

Efficacy and Safety of 5-Day Challenge for the Evaluation of Nonsevere Amoxicillin Allergy in Children



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What is already known about this topic? Penicillin allergy is the most commonly reported drug allergy and is associated with unfavorable medical and socioeconomical outcomes. Despite a negative allergy evaluation, a significant proportion of patients continue to avoid penicillin antibiotics.

What does this article add to our knowledge? The 5-day challenge to amoxicillin in children with a history of nonsevere amoxicillin allergy is a safe and effective method to diagnose and delabel their allergy, and it leads to a higher proportion of future penicillin use.

How does this study impact current management guidelines? The 5-day challenge to amoxicillin should be considered in this selected pediatric population, because it may reduce the socioeconomical burden associated with the unnecessary avoidance of these antibiotics.

BACKGROUND: Penicillin allergy is the most frequent drug allergy, among which aminopenicillins are reputed for causing delayed rashes in children, particularly in the context of viral infections. Despite a negative allergy evaluation, a significant proportion of individuals continue to avoid penicillin antibiotics for fear of an allergic reaction.

OBJECTIVE: To evaluate the safety and efficacy of a 5-day challenge to amoxicillin and the proportion of subsequent use of amoxicillin.

METHODS: Pediatric patients with a history of a reaction to amoxicillin were prospectively recruited in the study. All patients were challenged, and those with negative immediate challenges underwent an ambulatory 5-day challenge to amoxicillin to rule out nonimmediate reactions. Patients were called 2 years after their initial allergy evaluation to assess subsequent amoxicillin use and tolerance.

RESULTS: One hundred thirty children with a history of amoxicillin allergy underwent a graded drug provocation test (DPT) to amoxicillin. Three patients had a positive immediate challenge, 3 had a positive nonimmediate challenge, and 2 were equivocal. Of the 122 patients with a negative challenge, 114 (93.4%) were reached 2 years after their initial allergy evaluation: 75 had used antibiotics since, of which only 1 (1.3%) had refused to reuse amoxicillin because of fear of an allergic reaction. Finally, the 5-day DPT resulted in a 24.1% decrease in future penicillin avoidance compared with classical single-dose graded DPT performed for 1 day in a historical cohort ($P < .0001$).

CONCLUSION: The 5-day challenge is a safe and effective way to rule out nonimmediate amoxicillin allergy, and it ensures better compliance with future penicillin use. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1673-80)

Key words: Allergy; Amoxicillin; Challenge; Hypersensitivity; Pediatric; Prolonged challenge; Resensitization

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INTRODUCTION

Penicillin hypersensitivity is estimated to affect up to 10% of the population, and remains the most common antibiotic allergy.¹ Among penicillin antibiotics, amoxicillin is listed in the United States and Canada as first-line treatment for most bacterial infections affecting the respiratory tract in children, including pneumonia, otitis media, and sinusitis.²⁻⁴ Therefore, it should be no surprise that amoxicillin and amoxicillin/clavulanate are accountable for most hypersensitivity reactions to penicillin antibiotics in the pediatric population.⁵⁻⁷

The diagnosis of drug hypersensitivity can be classified into immediate and nonimmediate reactions.⁸ Immediate

*Abbreviations used**DPT- Drug provocation test*

hypersensitivity reactions occur within the first hour of treatment and are mediated by the development of specific IgE targeting penicillin epitopes.⁹ Nonimmediate reactions are thought to be induced by a T-cell–dependent mechanism, and usually develop after an hour following drug administration.¹⁰ With amoxicillin, nonimmediate reactions are more frequent and usually occur as mild maculopapular rash.^{11,12}

Only a minority of people reporting a history of amoxicillin hypersensitivity will exhibit positive reactions upon formal allergy testing.^{13,14} Therefore, allergy evaluation is important because it significantly reduces the burden associated with an inaccurate amoxicillin allergy diagnosis, which also influences the use of other penicillin antibiotics. Indeed, these patients may receive alternative drugs leading to suboptimal medical care because of reduced efficacy. Conversely, hospitalized patients may unnecessarily receive broad-spectrum antibiotics, which are associated with greater costs, increased rates of multiresistant bacteria, and poorer outcomes.¹⁵⁻¹⁸

Skin testing remains the criterion standard for ruling out amoxicillin allergy followed by drug provocation test (DPT).¹⁹ Nevertheless, studies have shown that despite a negative allergy evaluation with skin testing, as much as half the patients will continue to avoid penicillin antibiotics because of fear of a new allergic reaction.²⁰ As a matter of fact, a recent study conducted in our center revealed that a quarter of pediatric patients or their physicians will be reluctant to use penicillin antibiotics even after a negative DPT result.²¹ This phenomenon could be explained by the high prevalence of nonimmediate reactions occurring after the first day of treatment in these children, circumstances that are not completely assessed with standard 1-day DPT.²² Indeed, literature has emerged in the past decade regarding prolonged challenges to better detect nonimmediate penicillin antibiotic allergies in both pediatric²³⁻²⁵ and adult²⁶⁻²⁸ populations. These studies, however, were largely led in Europe, and little is known about the impact of prolonged challenges in North American populations.

In this study, we hypothesized that the use of a 5-day challenge with amoxicillin would not only be safe and effective in a North American setting but would also lead to an increase in future amoxicillin use in nonallergic patients when compared with single-dose graded DPT.

METHODS

Study design

From December 2013 to June 2015, we conducted a prospective study in the outpatient allergy unit of the pediatric tertiary care hospital CHU Sainte-Justine, Canada. Pediatric patients younger than 18 years and referred by physicians for a history of amoxicillin or amoxicillin/clavulanate allergy were recruited in a consecutive manner. On the basis of their chart and self-reported reactions, patients with a history of life-threatening IgE-mediated allergy (anaphylactic shock) or severe non-IgE-mediated allergy (Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, or any end-organ damage) were excluded from the study.

TABLE I. Patient characteristics of the 5-day challenge group at first visit

Characteristic	N = 130
Age (y)	
Mean	5.1
Range	0.7-17.0
Sex, male, n (%)	68 (52.3)
Ethnicity, n (%)	
Caucasian	90 (69.2)
North African	9 (6.9)
Latino	5 (3.8)
Other	12 (9.2)
Missing	14 (10.8)
Personal history of atopy, n (%)	
All	56 (43.1)
Atopic dermatitis	36 (27.7)
Allergic rhinitis	22 (16.9)
Asthma	25 (19.2)
Food allergy	3 (2.3)
Personal history of other drug allergy, n (%)	18 (13.8)
Family history of drug allergy, n (%)	40 (30.8)
Molecule of initial reaction, n (%)	
Amoxicillin	118 (90.8)
Amoxicillin/clavulanic acid	7 (5.4)
Presumed amoxicillin	5 (3.8)
Allergic reaction, n (%)	
Rash	130 (100.0)
Urticaria	46 (35.4)
Maculopapular rash	75 (57.7)
Macular rash	7 (5.4)
Undefined rash	2 (1.5)
Angioedema	8 (6.2)
Cough/bronchospasm	1 (0.8)
Vomiting	2 (1.5)
Anaphylaxis	0 (0.0)
Timing of allergic reaction, n (%)	
Within 24 h	26 (20.0)
After 24 h	99 (76.2)
Unknown	5 (3.8)
Time (y) elapsed between initial reactions and allergy workup, mean (range)	2.8 (0.1-14.0)

The study was divided into 3 phases: an initial evaluation at the outpatient allergy unit followed, if negative, by a 4-day ambulatory course with amoxicillin and, finally, a phone call follow-up 2 years after the initial evaluation. These data from this study were then compared with data from a previous but clinically similar group from our institution in which we performed only a single-dose graded DPT with penicillin V.²¹ The study was approved by the Ethics Committee of CHU Sainte-Justine, and written consent was obtained from patients or caregivers before enrollment in the study.

Initial evaluation: DPT

The patients were first assessed at the outpatient allergy unit at least 6 weeks after the index reaction. Demographical and clinical information, including personal and family history of atopy, the

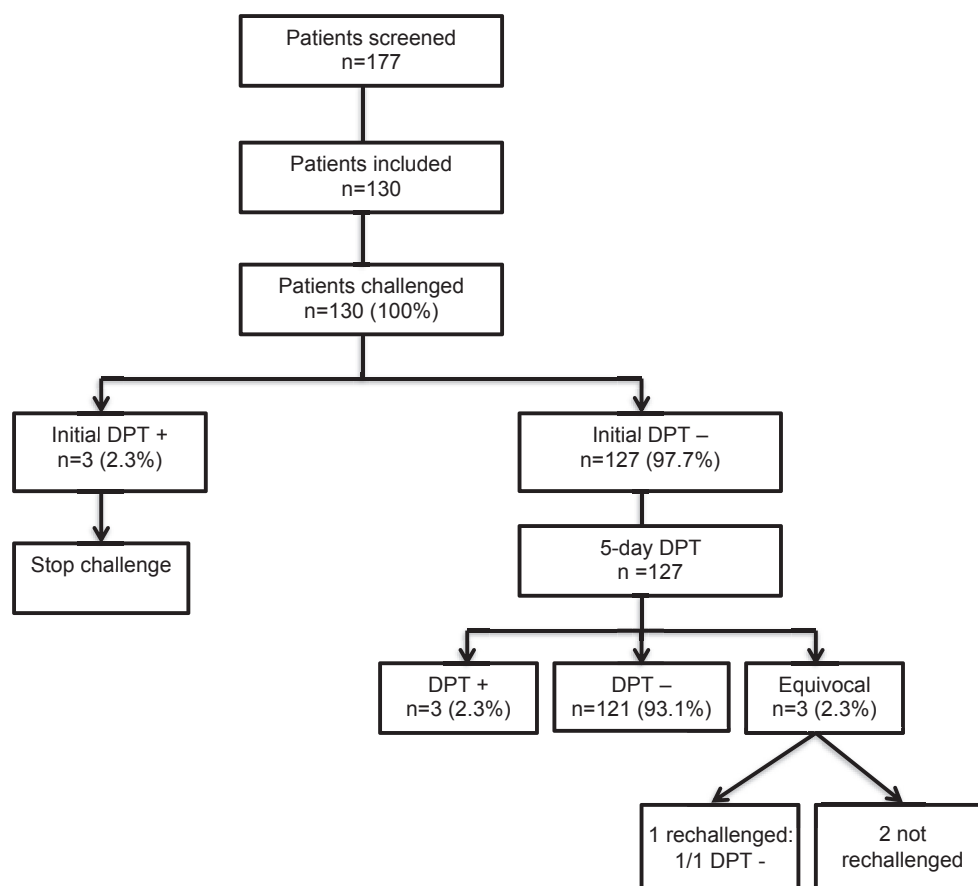


FIGURE 1. Drug provocation results.

TABLE II. Description of positive challenges

Patient	Positive challenge	Time between first dose and reaction	Reaction
Patient 1	Immediate	30 min	Urticaria and angioedema
Patient 2	Immediate	55 min	Urticaria
Patient 3	Immediate	30 min	Urticaria
Patient 4	5-day challenge	72 h after end of challenge	Papular rash of whole body
Patient 5	5-day challenge	72 h	Maculopapular rash of whole body
Patient 6	5-day challenge	48 h	Maculopapular rash of torso and limbs

culprit drug involved, timing of the reaction, and presenting signs and symptoms, was collected. Parental anxiety level at the time of the reaction was also assessed using a 4-item Likert-type scale of anxiety, ranging from low to extreme level. The allergist collected this information directly from the patients' caregivers using study case report forms.

All the participants underwent a single-dose graded DPT with amoxicillin (45 mg/kg/dose) in 3 steps: 1/100, 1/10, and full dose at 30-minute intervals. This was performed independently of skin tests that were performed in a double-blinded manner as previously described²⁹ using placebo, active extract, and positive controls in a random order to prevent any influence on interpretation of DPT results by patients or investigators or on subsequent use of penicillin antibiotics. Skin test results remained blinded at this phase of analysis.

Ambulatory challenge

To discard nonimmediate reactions, patients with negative initial DPT result were sent home with a therapeutic 4-day ambulatory course of amoxicillin (45 mg/kg/d) for a total challenge duration of 5 days. All patients were called at the end of the challenge to confirm compliance with the challenge and to document the occurrence of any reactions or adverse effects.

Two-year follow-up

Patients with negative challenges were called 2 years after their initial allergy evaluation to assess subsequent amoxicillin use and tolerance. For those patients having used antibiotics other than amoxicillin (or other penicillin antibiotics), the reason for using a nonpenicillin antibiotic and the willingness to use amoxicillin again if needed were assessed. These data were

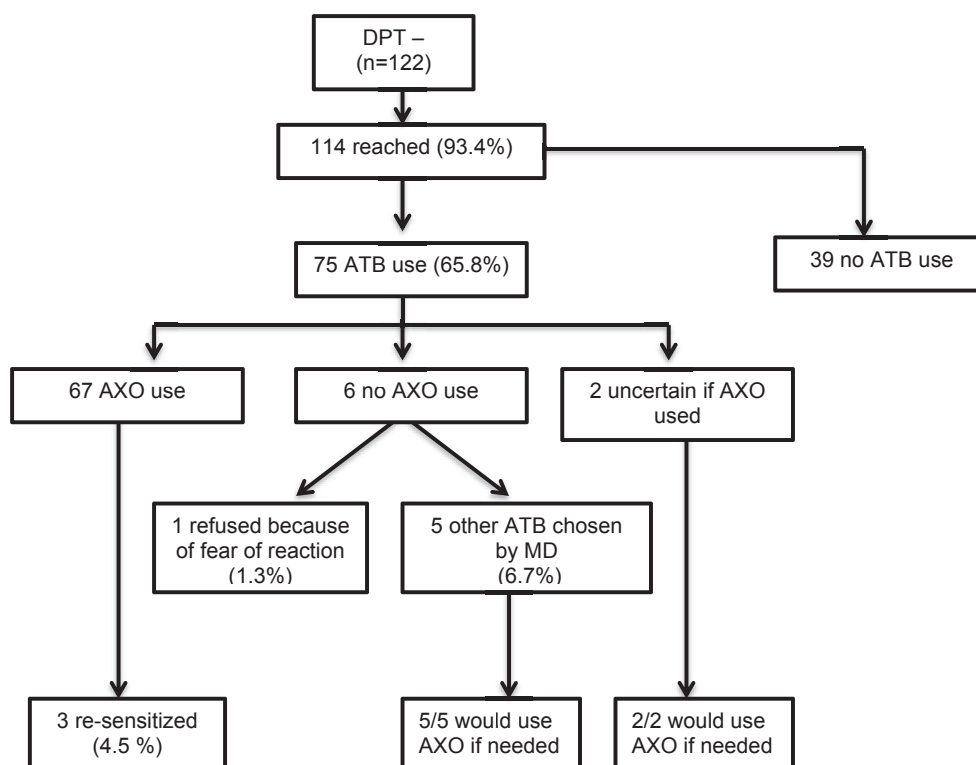


FIGURE 2. Amoxicillin subsequent use after negative DPT result. *ATB*, Antibiotic; *AXO*, amoxicillin; *MD*, physician.

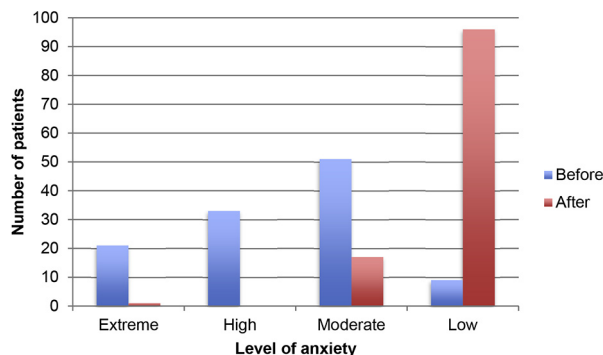


FIGURE 3. Level of parental anxiety at initial reaction (before) compared with present level of anxiety after allergist evaluation and 5-day challenge (after).

collected according to caregivers by using a telephonic follow-up questionnaire, and information was cross-checked with the patient's records and pharmacist in cases when caregivers were unsure.

Statistical analysis

The chi-square test was used to perform analysis of categorical variables, and mean values between groups were compared using the Student *t* test. A *P* value of less than .05 was defined as statistically significant.

RESULTS

Patient characteristics

Between December 2013 and June 2015, 177 pediatric patients were screened for participation, of which 130 were enrolled. No patient was excluded and the main reason for refusal among the 47 nonparticipants was lack of interest or time. Characteristics of the patients included are presented in Table I. Mean age at first medical visit was 5.1 years (range 0.7-17.0), and 52.3% were boys. On average, 2.8 years had elapsed between their index reaction and the initial evaluation.

Amoxicillin and amoxicillin/clavulanate were the culprit drugs in 90.8% and 5.4% of patients, respectively. In 5 patients (3.8%), the culprit drug was not identified, but because of age, indication, and local practice it was presumed to be amoxicillin. A history of a reaction happening within the first 24 hours of treatment was present in 20.0% of patients, whereas 76.2% of reactions happened after more than 24 hours of treatment. The timing of the reaction was missing in 3.8% of patients. Children mostly had a history of maculopapular rash (57.7%) or urticaria (35.4%). About 30.8% of the patients had a family history of drug allergy (mostly penicillin), 13.8% had multiple drug allergies, and 43.1% had a personal history of atopy, which included atopic dermatitis, allergic rhinitis, asthma, and/or food allergies. Finally, almost half the parents (48.3%) had been very or extremely frightened by their child's initial allergic reaction.

Initial evaluation: DPT

All 130 patients underwent a DPT on their initial visit (Figure 1). Of these, 3 patients (2.3%) had an immediate

TABLE III. Penicillin resensitization after negative 5-day challenge

Patient	5-day challenge	Number of amoxicillin courses tolerated since evaluation	Incriminated drug	Reaction
Patient 7	Negative	0	Amoxicillin	Urticaria at day 9
Patient 8	Negative	0	Amoxicillin	Mild papular rash on the face at day 8
Patient 9	Negative	2	Amoxicillin	Urticaria at day 4

TABLE IV. Comparison of characteristics in patients reached at 2-y follow-up

Characteristic	Single-dose graded challenge(n = 170)	5-day challenge(n = 114)	P value
Age (y)			
Mean	7.1	5.1	<.0001
Range	1.1-23.0	0.7-17.0	
Sex, male, n (%)	87 (51.2)	57 (50.0)	.90
Personal history of other drug allergy, n (%)	45 (26.5)	15 (13.2)	.008
Family history of drug allergy, n (%)	55 (32.4)	35 (30.7)	.80
Allergic reaction, n (%)			
Rash only	153 (90.0)	104 (91.2)	.84
Angioedema	13 (7.6)	7 (6.1)	.81
Cough/bronchospasm	3 (1.8)	1 (0.9)	.65
Vomiting	0 (0.0)	2 (1.8)	.52
Anaphylaxis	1 (0.6)	0 (0.0)	.99
Parents very or extremely frightened by their child's allergic reaction, n/n reached (%)	80 (47.1)	54 (47.4)	.99
Mean time (y) elapsed between allergy evaluation and questionnaire	3.1	1.9	<.0001

reaction (Table II). These 3 patients presented with mild urticaria and pruritus in less than 1 hour after the amoxicillin DPT, which resolved quickly with antihistamines. The first patient also presented with mild localized ear angioedema. No case of severe symptoms or anaphylaxis was documented.

Ambulatory challenge results

A 4-day ambulatory course (Figure 1) was continued at home for the remaining 127 patients to rule out delayed reactions. Among these patients, 3 were confirmed to have a nonimmediate allergy and 3 presented an equivocal reaction (both 2.3% of the total number of patients). For the remaining 121 patients, no related adverse event was documented during the entire 5-day DPT.

Of the 3 patients with a confirmed nonimmediate allergy, 2 patients reacted on the second day and the third day, respectively, during the ambulatory challenge, whereas the last patient reacted 3 days after having completed the ambulatory challenge. All reactions were mild isolated maculopapular rash and none had a reaction more severe than their initial reaction. Patients were treated with either simple observation or systemic antihistamines, and none received corticosteroids.

Moreover, 3 patients had equivocal 5-day DPT results that were considered to be negative after a careful reassessment that followed the 5-day DPT. Indeed, an additional diagnostic challenge was indicated for the first patient, and a medical consensus was reached for the other 2 without any need of additional investigation. The first patient presented with a probable contact dermatitis at day 3, the repeated challenge 4 weeks later yielded a negative result, and amoxicillin was used afterwards on 4

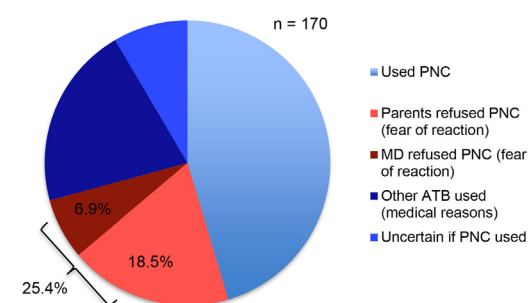
different occasions without any reaction. The second patient developed a rash and respiratory distress 24 hours after having completed the 5-day DPT, but was found to have a clear viremia and pneumonia upon evaluation at the emergency department. The third patient had a previous diagnosis of chronic urticaria when the initial evaluation was performed, and developed urticaria with angioedema 24 hours after the end of the 5-day DPT. This urticaria episode lasted for more than a month and was similar to her chronic urticaria episodes. Although these 3 patients were ultimately not allergic to amoxicillin, only the patient with a repeated negative DPT result was considered in the statistical analysis, because the ambulatory challenge could not be considered unquestionably negative for the remaining 2 patients.

Two-year follow-up

Out of the 122 patients with negative 5-day DPT result, 114 (93.4%) were reached 2 years later for assessment of amoxicillin use since their initial allergy workup (Figure 2). Of those reached, 75 (65.8%) had used antibiotics since, of which 67 (89.3%) had used penicillin antibiotics. Amoxicillin was the penicillin antibiotic used in all cases. Among the 8 patients exposed only to nonpenicillin antibiotics since the 5-day DPT, only 1 (1.3%) had refused to use amoxicillin because of fear of reaction despite a negative evaluation by an allergist. Similarly, no doctor (0.0%) refused to prescribe penicillin antibiotics after the negative 5-day DPT result because of the patient's allergic history.

When caregivers from the 5-day DPT group were asked how comfortable they felt if their child had to receive penicillin

Single-dose graded challenge (data from Picard *et al*, Allergy Asthma Proc. 2012)



Five-day challenge

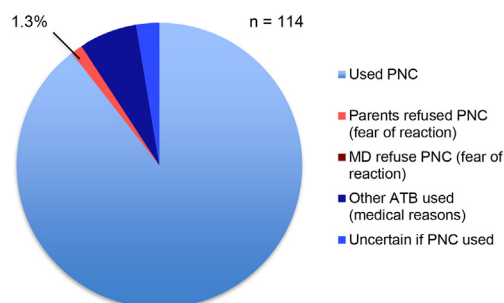


FIGURE 4. Comparison of PNC use after 1-day vs 5-day challenge. ATB, Antibiotic; MD, physician; PNC, penicillin. Data from Picard *et al*.²¹

antibiotics again, most of them felt reassured after their allergy evaluation. Indeed, although 47.4% of parents felt a high or extreme level of anxiety when their child presented their initial reaction to amoxicillin, only 1.7% still felt very or extremely anxious about their child receiving it in the future after a 5-day DPT (Figure 3).

Most children with a negative 5-day DPT result who were re-exposed to amoxicillin tolerated it without any reaction. However, 3 patients (4.5%) who were later given amoxicillin developed mild delayed cutaneous symptoms (Table III). One patient (patient 9) had tolerated 2 courses of amoxicillin without any reaction, but presented urticaria during his third treatment. The remaining 2 patients presented urticaria and a papular rash, respectively, at the end of their first amoxicillin treatment subsequent to their allergy evaluation.

Statistical group comparisons

When compared with our previous single-dose graded DPT,²¹ patient characteristics did not differ significantly between the single-dose graded DPT group and the 5-day DPT group, except that patients were slightly older in the single-dose graded DPT group (7.1 vs 5.1 years; $P < .0001$) and more frequently had a personal history of multiple drug allergy (26.5% vs 13.2%; $P = .008$). Only negative DPT results were considered in this analysis (Table IV).

Again, when compared, the refusal from caregivers to use penicillin despite a negative single-dose graded DPT result was 18.5% against 1.3% in 5-day DPT ($P < .0001$) (Figure 4).²¹ Of

note, there were no differences in the groups' baseline anxiety because almost half the parents in both groups (47.1% vs 47.4%; $P = .99$) were very or extremely frightened by their child's initial allergic reaction to penicillin. Similarly, avoidance of penicillin antibiotics by physicians despite a negative single-dose graded DPT result was 6.9% as opposed to 0.0% for the 5-day DPT ($P = .03$). Altogether, single-dose graded DPT resulted in as much as 25.4% of future penicillin antibiotics avoidance by fear of an allergic reaction by patients or doctors compared with only 1.3% with 5-day DPT ($P < .0001$).

DISCUSSION

Nonimmediate allergy to penicillin antibiotics is highly prevalent in the pediatric population⁷ and may be less prone to resolve spontaneously over time than IgE-mediated reactions.^{30,31} As with immediate allergy, DPT is the criterion standard for making the diagnosis.³² Immediate reading of skin testing has shown poor sensitivity in these cases.^{23,33} Both delayed-reading intradermal testing and patch testing have been used as *in vivo* methods for diagnosis of nonimmediate allergy with various levels of sensitivity and specificity.^{10,34,35}

Performing prolonged challenges to penicillin antibiotics has been suggested to increase sensitivity for nonimmediate penicillin antibiotics allergy by Mori *et al*²⁴ who reported an increase from 35.7% to 100% in a cohort of 200 children with suspected allergy to amoxicillin.²⁴ In a large cohort from Israel³⁶ in which 4% of patients exhibited late reactions on a 1-day challenge, an additional 6.1% were found to have mild delayed reactions on a prolonged 5-day challenge. Looking at children with non-immediate allergy to aminopenicillins diagnosed with prolonged DPT, Ponvert³⁴ and Blanca-Lopez²³ reported mean reaction delays of 3.8 days (range, 3 h to 10 days) and 5.8 days (range, 1 to 8 days), respectively.

In this study, completing the conventional DPT with a 5-day (total) home-based challenge allowed for the detection of twice as many patients with amoxicillin allergy. All 3 nonimmediate reactions were mild and limited to the skin, further indicating that this approach is safe in a pediatric setting. Replication of prolonged DPT findings in a North American context is critical for observations to be generalized.

In our experience, the main argument against the use of prolonged DPT has been that the subsequently reported reactions are mostly benign and that it could thus be deemed safe to simply allow patients to retake penicillin antibiotics at their next infections and wait to see if there is a reaction then. Although this may be true in theory, in reality, Warrington *et al*²⁰ showed that despite negative penicillin skin testing performed electively, 52% of patients or their physicians still prefer to use alternative antibiotics if needed. Another study by the same author but in an inpatient population in need of beta-lactam therapy showed similar results.³⁷ At discharge, 49% of patients with negative testing were still incorrectly labeled as being penicillin-allergic. More recently, Bourke *et al*³⁸ showed that in an adult cohort with a history of penicillin allergy with negative skin testing and negative single-dose penicillin DPT result, only 75.3% of patients were adhering to their allergy label modifications.

Here, we hypothesized that because most patients will have had their initial reaction after many days of treatments, parents and physicians may not be as reassured by a single-dose

challenge than by a prolonged DPT. Indeed, in this cohort, we found that only 1 patient (1.3%) refused subsequent penicillin antibiotics for fear of an allergic reaction compared with 25.4% in a control cohort with a classical intrahospital graded DPT performed for 1 day using penicillin V.²¹ Impressively, no parents reported that the physicians had chosen an alternative antibiotic because of fear of reaction after a 5-day DPT. This finding has major implications, because the ultimate objective of allergy testing is to allow future represcription of the suspected drug, which may not be met in many cases in the absence of a prolonged challenge. The presence of an allergy label has been associated with poorer outcomes, such as a higher rate of intensive care unit admission and mortality¹⁵ as well as substantial economic costs.^{17,39}

Interestingly, on follow-up, the 2 patients who had equivocal prolonged challenge but were not rechallenged both refused subsequent use of penicillin despite the reassurance from the allergist. In contrast, the patient with an equivocal challenge that was repeated (and subsequently yielded a negative result) agreed to use amoxicillin afterwards on several occasions. This further highlights how the patient's perspective must be taken into account during counseling in order for interventions to be impactful. This argues for repeating equivocal challenges to reassure patients even when medical staff is convinced that the reaction is unrelated.

Finally, 3 patients (4.5%) presented delayed cutaneous symptoms upon amoxicillin reuse despite a negative 5-day DPT result. It is unknown whether these reflected true drug-related delayed hypersensitivity reactions or virus-induced cutaneous manifestations. Rechallenging these patients outside of an infectious event will be needed to clarify this issue. Resensitization to penicillin antibiotics after negative allergy evaluation has been shown to be rare and is estimated to occur in 0% to 2% of patients.⁴⁰⁻⁴²

CONCLUSIONS

We have shown that the 5-day DPT approach is safe and effective in a North American cohort of children with suspected penicillin allergy. We have also found that it greatly increases compliance with future use of penicillin antibiotics, possibly by offering better reassurance to parents and physicians. This latter observation is of particular importance given the medical and economic burden associated with the unnecessary avoidance of these antibiotics.

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