

Direct oral amoxicillin challenge without preliminary skin testing in adult patients with allergy and at low risk with reported penicillin allergy

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ABSTRACT

Introduction: Ten percent of hospitalized patients report penicillin allergy; however, recent studies indicate that ~98% of these patients are not acutely hypersensitive. Unconfirmed penicillin allergy poses public health risks, and an evaluation of penicillin allergy labels is recommended to improve antibiotic stewardship. Although the most widely accepted protocol is penicillin skin testing, followed by oral amoxicillin challenge, time constraints and resources may preclude this. Recent literature supports the safety and efficacy of direct oral amoxicillin challenge in individuals at low risk.

Methods: We retrospectively evaluated direct oral challenge acceptance and outcomes in eligible adult outpatients with allergy and with a penicillin allergy label over a 6-month period. Direct oral amoxicillin challenge was recommended in patients with a history of benign rash, benign somatic symptoms, or unknown history associated with the last penicillin exposure >12 months ago. Those with severe reactions or reactions within 12 months of evaluation were not challenged. The patients were monitored for 60 minutes after challenge and were discharged with instructions to call in the event of a delayed reaction.

Results: There were 50 of 355 adults (14%) with a penicillin allergy label seen by a single allergist; of these patients, 38 (76%) met our criteria for a direct oral challenge. The index penicillin associated reactions were mostly remote, and 44 subjects (88%) reported reactions >10 years earlier. Four patients (8%) were de-labeled based on history alone. Twenty subjects (40%) consented to challenge in the clinic, and none developed immediate, or to our knowledge, delayed hypersensitivity reactions. Three of 20 patients (15%) developed self-limited subjective symptoms that were not deemed to constitute true immunoglobulin E mediated hypersensitivity. A total of 24 patients (48%) had the penicillin allergy label removed from their medical record.

Conclusion: This study added to the accumulating body of evidence that supports the safety and efficacy of direct provocative challenge without preliminary skin testing to exclude penicillin allergy in individuals at low risk. Larger prospective studies are necessary to confirm these observations.

(Allergy Asthma Proc 40:57–61, 2019; doi: 10.2500/aap.2019.40.4184)

Addressing penicillin allergy has emerged as a public health issue because erroneous labels are associated with significant clinical and economic consequences. Despite a prevalence of 10%, multiple recent U.S. studies indicate that ~98% of these patients who report penicillin allergy are not truly allergic and could safely receive penicillin.¹ The impact of penicillin allergy labels may be reduced by improving the accuracy of antibiotic allergy reporting in combination with multidisciplinary “de-labeling” approaches. In the context of the recently launched national antibiotic stewardship initiative, there is even more of an impetus to perform routine penicillin skin testing (PST) to aggressively de-label penicillin allergy.

Despite these recommendations, annually, only a fraction (<0.1% of 25 million) of patients with penicillin allergy are evaluated for this diagnosis.² This may be secondary to constraints of time, personnel, and other resources. Oral drug provocation testing (DPT) remains the criterion standard to rule out a clinically significant immunoglobulin E (IgE) mediated penicillin allergy. There is a body of emerging data about the safety of direct oral challenge, without preliminary skin testing, to confirm current penicillin tolerance, in individuals at low risk,^{3–7} with extremely low rates of acute reaction to DPT. Our objective was to bolster the accumulating evidence that supports direct DPT in subjects who report a low-risk history of penicillin allergy. We conducted a retrospective review of 50 adult allergy outpatients with a penicillin allergy label seen by a single allergist (MK) and evaluated outcomes of DPT in those with a remote history of benign, delayed hypersensitivity to penicillin.

METHODS

This was an institutional review board approved observational retrospective review of the routine care

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No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article
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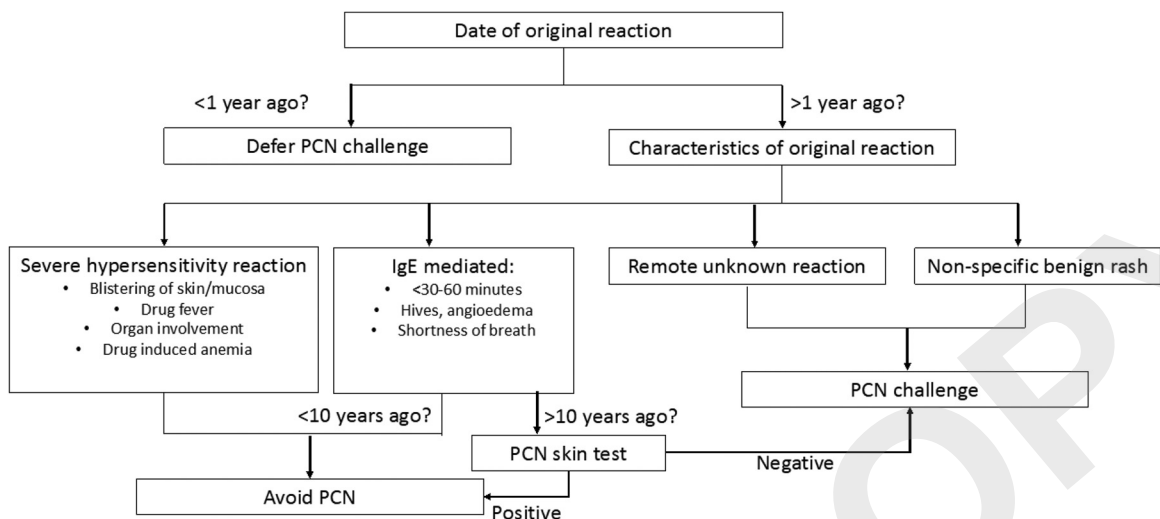


Figure 1. Screening algorithm to determine candidacy for direct amoxicillin challenge.

provided in an outpatient allergy clinic affiliated with Emory University Hospital (IRB00104902).

Identification of Subjects

The drug allergies noted in the electronic medical record (EMR) of all adult outpatients treated by a single allergy/immunology physician (MK) between January 1, 2018, and June 30, 2018, regardless of presenting diagnosis, were reviewed. The study subjects consisted of all patients with an incidental record of penicillin allergy, which was defined as any penicillin class antibiotic allergy entry in the drug allergy section of the EMR.

Criteria for DPT

The current standard of care in our allergy department is to obtain an in-depth penicillin allergy history in all patients labeled with a penicillin allergy. Eligibility for DPT was confirmed based on a standardized algorithm outlined in Fig. 1. Challenges were performed only after careful risk stratification based on the clinical history. We offer direct oral amoxicillin challenge to patients with a history of benign rash or benign somatic symptoms, or another unknown history associated with their last penicillin exposure if it occurred >12 months ago. We do not offer DPT if there is recent reaction within 12 months, a history of a penicillin-associated blistering rash, hemolytic anemia, or organ involvement. An inability to provide informed consent and ongoing ingestion of oral antihistamines or steroids were other exclusion criteria. In addition, patients whose original reaction was only gastrointestinal upset, and those who had uneventfully received penicillin since the original label with penicillin allergy, were de-labeled based on history and not offered DPT.

Oral Provocation Testing

A same-day DPT with a single dose of oral amoxicillin 500 mg was performed in eligible patients after obtaining informed consent. The patients were observed for 60 minutes after the therapeutic dose. Vital signs were taken and physical examination was performed at baseline and every 30 minutes. Isolated itching or dizziness associated with oral challenge, without other associated objective findings, such as rash or change in vital signs, were not deemed as constituting positive challenge reactions but were recorded. For patients with an uneventful DPT, the penicillin allergy label was removed from the EMR. The patients were warned about the possibility of a delayed reaction and were advised to contact the clinic in the event of a delayed rash.

RESULTS

Results of the study are summarized in Fig. 2. A total of 355 unique adult outpatients were seen by the allergist (MK) during the study period. The prevalence of penicillin allergy labels in this cohort was 14% (50 patients).

Demographic and Clinical Characteristics

Study subjects' demographics and clinical characteristics are presented in Table 1. The median age was 59 years (range, 18–81 years), and 40 were women (80%). The top five primary presenting diagnoses were chronic rhinitis (30%), asthma (32%), drug allergy (16%), food allergy (8%), and urticaria (10%).

Characteristics of Penicillin Allergy

Forty-four patients (88%) reported that >10 years had elapsed since their reactions. Only one patient

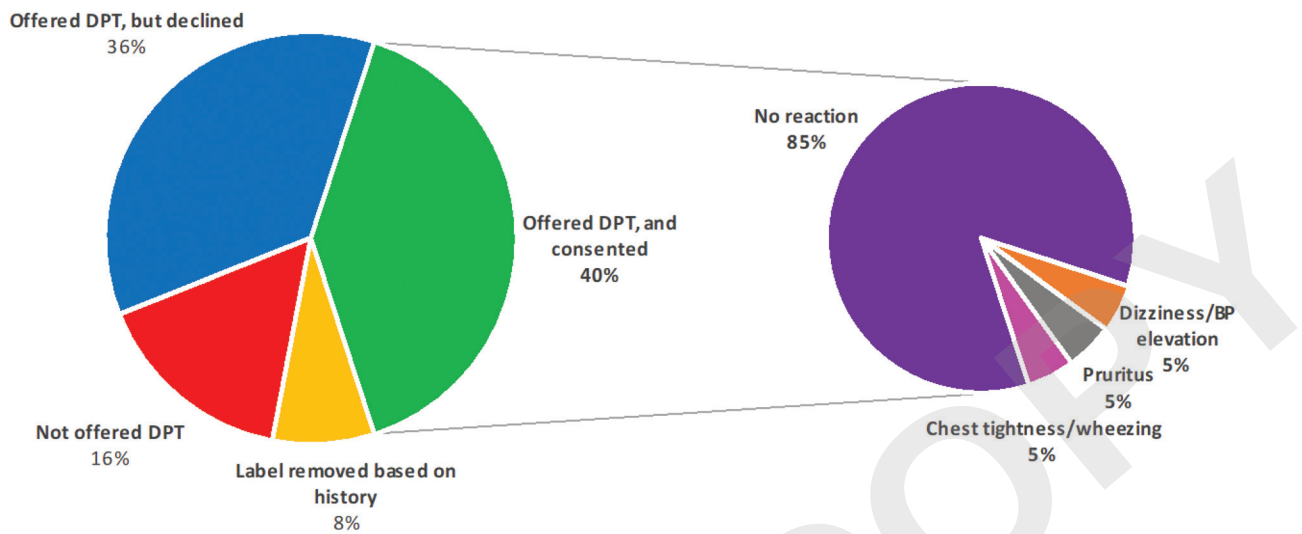


Figure 2. Summary of patient outcomes.

Table 1 Demographics and clinical characteristics (N = 50)

Women, no. (%)	40 (80)
Age, median (range), y	59 (18–81)
Index reaction, no. (%)	
>10 y	44 (88)
1–10 y	5 (10)
<1 y	1 (2)
Underlying presenting diagnosis, no. (%)	
Chronic rhinitis	15 (30)
Asthma	16 (32)
Drug allergy	8 (16)
Food allergy	6 (12)
Urticaria	5 (10)

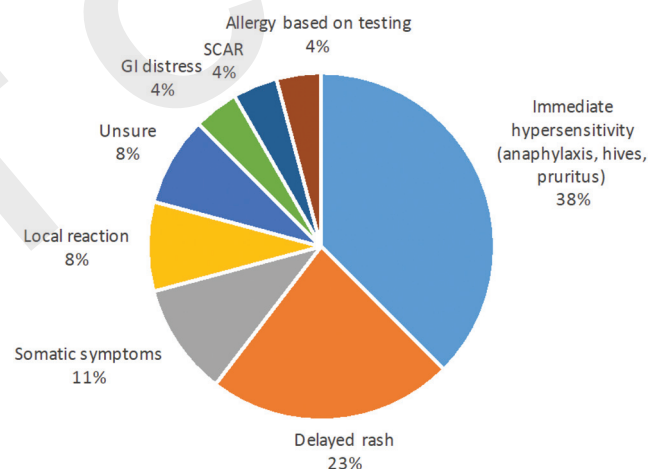


Figure 3. Characteristics of index reaction to penicillin.

described a reaction within the previous 12 months. Historical reactions were predominantly reported as urticaria, rash, or unknown reaction and are outlined in Fig. 3. Approximately 50% of the patients reported immediate onset reactions. Most patients could not recall specific penicillin or the route of administration responsible for the reaction. Seventeen patients (34%) had concomitant multiple drug allergy syndrome, defined as intolerance of more than three (including penicillin) unrelated medication classes.

Outcomes of Drug Challenges

Five patients (10%) did not meet criteria for DPT (four patients due to ongoing ingestion of antihistamines for chronic urticaria at the time of the visit and one patient due to recent reaction within the past year) and were excluded from participation. A total of three patients (6%) were excluded from undergoing DPT due to a history of blistering rash. The penicillin allergy

label was removed from charts of four patients (8%) based on history alone (two patients because a penicillin antibiotic had subsequently been tolerated after the original reaction, and in the other two due to an isolated history of gastrointestinal upset). Thirty-eight patients (76%) met the criteria for DPT; 20 (40%) consented to challenge. Eighteen (36%) declined challenge at the index visit. Nine of these 18 patients (50%) who were offered but declined DPT did so due to apprehension about a recurrent reaction despite qualifying per the algorithm. Time constraints were the reason most others declined.

More than half of the patients offered in-office challenge at the index visit (20 of 38 patients [53%]) were amenable to the procedure. There were no IgE-mediated reactions during DPT in any patient. Three patients (15%) developed subjective adverse reactions during DPT, but these were not considered positive challenges. These subjective reactions were manifested as diffuse pruritus, chest tightness, and dizziness, each

individual patient respectively. All of these reactions spontaneously resolved within minutes, and no treatment was administered. The outcomes of DPTs are outlined in Fig. 2. The patients were advised to contact the office *via* the nurse telephone line in the event of a delayed reaction, and there were no such reports. All the patients who were found to be acutely tolerant of penicillin, as well as those deemed to have an erroneous allergy label, had their allergy profiles updated to reflect the results. A total of 24 patients (48%) with a penicillin allergy label were thus de-labeled at the index visit.

DISCUSSION

The main findings of this retrospective study were the following: in this study of 38 patients deemed at low risk for true penicillin allergy and qualified for DPT, more than half consented to drug challenge with a full therapeutic dose of amoxicillin. None developed evidence of an immediate IgE-mediated type of reaction, and there were no reports of delayed hypersensitivity reactions. Subjective reactions were observed in 15% of the patients, but these were not constituted as a positive result of challenge. Forty-seven percent of the patients declined challenge at the index visit. The main reasons for refusal was uncertainty that penicillin could be safely ingested and the inability to wait out the 60-minute monitoring period.

In recent years, it has become apparent that up to 98% of patients labeled as penicillin allergic are found to be tolerant of penicillin.¹ Combined with the substantial clinical and economic consequences of a penicillin allergy label, this has driven current guidelines that encourage routine penicillin allergy verification in all patients with this diagnosis. Our protocol, as outlined in Fig. 1, is based on the recent growing body of evidence that explores the safety of direct oral challenges without antecedent skin tests in patients with a history of a low risk of true penicillin allergy. With or without careful selection, the vast majority of direct penicillin challenges in the literature had negative results. Tucker *et al.*⁶ reported outcomes in a cohort of 328 Marine recruits, only 5 (1.5%) of whom had immediate reactions during amoxicillin challenges.

A 5-day oral challenge protocol without preliminary PST was evaluated in a pediatric study of 130 children with previous non-immediate reactions to penicillin.⁷ Only six patients (4.6%) experienced mild reactions, of which, approximately half were delayed. Yet another pediatric study assessed the safety of DPT with amoxicillin in 818 children with a history of cutaneous reactions to penicillin.⁴ There were 17 immediate (2.1%) and 31 delayed (3.8%) reactions, all of which were mild. Most recently, Iammatteo *et al.*³ reviewed the outcomes of 155 direct amoxicillin challenges and

found a reaction rate of 2.6%. The absence of any reactions in our study may be attributed to exclusion of the patients with recent labels of penicillin allergy as well as the small study numbers.

The routine evaluation of all patients with a penicillin allergy label is increasingly being implemented in the outpatient setting. Ramsey and Mustafa⁸ recently described a penicillin allergy de-labeling strategy for outpatient allergists, which consisted of PST followed by oral challenge. If 58 of the 66 patients in this report, the PST results were negative and underwent uneventful challenge.⁸ Temino *et al.*⁹ implemented a similar policy in the outpatient setting; in 38 of 40 patients, the PST results were negative, with only one patient who experienced a delayed rash after challenge.

We chose to forego PST in our protocol due to the inherent limitations with this procedure. PST results are only useful in the setting of IgE-mediated allergy and offer no predictive value for non-IgE mediated reactions that account for the vast majority of patients with penicillin allergy. Analysis of emerging data indicates that a positive PST result does not necessarily equate with challenge reactions. There also seems to be a poor correlation between a positive oral challenge and PST and/or *in vitro* results. Sixty percent of the patients with a positive PST result had a negative challenge result to the culprit penicillin in a recent study.¹⁰ Several other studies also reported negative challenge results in patients with a positive skin test result and *vice versa*.^{5,11,12} Positive PST results may be transient and can resolve within a few months.¹³ In addition, PST may be prohibited in some settings by personnel, time, and/or other resource constraints. There has also been concern regarding the need for either a minor determinant mixture or amoxicillin as reagents for PST¹⁴; neither of these are currently commercially available in the United States.

A major limitation of the present study is that it was conducted by a single allergist (MK) in one center, and thus the results are not generalizable. The risk of direct challenge is unlikely to be shown in small samples. Further, concerns exist as to whether a single therapeutic dose of amoxicillin is sufficient to confirm or rule out clinically significant delayed hypersensitivity to penicillin. Although the patients were instructed to contact the clinic, delayed findings, if they occurred, had the potential to be missed. Also, this approach should be confined to health-care settings by clinicians with the knowledge, training, and experience to select patients at appropriately low risk for the procedure and who are comfortable with management in the unlikely event of a systemic allergic reaction.

Also, most of the data that support DPT originated from single-center studies. This approach of DPT without antecedent skin testing, pending further multi-institutional studies with larger cohorts, should be con-

sidered only in patients with a history of mild cutaneous reactions or similarly benign symptoms. Despite these limitations, our study group was quite heterogeneous in terms of demographics and comorbidities, which supported the effectiveness and applicability of this protocol. Although a severe reaction history warrants an extremely cautious and stepwise approach, a simple and streamlined protocol might be appropriate for most patients at lower risk.

CONCLUSION

The approach of offering DPT to selected patients at low risk regardless of the presenting chief concern seemed to be part of an effective strategy to de-label penicillin allergy in an outpatient allergy setting.

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