

Clinical Communications

Readiness for PENicillin allergy testing: Perception of Allergy Label (PEN-PAL) survey

David T. Coleman, MD^a, Cosby A. Stone, Jr., MD, MPH^a, Wei-Qi Wei, MD, PhD^b, and Elizabeth J. Phillips, MD^{c,d,e,f}

Clinical Implications

- Patients reporting penicillin allergy believe their allergy to be permanent, would take penicillins if tested negative, but are rarely referred for penicillin testing, leading to differential antibiotic utilization.

Although 8% to 20% of patients are reported to carry a penicillin allergy label (PAL), more than 95% of these individuals will be negative on standardized penicillin allergy (PA) testing.¹⁻³ Patients with a PAL are subject to adverse health outcomes, including increased nosocomial infections, surgical site infections, prolonged time to administration of emergent antibiotics, prolonged hospitalizations, and hospital readmissions.⁴⁻⁶ PA testing has been shown to be safe and facilitates antibiotic stewardship, and data suggest that it is likely to be cost effective.^{1,7,8} Although much is published regarding the worse outcomes of a PAL and approaches to remove a PAL,⁹ little is known about willingness of patients with PA to undergo PA testing. Therefore, we conducted the “Readiness for PENicillin allergy testing: Perception of Allergy Label” (PEN-PAL) survey to ascertain beliefs, perceptions, and experiences of a current self-reported PA patient population and to identify potential barriers to testing.

A survey (Figure E1, available in this article’s Online Repository at www.jaci-inpractice.org) was created using REDCap (Research Electronic Data Capture), an established secure web-based application for creating and managing online surveys and databases. Of note, the only mandatory question was whether the patient reported either a current PA, reported a historical PA that was removed, or reported no PA. The participants were free to omit answers to all other questions if they did not recall the answer or if they chose not to answer, and thus, the denominator of responses varied slightly by question. An e-mail with the survey was sent to 18,943 adult patients (≥ 18 years of age) preconsented to receive institutional review board–approved study advertisements in the context of the MyResearch at Vanderbilt (MRV) program, with 3 reminder e-mails, from late October 2019 to early December 2019. Additional details regarding REDCap and MRV can be found in the Methods section of this article’s Online Repository at www.jaci-inpractice.org.

For continuous variables, median and interquartile range were calculated. Statistical comparisons were performed between the 3 PA status groups. For categorical variables, Fisher’s exact test or Pearson’s χ^2 statistic were used. The Wilcoxon rank-sum test was used to compare continuous variables. Statistical analysis was performed using Stata 15.0.

Of 18,943 eligible participants of MRV, 5284 (28%) completed the survey. Of them, 1047 (20%) reported a current PA, 4091 (77%) reported no PA, and 146 (3%) reported a

historical PA that was removed. Participants reporting a current PA were more likely to be female (Pearson, $P < .005$) (Table 1).

Patients reporting a current PAL experienced their index reaction at a median age of 16 (interquartile range, 6-30) years with most reactions occurring ≥ 10 years ago (915 of 1040, 88%). The 3 most common types of reactions were rash only (510 of 1037, 49%), an unknown reaction (141 of 1037, 14%), or “anaphylaxis” (139 of 1037, 13%), and all reactions recalled are detailed in Table E1 (available in this article’s Online Repository at www.jaci-inpractice.org). Of the 116 of 998 (12%) who endorsed receiving epinephrine, 77 (66%) recalled the index reaction of “anaphylaxis” and 39 (34%) received epinephrine but did not recall the index reaction of “anaphylaxis.” After the index reaction, of those who recalled their highest level of care required (805 of 1034, 78%), most required only an outpatient visit, phone call, or self-discontinued penicillin (612 of 805, 76%), whereas few used the emergency department (106 of 805, 13%), inpatient floor (62 of 805, 8%), or the intensive care unit (17 of 805, 2%).

Antibiotic utilization differed among those reporting a current PA and the other groups (Figure 1). Compared with no reported PA, participants reporting a current PA less frequently recalled receiving penicillin** (subsequent to index reaction) (11% vs 70%), amoxicillin** (24% vs 79%), amoxicillin/clavulanate** (12% vs 46%), and cephalexin* (40% vs 45%), and more frequently recalled receiving fluoroquinolones** (11% vs 7%), macrolides** (15% vs 6%), tetracyclines** (8% vs 4%), clindamycin** (6% vs 1%), sulfa antimicrobials* (6% vs. 4%), and vancomycin* (2% vs 1%) (Pearson χ^2 * $P < .05$, ** $P < .005$). Compared with participants reporting a historical PA that was removed, participants reporting a PA less frequently recalled receiving penicillin** (subsequent to index reaction) (11% vs 47%), amoxicillin** (24% vs 63%), and amoxicillin/clavulanate** (12% vs 35%), and more frequently recalled receiving clindamycin* (11% vs 6%), tetracyclines* (8% vs 2%), and macrolides* (15% vs 8%) (Fisher’s exact test * $P < .05$, ** $P < .005$) (Figure 1). Furthermore, 198 of 1040 (19%) with a PAL had taken and tolerated a penicillin, but continued to self-report their PAL.

Participants reporting a current PA often discussed their PA with a primary care provider (639 of 1035, 61%), but that conversation rarely comprised the negative consequences of a PA (73 of 1040, 7%), and the minority were offered referral to an allergist for PA testing (38 of 1040, 4%). Regarding surgeries in patients with PA, 869 of 1039 (81%) reported both a PA and a surgery since their index reaction, and majority of these (747 of 861, 87%) had a preoperative discussion of their PA with a provider. The minority of these participants perceived that their PA had an adverse effect on their medical care (167 of 1040, 16%). Most (799 of 989, 81%) believed their PA to be permanent, and many believed it “likely” or “very likely” to react to penicillin today (397 of 1039, 38%). Despite this, a high proportion (813 of 1016, 80%) would take penicillin for an indicated cause if an allergist tested them and found it to be safe. Overall, 561 of 1024 (55%) were interested in PA testing.

This survey is the first that attempts to capture a large population-based sample of attitudes and experiences of a

TABLE I. Demographics of PEN-PAL survey participants

Demographic	No penicillin allergy (n = 4091)	Current penicillin allergy (n = 1047)	Removed penicillin allergy (n = 146)	P value
Median age [IQR]	62 [51-70]	61 [51-69]	64 [51-71]	NS
Gender, n (%)				
Male	1599 (39)	275 (26)	45 (31)	<.005
Female	2464 (60)	769 (73)	99 (68)	
Other	2 (0)	0 (0)	1 (1)	
Declined to answer	26 (1)	3 (0)	1 (1)	
Race, n (%)				
White	3720 (92)	972 (93)	136 (93)	NS
African American	167 (4)	44 (4)	3 (2)	
Other	177 (4)	26 (2)	7 (5)	
Declined to answer	27 (1)	5 (0)	0 (0)	

IQR, Interquartile range; PEN-PAL, PENicillin allergy testing: Perception of Allergy Label.

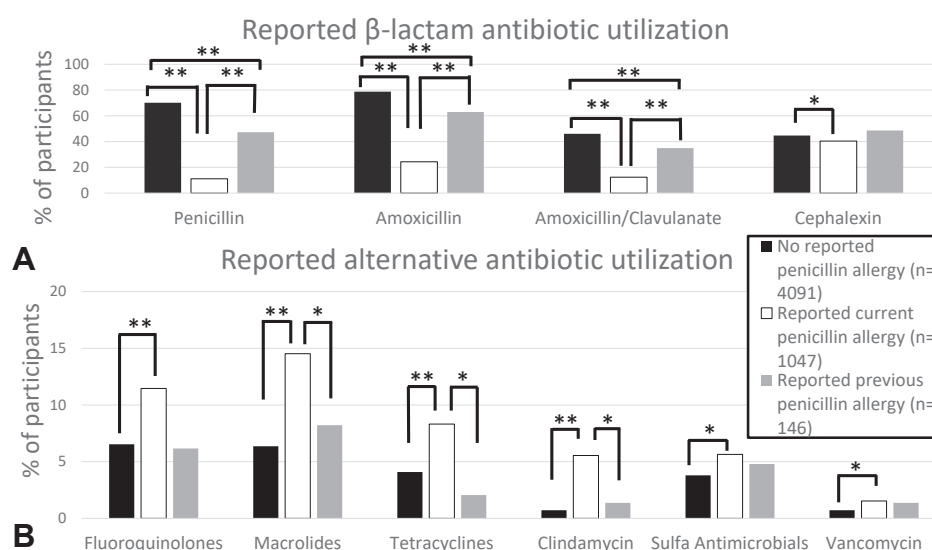


FIGURE 1. Reported antibiotic utilization, by penicillin allergy (PA) status. **A**, Participants reporting a current PA less frequently reported utilization of penicillin** (after index reaction, when applicable), amoxicillin**, amoxicillin/clavulanate**, and cephalexin*. **B**, Participants reporting a current PA more frequently reported utilization of fluoroquinolones**, macrolides**, tetracyclines**, clindamycin**, sulfa antimicrobials*, and vancomycin* (* $P < .05$, ** $P < .005$, no bar = NS).

patient with current reported PA, and although the survey link was only sent to those accessing care at a tertiary medical center, we believe that the conclusions are generalizable to a population level. Limitations of the study that we do not believe will significantly change conclusions are that many of the answers involve the participants' recollection of reaction details and medications, and we did not ask the participants whether they had other antibiotic allergies, which may independently alter the antibiotics received.

We identified educational points for both patients and providers. Notably, >80% of those with a current PA perceived their PA as permanent. However, if the reported histories of rash only, "my family member told me I'm allergic but I don't recall," gastrointestinal distress, unknown history, and family history of PA were applied to a recently validated PA risk stratification scheme,^{9,10} 71% of our PA participants' reported histories would be categorized as low risk, and thus likely to tolerate a single-dose

amoxicillin oral challenge today. Most (561 of 1024, 55%) with a current PAL were interested in PA testing, and the majority (813 of 1016, 80%) indicated that they would take a penicillin if testing was negative. Despite this, primary care doctors rarely referred our participants for PA testing (38 of 1040, 4%).

Self-reported antibiotic utilization was different between those with and without a current PAL. PAL participants recalled significantly fewer β -lactam prescriptions and increased prescriptions of antibiotics associated with potentially reduced treatment efficacy. Those with a current PAL also recalled fewer β -lactam prescriptions than those with a historical PAL that was removed, highlighting the importance of PAL testing in guiding antibiotic prescribing patterns.

PAL patients believed their PAL to be permanent and several retained a PAL despite proven tolerance. Although they expressed interest in formal allergy assessment, and most would take penicillin if tested negative, they were rarely referred, leading

to differential antibiotic utilization in favor of a broader spectrum and potentially less effective therapy.

Acknowledgments

The authors would like to thank Douglas Conway, BA, and James Ryan Moore, BS, of the Vanderbilt Institute for Clinical and Translational Research of Vanderbilt University Medical Center for their effort in survey distribution.

This project was supported by CTSA Award No. UL1TR000445 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

^aDivision of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn

^bDepartment of Biomedical Informatics, Vanderbilt Medical Center, Nashville, Tenn

^cDivision of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tenn

^dDepartment of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tenn

^eDepartment of Pathology, Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, Tenn

^fInstitute for Immunology & Infectious Diseases, Murdoch University, Murdoch, WA, Australia

D. T. Coleman received a Vanderbilt Institute for Clinical and Translational Research (VICTR) grant 53885. C. A. Stone receives funding from AHRQ K12 HS026395. W.-Q. Wei receives funding from NIH NHLBI 1R01HL133786. E. J. Phillips receives funding from National Institutes of Health (1P50GM115305-01, R21AI139021 and R34AI136815 and 1 R01 HG010863-01) and the National Health and Medical Research Council of Australia).

Conflicts of interest: E. J. Phillips is a Drug Allergy Section Editor for and receives royalties from UpToDate. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 13, 2020; revised March 11, 2020; accepted for publication March 20, 2020.

Available online ■■

Corresponding author: Elizabeth J. Phillips, MD, Vanderbilt University Medical Center, 1161 21st Avenue South, A-2200, Medical Center North, Nashville, TN 37232-2582. E-mail: elizabeth.j.phillips@vanderbilt.edu.

2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2020.03.049>

REFERENCES

1. Trubiano J, Adkinson N, Phillips E. Penicillin allergy is not necessarily forever. *JAMA* 2017;318:82-3.
2. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Curr Allergy Asthma Rep* 2014;14:476.
3. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259-73.
4. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014;133:790-6.
5. Blumenthal K, Ryan E, Li Y, Lee H, Kuhlen J, Shenoy E. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis* 2018; 66:329-36.
6. Conway E, Lin K, Sellick J, Kurtzhalts K, Carbo J, Ott MC, et al. Impact of penicillin allergy on time to first dose of antimicrobial therapy and clinical outcomes. *Clin Ther* 2017;39:2276-83.
7. Blumenthal K, Li Y, Banerji A, Yun B, Long A, Walensky R. The cost of penicillin allergy evaluation. *J Allergy Clin Immunol Pract* 2018;6:1019-1027. e1012.
8. Mattingly T II, Fulton A, Lumish R, Williams AMC, Yoon S, Yuen M, et al. The cost of self-reported penicillin allergy: a systematic review. *J Allergy Clin Immunol Pract* 2018;6:1649-1654.e1644.
9. Stone C Jr, Trubiano J, Coleman D, Rukasin C, Phillips E. The challenge of de-labeling penicillin allergy. *Allergy* 2020;75:273-88.
10. Stone C Jr, Stollings J, Lindsell C, Dear ML, Buie RB, Rice TW, et al. Risk-stratified management to remove low-risk penicillin allergy labels in the intensive care unit [published online ahead of print February 21, 2020]. *Am J Respir Crit Care Med*. <https://doi.org/10.1164/rccm.202001-0089LE>

ONLINE REPOSITORY

METHODS

REDCap

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Vanderbilt University Medical Center.^{E1,E2} REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

MyResearch at Vanderbilt

MyResearch at Vanderbilt is a participant repository recruitment tool available to Vanderbilt researchers that reaches over 18,000 My Health at Vanderbilt users who have previously confirmed that they would like to be contacted directly for research. This repository provides investigators a forum for advertising for volunteers for a specific study. E-mail notifications are limited to institutional review board–approved language, describe study specifics, and provide contact information. To use this initiative, investigators complete a MyResearch Access Request that is reviewed to ensure that the recruitment tool and requested number of contacts are appropriate.

1. Sole mandatory question: Do you have a penicillin allergy?
 - a. Yes
 - b. No
 - c. I had a penicillin allergy, but it has since been disproven
 2. Age: (list age)
 3. Sex
 - a. Male
 - b. Female
 - c. Other
 4. Race/ethnicity
 - a. White
 - b. African American
 - c. Latino
 - d. Asian
 - e. Mixed
 - f. Other
 - i. List other race/ethnicity
 5. Do you recall needing antibiotics for any reason in your lifetime?
 - a. Yes
 - b. No
 6. Which antibiotics have you taken without issue in your lifetime? Choose all that apply, only choose if you are confident
 - a. I have confidently taken none of these specifically listed here
 - b. Penicillin
 - c. Amoxicillin (Amoxil)
 - d. Amoxicillin/Clavulanic acid (Augmentin)
 - e. Cephalexin (Keflex)
 - f. Ceftriaxone (Rocephin)
 - g. I have taken an antibiotic not on this list
 - i. Which other antibiotics not listed in the previous question have you taken without issue in your lifetime?
 - h. Unsure
 7. (Answered by those reporting to be female only) Are you currently or have you ever been pregnant?
 - a. Yes
 - b. No
 8. (Answered by those reporting to be female and penicillin allergic only) Do you perceive your penicillin allergy affected your pregnancy, delivery, or time while nursing/breastfeeding in any way?
 - a. Yes
 - b. No
 - c. I became allergic to penicillin after my last pregnancy
 - i. Please list how you perceive your penicillin allergy affected your pregnancy, delivery, or time while nursing/breastfeeding
 9. (Answered by those reporting to be female only) Did you require antibiotics while pregnant, during delivery, or when you were nursing/breastfeeding?
 - a. Yes
 - b. No
 - i. Please list the antibiotics you confidently remember taking while pregnant, during delivery, or when you may have been nursing/breastfeeding
- Remainder of questions answered by those reporting to be currently penicillin allergic only
10. How many years ago did you acquire your penicillin allergy?
 - a. Less than 1 year ago
 - b. Greater than 1, but less than 5 years ago
 - c. Greater than 5, but less than 10 years ago
 - d. Greater than 10 years ago
 - e. I did not personally have a reaction to penicillin
 - f. Not sure
 11. Around what age did you acquire your penicillin allergy? (List age)
 12. What was your reaction to penicillin?
 - a. Rash only
 - b. Anaphylaxis
 - c. Gastrointestinal distress only
 - d. My family member told me I'm allergic. I do not remember the reaction
 - e. I avoid penicillin because of a family member who did not tolerate penicillin
 - f. Unknown
 - g. Other
 - i. Please list other reaction
 13. During the event leading to your penicillin allergy, what was the most involved level of care you required?
 - a. It was stopped without talking to a provider
 - b. A health care practitioner recommended stopping it over the phone
 - c. Urgent Care/Primary Care doctor visit
 - d. Emergency room
 - e. Inpatient hospitalization, not requiring the intensive care unit
 - f. Inpatient hospitalization, requiring the intensive care unit
 - g. The penicillin allergy label was acquired based on a reaction that occurred with a relative
 - h. Do not remember
 14. Did your reaction to penicillin require epinephrine (otherwise known as Epi, EpiPen) injection?
 - a. Yes
 - b. No
 15. If you were prescribed penicillin today, how likely would it be for you to have a reaction to it?
 - a. Very likely
 - b. Likely
 - c. Unsure
 - d. Unlikely
 - e. Very unlikely

FIGURE E1. PEN-PAL survey questions.

FIGURE E1. Continued.

16. Do you recall needing antibiotics for any reason SINCE ACQUIRING YOUR PENICILLIN ALLERGY?

- a. Yes
- b. No

17. Did your provider discuss your penicillin allergy prior to prescribing those antibiotics?

- a. Yes
- b. No

18. Which antibiotics have you taken without issue SINCE ACQUIRING YOUR PENICILLIN ALLERGY? Choose all that apply, only choose if you are confident.

- a. I have confidently taken none of these specifically listed here
- b. Penicillin
- c. Amoxicillin (Amoxil)
- d. Amoxicillin/Clavulanic acid (Augmentin)
- e. Cephalexin (Keflex)
- f. Ceftriaxone (Rocephin)
- g. I have taken an antibiotic not on this list
 - i. Which other antibiotics not listed in the previous question have you taken without issue SINCE ACQUIRING YOUR PENICILLIN ALLERGY?
- h. Unsure

19. Has your primary care provider talked to you about your penicillin allergy?

- a. Yes
- b. No

20. Has your primary care provider offered to refer you for penicillin allergy testing?

- a. Yes
- b. No

21. Has any provider ever reported to you that your penicillin allergy is affecting your medical treatment?

- a. Yes
- b. No

22. Have you had a surgery since acquiring your penicillin allergy?

- a. Yes
- b. No

23. In the time leading up to your surgery, did a health care practitioner ask you about your penicillin allergy?

- a. Yes
- b. No

24. Do you believe that your penicillin allergy is permanent?

- a. Yes
- b. No

25. If your regular healthcare provider wanted to prescribe penicillin, and an allergist tested you and found it to be safe, would you take it?

- a. Yes
- b. No
 - i. If not, please list why

26. Would you be interested in being referred for penicillin allergy evaluation?

- a. Yes
- b. No

FIGURE E1. Continued.

FIGURE E1. Continued.

TABLE E1. Index reactions recalled by those reporting a penicillin allergy (n = 1037)

Reaction	Number (%)
Rash only	510 (49)
“A family member told me; I don’t remember”	141 (14)
Anaphylaxis	139 (13)
Swelling	68 (7)
GI distress	47 (5)
Unknown	34 (3)
Hives	33 (3)
Family history of penicillin allergy	5 (0.5%)
Other	60 (6)

GI, Gastrointestinal.**REFERENCES**

- E1. Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377-81.
- E2. Harris P, Taylor R, Minor B, Elliott V, Fernandez M, O’Neal L, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.