mechanism for histamine release and symptoms consistent with immediate hypersensitivity reactions, but without detectable specific IgE to penicillin [26]. The authors identified activation of the RhoA/ROCK signaling pathway as the mechanism responsible for these findings and affected mice responded to antihistamines and a ROCK inhibitor. Examining intracutaneous testing in penicillin-allergic patients with cutaneous microdialysis, Tannert and coworkers noted that histamine was detected in only 4 of 13 test positive patients, all of whom were challenge positive or had experienced recent anaphylaxis. The authors contend that the lack of histamine release may point to the role of other mediators or cells types other than mast cells [27].

Other studies have also demonstrated the poor predictive value of ST with regard to challenge outcomes [28, 29]. Such findings have spurred interest in direct oral challenges to confirm current tolerance in patients deemed to be low risk by clinical history and other factors.

Recent Results, Direct Oral Challenge Testing

The obvious benefits of delabeling patients with a reported penicillin allergy, the significant number of patients labeled as allergic, and robust data regarding the safety of testing and potential limitations of using penicillin skin testing in low-risk patients have led an increasing number of researchers to examine direct oral challenge (OC) pathways. One of the difficulties has been how to codify and rigorously examine which patients are "low risk." Some features suggested by researchers have included a history of an isolated cutaneous reaction and exposure more than 1 year prior to evaluation [4]. These historical hallmarks have been incorporated by some researchers into patient questionnaires to guide risk stratification and testing (see Table 4) [30, 31].

Some of the earliest authors to suggest direct OC testing applied questionnaires or reviewed data from cohorts that underwent the more typical approach of skin testing (ST) prior to OC. Bourke and coworkers assessed 401 patients with a history of both immediate ($n = 151$) and non-immediate ($n = 250$) reactions. The authors identified history of an immediate type reaction and testing performed within 6 months of a reaction as predictors of a positive skin test and suggested that low-risk patients could be assessed with a direct OC alone [32]. A similar approach and findings can be seen in work by Vyles and coworkers in which a questionnaire was applied to 100 children aged 4 to 18 years, disproving a reported penicillin allergy in all children categorized as low risk. In this study, the authors noted that tools such as questionnaires might readily identify low-risk patients and greatly aid in rapidly clearing reported penicillin allergy in environments such as the Emergency Department [31].

Delayed onset or non-immediate reactions associated with a reported penicillin allergy have been assessed by a number of recent OC protocols. Confino-Cohen and coworkers performed ST on 642 patients with a history of non-immediate reaction and, regardless of results, proceeded to OC (5.3% had positive skin test results and 32.4% equivocal results). Patients then completed a graded initial dose followed by a 5-day course of amoxicillin. Of patients, 1.5% experienced an immediate reaction (7 of 9 had negative ST), which was mild and limited to a rash in all cases and only 6.1% developed mild, delayed reactions at home [33]. Similarly, a pediatric population was assessed using an initial graded OC followed by a 5-day course without prior ST, as long as there was no history of a severe or life-threatening reaction. One hundred thirty children as young as 1 year old underwent OC, and 93.8% passed with only mild cutaneous symptoms noted in those with positive immediate or delayed reactions [34].

An increasing number of studies have also examined the use of graded dose OC or direct, single-dose OC. These studies have been marked by inclusivity of patients assessed, generally only excluding patients with severe or life-threatening reactions. One of the earliest examples was a 2016 study published by Mill and coworkers which assessed 818 children with a mean age of 1.7 years by graded OC and found 94.1% to be tolerant [35•]. This trial was performed because of an inability for the investigators to get commercially available penicillin skin testing reagent in Canada at that time (personal communication with Moshe Ben-Shoshan). They found that 2.1% of children demonstrated an immediate reaction and 3.8% a non-immediate reaction, all of these patients demonstrated mild cutaneous symptoms with the exception of one instance of serum-sickness-like reaction. All children who experienced immediate reactions were skin tested 2–3 months later and only 1 of 17 had a positive ST. [35•] Similar results were seen in a study published earlier this year in which 155 patients ≥ 7 years old completed graded dose OC and only 2.6% developed immediate reactions, all of which were mild [36].

Though less commonly encountered in the literature, a number of researchers have published or presented data for single dose amoxicillin OC. We completed an initial study of 402 Marine recruits, 328 of whom were assessed by 250 mg amoxicillin OC without prior ST. 5 (1.2%) or these patients developed any symptoms related to the OC with four developing cutaneous symptoms alone and the fifth developing globus sensation which was treated conservatively with intramuscular epinephrine [37].

We recently summarized the outcomes of a total of 3299 direct oral challenges, published by 6 groups between 2016 and 2018, and also included some of our own patients [4, 28, 33, 34, 35•, 36, 37]. There were 42 (1.3%) [95% CI, 0.9 to 1.7%] acute positive challenge reactions and 130 (3.9%) [95% CI, 3.3 to 4.7%] delayed positive challenge reactions [4].

Resensitization Risk

Reactions will occur in a small fraction of all individuals receiving any therapeutic antibiotic after negative penicillin allergy testing. Resensitization or new sensitization after a negative penicillin allergy test is very rare. Solensky and coworkers noted no resensitization in a group of 40 individuals exposed to multiple courses of penicillins [38]. New reactions will be reported after about 3% of all subsequent therapeutic penicillin exposures, but resensitization or new immunologically mediated sensitization will occur in less than 5% of these cases [39, 40].

Current Penicillin Hypersensitivity Testing Recommendations

Our current penicillin hypersensitivity testing recommendations are outlined in Table 1.

Higher-risk patients may benefit from puncture and intradermal skin testing with penicilloyl-polylysine, using 5 mm of wheal and flare greater than wheal as the criteria for a positive test [4]. If skin tests negative, an oral challenge is still needed to confirm current tolerance. The use of native penicillin G, particularly if not freshly prepared daily or frozen at − 70 °C can least to elevated rates of false positive skin test results (personal report from staff at ALK). We have not found using native penicillin G is necessary or increases safety [4].

Our Cumulative Clinical Experience Using Direct Oral Challenges as Part of a Penicillin Allergy Delabeling Strategy

At the Walter Reed National Military Medical Center, we have evaluated 478 children and adults using the proposed screening criteria outlined in Table 2, see Table 3 [41].

At the Marine Corps Recruit Depot in San Diego, we have tested an additional 380 recruits using exclusively direct amoxicillin OC, with only three additional positive challenges, consisting of pruritus only (1.1% reaction rate), since our previous publication [37]. Our cumulative experience is displayed in Table 4.

At Kaiser Permanente in San Diego, we have tested 1205 adults and children between January 1, 2017, and December 31, 2018, using the currently recommended criteria outlined in Table 1, some of whom have been included in previous publications, [4] see Table 5.

Table 1 Current penicillin hypersensitivity testing recommendations

Direct oral amoxicillin challenge can be performed in any patients with a history of the following symptoms associated with penicillin occurring more than 12 months ago:

- Any benign rash
- GI symptoms
- Headaches
- Other benign somatic symptoms
- Unknown history

Request allergy to penicillin skin test first if

- The reaction to penicillin has occurred within the past 12 months
- The patient has any history of shortness of breath or anaphylaxis associated with penicillin

and proceed to amoxicillin challenge only if skin test negative

Do not perform any penicillin allergy testing if there is a history of penicillin-associated

- Blistering rash involving ≥ 10% of body surface area with skin loss
- Hemolytic anemia
- Nephritis
- Hepatitis

Discussion

Efficient and effective clearance of a reported penicillin allergy, particularly for the large portion of patients who are of low risk, is an important factor in liberating these often first-line,

Table 2 Proposed screening questionnaire to grade penicillin allergy history risk

Penicillin allergy questionnaire	Yes	No
1. Did your reaction occur within the past year?		
2. Did your reaction involve any systemic symptoms other than a rash or other skin symptoms? If unknown, mark NO.		
3. Was your reaction life-threatening (i.e., severe anaphylaxis requiring epinephrine, Emergency Room visit, hospitalization, intubation)?		
4. Did your reaction involve blistering, ulceration, sloughing of your skin or lining of your mouth, eyes, genitals—OR—diagnosed with Stevens–Johnson syndrome or toxic epidermal necrolysis?		
5. Did your reaction involve any organ dysfunction/failure—OR—were you diagnosed with serum sickness, drug reaction with eosinophilia, acute interstitial nephritis?		

- If the patient has tolerated any penicillins following their initial reaction, they are delabeled and no additional testing is indicated

- If all questions 1–5 are NO, patient is deemed low risk, proceed to oral challenge with 250 mg amoxicillin. Monitor for 1 h

- If any answers 1–3 are YES, patient is higher risk, skin testing recommended and if negative with adequate controls, proceed to 250 mg amoxicillin challenge

- If any answers 4–5 are YES, continued avoidance recommended

Table 3 Walter Reed National Military Medical Center (February 2016 to June 2018)

59 (12.3%) children*, 419 (87.7%) adults	
Ages from 1.5 to 90 years old	
Skin test prior to direct challenge, $N = 151$ (31.6%)	
15 (25%) children, 136 (32%) adults	
Positive	2 (1.3%)**
Negative	149 (98.7%)
Negative oral challenge	147 (97.3%)
Positive oral challenge	2 (1.3%)**
Direct oral challenge, $N = 327$ (68.4%)	
44 (75%) children, 283 (68%) adults	
Negative oral challenge	327 (100%)
Positive oral challenge	0

*≤ 18 years old

**Positive oral challenge following negative skin testing, cutaneous reactions only (2), 3 of 4 patients positive on skin testing or challenge had initial reaction < 12 months prior

narrow spectrum agents. With approximately 32 million Americans labeled as penicillin allergic, the need outstrips available resources and approaches that mandate ST prior to OC in all penicillin "allergic" patients [2, 3••]. The emergence and establishment of antibiotic stewardship programs (ASPs) and the benefits of targeted, responsible antibiotic practice bolster the need to remove the impediment of reported penicillin allergy [42]. Given the significant healthcare benefits and in light of the daunting number of patients labeled as penicillin allergic, a critical need for more efficient methods for assessing and delabeling patients has emerged. Direct OC in those patients who are at low risk for reaction has emerged as a safe, timely, and effective means to delabel these patients' penicillin allergy (Tables 4 and 5).

The structure of recent studies that have examined direct OC in selected patients with a reported penicillin allergy have varied slightly. Salient features of a patient's history such as non-immediate symptoms, cutaneous-only symptoms, and a more remote history of reaction are often shared across study groups and provide a working template for broader clinical implementation of direct OC assessment of patients. As highlighted above, widely applied ST approaches unnecessarily retain penicillin allergy labels through false positive results and poor correlation with OC. In the absence of enhanced patient safety or risk stratification, unfocused ST penalizes patients who might otherwise be successfully delabeled. Direct OC assessments in low-risk patients definitively address the question of penicillin allergy while circumventing the issues highlighted with broad use of ST in labeled patients.

The benefits of OC extend beyond initial clearance to the persistence of delabeling in the medical record and in patients' willingness to embark on future beta-lactam antibiotic courses. Early in the development of ASPs, Rimawi and

Table 4 Marine Corps Recruit Depot, San Diego (July 2014 and September 2018)

708 male Marine recruits, ages 17 to 28

Characteristic	*N* (%)
Inciting medication	
Penicillin	487 (68.8%)
Amoxicillin	180 (25.4%)
Other or unknown	41 (5.8%)
Reaction type	
Cutaneous (low risk)	531 (75.0%)
Gastrointestinal (low risk)	6 (0.8%)
Unknown (low risk)	156 (22.0%)
Multisystem or respiratory (higher risk)	15 (2.1%)
Age at reaction	
< 1	264 (37.3%)
1–6	202 (28.5%)
7–12	79 (11.2%)
> 12	29 (4.1%)
Unknown	134 (18.9%)
Direct oral challenge	708
Negative oral challenge	700 (98.9%)*
Positive oral challenge	8 (1.1%)

*All patients with a negative oral challenge received and tolerated intramuscular penicillin G benzathine

coworkers noted the poor translation of negative ST results to removing a reported allergy from healthcare records [43]. Other studies have demonstrated similar findings [44, 45]. By contrast, the use of OC has been shown to be effective in efficiently clearing a reported allergy and translating into

Table 5 Kaiser Permanente San Diego (January 1, 2017, to December 31, 2018)

- 1205 children and adults
  - 399 (33.1%) had penicillin skin testing first
    - 6 (1.5%) skin test positive
    - 7 (1.8%) acute oral challenge positive after negative skin testing*
    - 1 (0.3%) delayed oral challenge positive**
    - 16 (4.0%) subjective oral challenge reactions
  - 806 (66.1%) had direct oral amoxicillin 250 mg challenge
    - 2 (0.2%) acute oral challenge positive*
    - 9 (1.1%) delayed oral challenge positive**
    - 23 (2.9%) subjective oral challenge reactions
  - Overall 25 (2.1%) positive
    - 15 (1.2%) acutely positive (IgE-mediated)
    - 10 (0.8%) delayed-onset positive (T cell-mediated)
    - 39 (3.2%) subjective oral challenge reactions

*$p = 0.0072$;**$p = 0.1799$. None of the acute reactions were serious, and all were managed with oral antihistamines or intramuscular adrenaline. None of the delayed reactions were serious. Acute subjective reactions were more common than acute objective reactions ($p = 0.0008$)

future use of beta-lactam antibiotics [6, 46]. Most recently, researchers from Israel published data demonstrating the use of a penicillin subsequent to successful OC in 70% of patients and in the remainder who did not use a penicillin, the main reason was typically a lack of clinical indication to use these agents [46]. We have noted that a 1-day challenge results in low rates of adverse reactions with subsequent exposures [6•].

Conclusions

Using other non-commercially available skin test reagents for penicillin skin testing leads to an increased number of false positive results and no improvement in overall safety. Recommending the routine use of native penicillin or minor determinants, such as penilloate or penicilloate, inhibits all testing because of the difficulty of both obtaining these unstable reagents and properly preparing and storing them. Direct oral challenge with amoxicillin obviates these drawbacks, and growing data has helped support key historical features to specifically identify patients at low risk. These patients represent the vast majority of those with a reported penicillin allergy and can be safely and successfully delabeled by direct oral challenge. To date, most reports using direct oral challenge for penicillin delabeling have been published by groups with allergists as authors or coauthors. We are looking forward to reports on this topic from non-allergists.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest EM is a partner in the Southern California Permanente Medical Group. EM has received research support from the Southern California Permanente Medical Group, grants from ALK Abello, Inc. to study adverse drug reactions, and has served on clinical trial safety and monitoring committees for BioMarin, Ultragenyx, and Audentes.

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