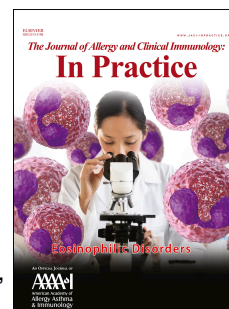


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Title: Re-Labeling of Penicillin Drug Allergy after Evaluation in a Drug Allergy Clinic

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Conflicts of interest

The authors declare that there are no financial/personal interest or beliefs that could affect her objectivity, or inappropriately influence her actions in writing this paper.

Clinical Implications Statement: More than 90% of patients after evaluation in a Drug Allergy Clinic had their penicillin allergy de-labeled, but re-labeling still occurred in 5.3% of patients. Continued education of healthcare providers to prevent inappropriate allergy re-labeling is imperative.

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Penicillins (PCN) are a commonly labeled drug allergy and yet, many patients are inappropriately labeled with this allergy status.¹ Medical staff may not have adequate training or time to evaluate a patient's drug allergy history to determine if a labeled allergy is a true allergy. Implications of having a penicillin allergy label include the use of second-line antibiotics, risk of adverse effects, antibiotic resistance, increased inpatient/outpatient costs, and increased mortality.² Therefore, it is important to prevent erroneous re-labeling of penicillin allergy labels. There is limited literature surrounding re-labeling of drug allergies in patients with a previous de-labeling after a negative allergy evaluation. Re-labeling of the penicillin allergy label has been found in 9.4%-36% of patients.³⁻⁵ Blumenthal et al documented an erroneous re-labeling rate of 2%.³ Other studies have found that 37.6% to 51.2% of patients have a persistent penicillin allergy label despite a negative evaluation.⁶⁻⁸ This may be because patients choose to avoid penicillin treatment and/or de-labeling and allergy labels not always being removed from the electronic medical record (EMR).⁶ One study found that a multidisciplinary approach using computerized protocols, EMR alerts, education by a pharmacist, wallet cards, and follow-up communication effectively reduced the allergy re-labeling rate from 12.9% to 2.5%.⁴

Our institution has a Drug Allergy Clinic (DAC) with a multidisciplinary approach. Patients are scheduled with a staff physician/pharmacist team or with other allergy trained clinic staff physicians, advanced practice providers or fellows. During evaluation, patients undergo a thorough drug allergy review, skin prick/intradermal testing and/or drug challenge, and subsequent allergy status updates or de-labeling in the EMR. Patients are given an after-visit summary, written home care instructions, and counseling about their allergy status. Beginning in November 2017, the DAC implemented an after-visit wallet card specifically documenting a negative penicillin allergy status.

This was a retrospective study of all patients aged 18 and older evaluated in the DAC for penicillin allergy from August 1, 2016 to July 1, 2018 with review of allergy label status through January 1, 2019. Patients < 18 years of age, those evaluated for non-penicillin drug allergies, and prisoners were excluded.

This project received Institutional Review Board approval. Patients were divided into 2 cohorts, patients evaluated by a physician/pharmacist team, the MD/PharmD group, and patients seen by a provider without a pharmacist, the provider only group (6 staff physicians, 1 ARNP, 1 PA and 6 fellows). The primary outcome was the rate of penicillin allergy re-labeling after having the allergy de-labeled. Secondary outcomes compared between the cohorts included , re-labeling rates before and after wallet card implementation, time to re-labeling, and reasons for re-labeling.

The baseline demographics of the 353 patients evaluated are found in Table I. The patients were similar between the MD/PharmD group and the provider only group. However, the patients seen by the MD/PharmD were significantly older (64 vs 59 years, $p < 0.01$) and had a significantly higher proportion of patients evaluated with drug reactions that occurred > 10 years ago (86% vs 64%, $p < 0.001$). A total of 322 of 353 (91.5%) patients evaluated had their allergy de-labeled and this was similar between the groups ($n=152$ in MD/PharmD group and $n=170$ in provider only group). Thirty-one patients (8.5%) were not de-labeled due to reasons including: unsafe to test ($n=10$), unable to test/refusal to test ($n=8$), patient refusal to de-label the allergy after evaluation ($n=3$), provider forgot to de-label ($n=7$, all in provider only group), indeterminate test ($n=2$, 1 with dermatographia), and positive penicillin allergy evaluation ($n=1$, hives during the oral amoxicillin challenge after a negative skin test). There were no positive penicillin skin tests during this study, which indicates that the overall vast majority of patients had a mislabeled penicillin allergy.

For the primary and secondary outcomes (Table II), 17 patients (5.3%) of the total de-labeled patients ($n=322$) had the allergy re-labeled after the evaluation visit (7 in MD/PharmD group, 10 in provider only group), with similar re-labeling rates between the groups (5.9% versus 4.6%). Re-labeling occurred most frequently within 3 months of the evaluation (47%, $n=8$). Less penicillin allergies were re-labeled (41.2% versus 58.8%) after wallet card implementation, but this was not statistically significant [$p = 1.00$ (95% CI -0.354, 0.354)]. Medical assistants ($n=11$), registered nurses ($n=5$) and pharmacists ($n=1$) were those

that re-labeled the allergy. It is estimated that 88%, 15 of 17, re-labeled allergies were likely inappropriate (re-labeled in error, re-labeled and then de-labeled again, and no reason identified for re-labeling). Two patients, 1 in each group, that both had a negative penicillin skin testing and amoxicillin oral challenge were re-labeled due to suspicion of an allergy (details of reactions in Table II).

This study reviewed a 353 patients evaluated over a 2.5-year period and found that > 90% of patients had the penicillin allergy de-labeled. The overall re-labeling rate was low at 5.3% and similar between groups, which is lower in comparison to other identified studies.³⁻⁵ The majority (88%) of allergy re-labeling was likely inappropriate, although it was not possible to ascertain exactly why re-labeling occurred. After review of the two patients where re-labeling was intentional, neither may have been true allergic reactions. Routinely documenting a specific explanation in the EMR surrounding allergy de-labeling may provide a stop alert for re-labeling an allergy in error. There was a lower re-labeling rate with the wallet card implementation, which supports expansion of using wallet cards for all drug allergy evaluations. The study limitations are the retrospective nature with potential for collection bias and the multiple providers with variable workflows in the DAC. Also, patients were not evaluated for re-exposure to a penicillin after being de-labeled. It has been shown that patients who are re-exposed to a negatively tested beta-lactam still have a high rate, 94.1%, of tolerating penicillin.⁹ In conclusion, it is imperative to educate all providers on the negative implications of inappropriately re-labeling drug allergies, which can improve antimicrobial stewardship.

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131 **Table I – Patient Demographics Upon Evaluation in the Drug Allergy Clinic**

Demographics (n=353)	MD/PharmD Patients (n=168)	Provider Only Patients (n=185)	P-Value*
Female – No. (%)	118 (70.2)	130 (70.3)	1.00
Mean Age – Yrs (Range)	64 (23-91)	59 (18-88)	<0.01
Medication Allergy – No. (%)			0.09
Penicillin	142 (84.5)	140 (75.7)	
Amoxicillin	22 (12.5)	31 (16.8)	
Amoxicillin/clavulanate	15 (3.0)	12 (6.5)	
Ampicillin	4 (2.4)	3 (1.6)	
Other PCN derivatives	2 (1.2)	4 (2.2)	
Unknown	1 (0.6)	8 (4.3)	
Age Reaction Occurred – Yrs (%)			0.20
<18	79 (47)	62 (33.5)	
≥18	82 (48.8)	68 (36.8)	
Unknown per pt report	7 (4.2)	13 (7.0)	
Missing from chart	0	42 (22.7)	
Time Since Allergy – Yrs (%)			<0.001
<5	9 (5.4)	25 (13.5)	
6-10	7 (4.2)	30 (16.2)	
>10	145 (86.3)	119 (64.3)	
Unknown	7 (4.2)	11 (5.9)	

132 *Descriptive analyses methods (e.g. Fisher's, Chi-Squared) used as appropriate for variables

133 Table II – De-labeling and Re-labeling Rates of Patients Evaluated in the DAC

Outcomes	Total Drug Allergy Clinic Evaluations (n=353)	MD/PharmD Patients (n=168)	Provider Only Patients (n=185)	P-Value*
Patients De-labeled – No. (%)	322 (91.2)	152 (90.4)	170 (91.9)	--
Skin-testing with single dose challenge	231 (71.7)	110 (72.4)	121 (71.2)	
Skin-testing only	66 (20.5)	23 (15.1)	43 (24.7)	
Drug challenge only	11 (3.4)	5 (3.0)	6 (3.5)	
Ruled out with history alone	14 (4.3)	14 (9.2)	0	
Patients Re-Labeled After De-labeling– No. (%)	17 (5.3)	7 (4.6)	10 (5.9)	1.00 (95% CI -0.354, 0.354)
Pre-Wallet Card	10 (58.8)	4 (57.2)	6 (60)	
Post-Wallet Card	7 (41.2)	3 (42.8)	4 (40)	
Time Elapsed from De-Labeling to Re-Labeling – No. (%)				0.495
< 3 months	8 (47.0)	3 (42.9)	5 (50)	
3-6 months	3 (17.7)	1 (14.3)	2 (20)	
6-9 months	0	0	0	
9-12 months	2 (11.8)	2 (28.5)	0	
> 12 months	4 (23.5)	1 (14.3)	3 (30)	
Reason for Re-Labeling – No. (%)				0.870
Possible Subsequent Allergy	2 (11.8)	1 (14.2) [±]	1 (10) [‡]	
Re-labeled in Error	9 (52.9)	3 (42.9)	6 (60)	
Re-labeled and Then De-labeled Again	5 (29.4)	3 (42.9)	2 (20)	
No Reason for Re-labeling Identified	1 (5.9)	0	1 (10)	

134 *Descriptive analyses methods (e.g. Fisher's, Chi-Squared) used as appropriate for variables

135 [±] Unknown reaction to penicillin 65 years prior, that had a rash on the neck, chest and face 9 days after
 136 negative penicillin skin testing the single dose amoxicillin.

137 [‡]Patient had hives and lip angioedema 7 hours after taking amoxicillin/clavulanate 16 months after de-
 138 labeling. Patient had tolerated 4 courses of amoxicillin/clavulanate since the de-labeling and had a
 139 subsequent negative skin testing and tolerated oral challenge to amoxicillin 1 year later.