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BRIEF REPORT

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Direct Amoxicillin Challenges for Penicillin Allergy Through Pediatric Primary Care Group Visits: A Pilot Study

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Novel strategies are needed to expand equitable access to penicillin allergy testing. We performed a pilot study of penicillin allergy testing through direct challenges performed at pediatric primary care group office visits. Ninety-five percent of subjects were delabeled with no severe reactions noted, providing conceptual basis for further implementation studies.

Keywords. delabeling; drug challenge; infectious disease; penicillin allergy; primary care.

Penicillin allergy labels (PAL) are ubiquitous, but most patients with a penicillin allergy label can safely tolerate penicillins [1, 2]. Unnecessary penicillin avoidance is associated with numerous adverse health outcomes in children including fewer efficacious antibiotic options, worse infectious outcomes, and increased potential for antimicrobial resistance [3–5]. As such, proactive PAL delabeling has emerged as a crucial tool to mitigate these negative impacts [6]. In children, direct oral challenge testing without any preceding skin testing has emerged as a safe and effective testing strategy for the majority of patients; a recent meta-analysis of 28 studies capturing 8334 direct penicillin challenges to evaluate pediatric PAL demonstrated a positive challenge rate of 5.23% (95% confidence interval, 4.17–6.39) with only 1 (0.012%) reported episode of anaphylaxis [2]. However, there is significant discordance between the availability of PAL testing (penicillin allergy testing [PAT]) and the prevalence of PAL. Novel strategies are needed to achieve equitable access to PAT, and there is an increased emphasis on expanding PAT across pediatric disciplines to improve access to care [7–9]. In particular, families have identified a significant level of trust and willingness to complete PAT with their pediatrician; in 1 study surveying 100 families in a general pediatric practice, 64% stated they were comfortable completing PAT at their pediatrician's office [10]. However, significant barriers exist in implementing PAT in general pediatric settings; in a survey of 58 pediatricians assessing perceptions of PAT, concerns regarding insufficient clinic time, space, and staffing were among the most frequently cited barriers to implementing PAT in their clinics [11]. Outpatient group visits have been used in the management of numerous disease processes, and offer an opportunity to optimize the efficiency of clinic resources; however, this has not been reported in PAT. To address this, we report a novel strategy of direct amoxicillin challenge testing to evaluate PAL in an outpatient general pediatric setting using group visits.

METHODS

This retrospective pilot study assessed an intervention of pharmacist-driven group amoxicillin challenge visits to evaluate pediatric PAL from 1 June 2022 through 10 October 2024. Children aged 2–17 years who receive care through the general pediatric clinics at 2 urban community oriented primary care clinics and had a PAL were identified. An outreach phone call determined interest in PAT. Referrals from providers were also available for PAT. Subsequently, a PAT pharmacist called the family to assess the index reaction to penicillin and educate about direct challenge testing. Patients without a history of mucosal ulcers, skin peeling, a history of a severe cutaneous adverse reaction (SCAR) to penicillin, or a history of penicillin-induced single-organ injury (eg, drug-induced liver injury) were invited to attend an amoxicillin challenge group visit that was held monthly in an education room located in the general pediatric clinics. Patients eligible for amoxicillin challenge testing were screened on the day of testing for acute illness, fever, rash, or active respiratory symptoms; if present, challenge testing was rescheduled. At the group challenge visit, a 2-step graded amoxicillin challenge was performed by a PAT pharmacist, with an amoxicillin 50-mg dose administered, followed by a 5-minute observation period. If no symptoms were observed, an amoxicillin 200-mg dose was given followed by a 60-minute observation period. The education room where challenges were performed was adjacent to the clinical rooms

Received 06 February 2025; editorial decision 15 April 2025; accepted 21 April 2025; published online 24 April 2025

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Open Forum Infectious Diseases®

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https://doi.org/10.1093/ofid/ofaf236

in the outpatient clinic building. The PAT pharmacist was trained in the recognition and management of anaphylaxis and had an intramuscular epinephrine autoinjector readily available. Prescription medications such as amoxicillin were authorized through a Drug Therapy Protocol, filed with the state of Texas, which allows the pharmacist to order the necessary drugs to perform allergy testing, administer the test, and use prescription rescue medications if needed. Management of positive reactions followed a prespecified management plan, which included cetirizine for isolated urticaria and hydrocortisone 1% cream for isolated delayed papular eruptions. For symptoms extending beyond these, an escalation plan was in place for further evaluation and management by clinic nursing staff and an assigned pediatrician, although this was not required in any cases. Caregivers received a follow-up phone call to assess delayed reactions at 7–10 days after testing.

Patient Consent Statement

The University of Texas Southwestern Office of Human Research Ethics/Institutional Review Board approved the study protocol. Verbal consent was obtained prior to amoxicillin challenge testing per institutional clinical protocol. As a retrospective series, written informed consent was not required for inclusion in this study by the institutional review board.

RESULTS

Over the study period, 120 children were referred for the amoxicillin challenge group visit. Sixty-one challenges were completed, with demographics outlined in Table 1. The median age of index reaction and challenge completion was 2 (interquartile range 1–3) years and 11 (interquartile range 6–13) years, respectively. Fifty-two (85%) reported a cutaneous-only index reaction to a penicillin, and 18 (30%) reported a reaction within 1 hour of penicillin dose at index reaction. Two patients reported angioedema at index reaction; there were no anaphylactic index reactions. Three patients, 12 patients, and 46 patients completed challenge within 1 year, between 1–5 years, and greater than 5 years of index reaction. Of the 61 challenges, 58 (95%) tolerated with no reaction. For the 3 positive challenges, all reactions were mild, cutaneous-only reactions. Two patients developed symptoms within 1 hour of challenge testing, 1 with isolated pruritus and 1 with a pruritic rash, with rapid resolution of symptoms without treatment and with an oral antihistamine, respectively. One patient developed a delayed morbilliform eruption that resolved with topical hydrocortisone. Of these positive challenges, the patient with the immediate pruritic rash completed challenge 1 year after index reaction; the patients with isolated pruritus and delayed morbilliform eruption completed challenge greater than 5 years after index reaction. Of the 58 patients who were delabeled with a minimum of 5-month follow up, no patients had a penicillin allergy relabeled after mean follow up at 20.7 ± 9.8 months.

Table 1. Patient Demographics and Diagnostic Challenge Results for Children Completing Direct Amoxicillin Challenges Through Group Visits in the Pediatric Primary Care Setting

Characteristic	Total n = 61
Age	
At index reaction (median, IQR), y	2 (1–3)
At challenge (median, IQR), y	11 (6–13)
24–36 mo (n, %)	4 (7%)
3–5 y (n, %)	5 (8%)
6–12 y (n, %)	25 (41%)
>12 y (n, %)	27 (44%)
Female (%)	33 (54%)
Index reaction characteristics[a]	
Cutaneous-only reactions	52 (85%)
Immediate reactions (<1 h)	18 (30%)
Implicated penicillin at index reaction	
Amoxicillin	44 (72%)
Amoxicillin/clavulanate	6 (10%)
Unknown	11(18%)
Negative amoxicillin challenge testing	58 (95%)
Positive challenges requiring additional treatment beyond oral antihistamines	0%
Group visit size: participants (median, IQR)	2 (1–3)
Relabeling after minimum 5 mo follow up	
Relabeling rate	0/58 (0%)
Median period of follow up (median, IQR), mo	20.1 (13.4–30.1)

Abbreviation: IQR, interquartile range.

[a]Immediate reactions, defined as occurring within 1 hour of penicillin administration, and cutaneous-only reactions are not mutually exclusive.

DISCUSSION

To our knowledge, this is the first study utilizing group visits to perform amoxicillin challenge testing to evaluate PAL. The observed delabeling rate is consistent with previously reported experiences [2, 12]. All positive reactions were mild, isolated cutaneous symptoms that required at most oral antihistamines for resolution. This suggests that this approach has similar efficacy and safety to other pediatric PAL delabeling interventions [2, 13, 14]. Novel elements of this strategy include utilizing group visits to optimize efficiency for clinic staff and physical clinic space, a strategy implemented as a component of comprehensive care in pediatric asthma and obesity that addresses a significant concern identified by general pediatricians as a barrier to implementing PAL delabeling in their clinic [11, 15, 16]. While a PAT pharmacist performed direct amoxicillin challenge testing in this present study, this is not a resource that is universally available; other healthcare professionals are equipped to perform this testing, including nurses, a strategy employed with performing direct amoxicillin challenges during routine healthcare maintenance visits [14]. In the protocol

outlined in the present study, we aligned the inclusion and exclusion criteria with Mill et al, 1 of the first large prospective studies to evaluate direct amoxicillin challenge testing in pediatric patients in the allergist outpatient setting [13]. In this study, the authors only excluded SCARs and did not exclude a history of anaphylaxis; notably, of the 818 challenges completed, none reported an anaphylactic index reaction. We affirm that a recent confirmed anaphylaxis episode in the setting of penicillin warrants skin testing; however, in children, penicillin-induced anaphylaxis is exceedingly rare [2], many mimickers of anaphylaxis exist and as such reported "anaphylaxis" is relatively common [17], and validated clinical tools based on history to distinguish anaphylaxis from nonanaphylaxis are lacking. With these factors in mind and in consideration of the extensive experience of our PAT pharmacist team, we chose to not exclude these patients to prevent the net effect of potentially restricting access to delabeling unnecessarily. As such, we acknowledge that our approach may not be universally generalizable; for institutions implementing challenge testing for the first time, it may be reasonable to limit index reactions to cutaneous-only reactions based on local institutional factors and experience. Considering the generalizability of the recognition and management of anaphylaxis in the general pediatric outpatient setting, healthcare professionals routinely weigh and accept the risk and benefit of administering other drugs. For example, vaccines are known to have a rare risk for anaphylaxis, and the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices states that that "vaccine providers should be familiar with identifying immediate-type allergic reactions, including anaphylaxis, and be competent in treating these events at the time of vaccine administration" [18]. As such, many healthcare professionals practicing in the outpatient general pediatric setting have already implemented protocols and training to manage potential immediate reactions.

As a single-center study, results may not be generalizable to every general pediatric clinic; furthermore, index reaction characterization may be influenced by recall bias given retrospective design. This pilot study provides important proof-of-concept of a novel penicillin allergy delabeling strategy that addresses barriers to implementing challenge testing in the primary care outpatient center setting by optimizing efficiency for clinic staff and physical clinic space to address the need to increase equitable access to PAL delabeling.

Notes

Acknowledgments. The authors acknowledge Steven Lopez and Rene Ramirez, who contributed to the implementation of the delabeling intervention through facilitating the referral and screening process.

Author contributions. T.C., C.M., K.A., D.K., and C.T. conceptualized and designed the study. C.M. and M.S. collected data. T.C. and M.S. carried out initial analyses. T.C. drafted the initial manuscript. All authors critically reviewed and revised the manuscript. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

Financial support. No funding was received for this study.

Potential conflicts of interest. T.G.C. and D.A.K. receive grant support from the National Institutes of Health (grant U01 AI184071). T.G.C. reports personal fees from Sarepta Therapeutics outside the submitted work. All other authors: No reported conflicts.

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