

Clinical Communications

Penicillin allergy labels drive perioperative prophylactic antibiotic selection in orthopedic procedures

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

- Penicillin allergy labels influence perioperative surgical prophylaxis selection in orthopedic procedures. Penicillin allergy labels were associated with decreased cefazolin prescriptions and increased clindamycin prescriptions.

Although the incidence of penicillin allergy labels (PALs) in the United States is 8% to 20%, more than 95% of patients with PALs tolerate penicillins.¹ PALs are associated with adverse outcomes, including increased nosocomial infections, increased length of stay, and readmissions.²

In surgical patients, PALs are associated with increased surgical-site infections (SSIs)³ likely due to prophylactic antibiotic choice. For most surgeries, a first-generation cephalosporin such as cefazolin is the preferred prophylactic antibiotic due to decreased costs and lower rates of SSIs.^{4,5} In orthopedic procedures, vancomycin is more frequently underdosed and associated with increased rates of prosthetic joint infections.⁴ PAL surgical patients often receive vancomycin and clindamycin over cefazolin for concern of penicillin and cephalosporin cross-reactivity. However, a recent study showed most PAL surgical patients who underwent PAL testing were delabeled, and safely received cefazolin perioperatively.⁶ To guide changes in prescribing practices, we conducted this retrospective chart review using iterative natural language processing (NLP)⁷ and manual chart review to evaluate the relationship between PAL and perioperative antibiotic choice for orthopedic procedures.

Vanderbilt University Medical Center's deidentified Synthetic Derivative (SD) was used to find patients who had undergone at least 1 orthopedic surgery procedure. Age, sex, date of birth, perioperative antibiotics, PAL, and antibiotics received before the surgery were documented. Our definitions for orthopedic surgeries, perioperative antibiotics, and PALs can be found in the [Methods](#) section in this article's Online Repository at www.jaci-inpractice.org. Manual chart review of patients without PALs receiving clindamycin was performed, reviewing all drug allergy labels and physician notes around the time of surgery, when available.

Statistical comparisons (Stata 15.0, StataCorp LLC, College Station, Texas) were performed between patients with or without a PAL. Fisher exact test or Pearson χ^2 test was used for categorical variables and Wilcoxon rank-sum test for continuous variable analysis. Logistic regression was used to determine the odds of receiving different antibiotic agents as antimicrobial prophylaxis based on PAL status, adjusting for age, sex, and race.

Of the 17,180 SD patients who underwent orthopedic surgery, 2,353 (13.7%) had a PAL and the PAL group was more

likely to be older ($P < .0005$), female ($P < .005$), and white ($P < .05$) (Table 1).

Perioperative antibiotic selection data were available to review for 9300 surgeries, of whom 1412 (15.2%) were patients with PALs. Surgeries in patients with PALs less frequently used cefazolin (28.4% vs 80.4%) compared with surgeries in patients without PALs, and more frequently used clindamycin (66.9% vs 5.6%) (both $P < .0005$). There were no differences in administration of vancomycin (Figure 1). A PAL greatly decreased the odds of receiving cefazolin in unadjusted logistic regression analysis (odds ratio [OR], 0.10; 95% CI, 0.08, 0.11; $P < .0005$), including when adjusting for age, sex, and race (adjusted odds ratio [aOR], 0.10; 95% CI, 0.09, 0.11; $P < .0005$). In the setting of a PAL, female sex was associated with decreased odds of receiving cefazolin (aOR, 0.77; 95% CI, 0.69, 0.85; $P < .0005$), and black race was associated with increased odds of receiving cefazolin (aOR, 1.30; 95% CI, 1.10, 1.52; $P < .005$). A PAL greatly increased the odds of receiving clindamycin in unadjusted analysis (OR, 34.6; 95% CI, 29.9, 40.1; $P < .0005$), including when adjusting for age, sex, and race (aOR, 33.7; 95% CI, 29.0, 39.1; $P < .0005$). In the setting of a PAL, female sex was also associated with increased odds of receiving clindamycin (aOR, 1.45; 95% CI, 1.24, 1.68; $P < .0005$). PAL did not change the odds of receiving vancomycin (OR, 1.13; 95% CI, 0.89, 1.45; $P = .32$).

There was a statistically insignificant trend to an increased rate of SSI among patients with PALs (1.49% vs 1.15%; $P = .29$); however, we were underpowered to show a difference. Based on recent data showing increased SSIs in patients with PALs,³ future studies to analyze the relationship between SSIs and differential antibiotic selection will be important.

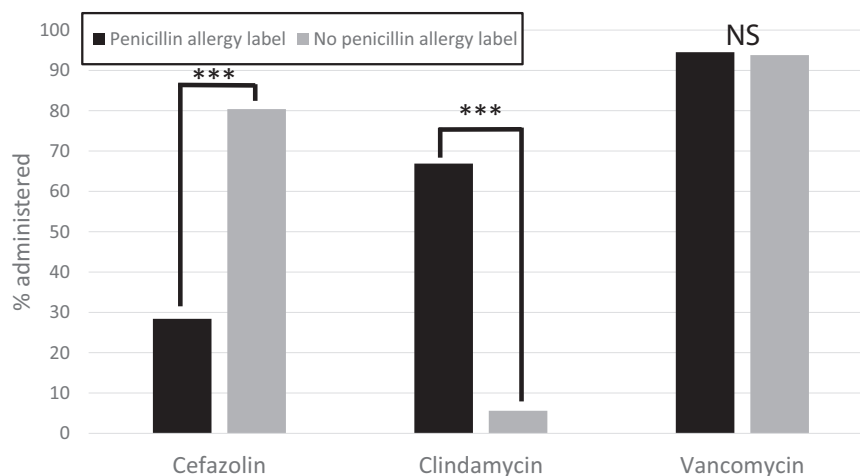
Upon our first data pull with NLP, we initially noted a much larger number of cases in which clindamycin was used in patients without PALs. After manual chart review, 550 of these cases were ultimately found to be patients with PALs who mostly had PAL free-text inputs missed by our initial NLP protocol (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). After refining our NLP algorithm, we captured 97% of these 550 cases and reperformed all analyses, with the results above.

Given the strong relationship between a PAL and clindamycin, it remained perplexing that the refined algorithm *still* found that 5.6% (436) of non-PAL surgeries used clindamycin; therefore, 150 of these surgeries were manually reviewed to hypothesize the reason. Of these 150 surgeries, 71 (47.0%) were free-text labeled as allergic to an antibiotic other than "penicillin," including an aminopenicillin (22 [14.7%]), another penicillin (3 [2%]), a cephalosporin (41 [27.3%]), or vancomycin (5 [3.3%]). Evidence of an inpatient infectious disease consultation recommending clindamycin usage was seen in 4 (2.7%), and trauma cases were seen in 4 (2.7%). The reasoning for clindamycin selection was not clear in 71 (47%) cases.

Of the patients with PALs, 553 charts were reviewed for all medications administered between the first documented instance of the PAL in the medical record and the orthopedic surgery. Of the 553 patients, 40 (7.2%) had record of taking and tolerating a penicillin before their scheduled surgery but still retained their PAL.

TABLE I. Demographic characteristics (n = 17,180)

Characteristic	PAL (n = 2,353)	No PAL (n = 14,827)	P value
Year of birth, median (interquartile range)	1947 (1940-1956)	1949 (1941-1956)	<.0005 (Wilcoxon rank sum)
Sex: female, n (%)	1,615 (68.6)	8,339 (56.2)	<.005 (χ^2 test)
Race, n (%)			<.05 (Fisher exact test)
Black	194 (8.3)	1,432 (10.2)	
Asian	13 (0.6)	83 (0.6)	
White	2,115 (90.8)	12,519 (88.8)	
Other	7 (1.3)	60 (0.4)	

**FIGURE 1.** Percentage of orthopedic surgeries using cefazolin, clindamycin, and vancomycin, by penicillin allergy status. Patients with a penicillin allergy label were less likely to receive cefazolin, *** and more likely to receive clindamycin *** compared with patients without penicillin allergy label. There was no difference in receipt of vancomycin (*** $P < .0005$; NS = not significant).

Overall, orthopedic patients with PALs at our institution received more clindamycin, and less cefazolin. PAL status predicted these antibiotic patterns, even after adjustment for age, sex, and race. When reviewing charts of patients without PALs who received clindamycin, roughly half had other β -lactam allergy labels, or a vancomycin allergy label. Thus, drug allergy labels are the main driver of clindamycin selection.

Limitations of this study involve the automated gathering of incomplete data in the SD. When we used NLP, we initially missed many patients with free-texted PAL and shorthands. This is likely a common potential setback with any study using NLP to quickly gather patients with PALs and required refinement of our algorithm to recapture 97% of them. We do not believe our conclusions would be significantly changed on the basis of missing a few of these patients.

Some (7%) of the patients with PALs had receipt of a penicillin before their orthopedic procedure. Education of providers that penicillin tolerance is grounds for PAL removal, coupled with chart review to ascertain instances of penicillin tolerance before surgery, would result in appropriate reconciliation of the PAL.

We confirm that PAL drives selection of alternative antibiotics in orthopedic procedures, and in most cases, this is unnecessary and potentially harmful.^{3,6} Because most PALs are labeled in childhood and more than 80% of patients will undergo surgery after their penicillin index reaction,⁸ this avoidance affects most patients with PALs. This information is helpful in guiding risk

stratification for delabeling by history or testing⁹ to improve perioperative antibiotic use and postoperative outcomes.

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

^bDepartment of Biomedical Informatics, Vanderbilt University 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

C.A.S. receives funding from the Agency for Healthcare Research and Quality (grant no. K12 HS026395). W.-Q.W. receives funding from the National Heart, Lung, and Blood Institute (grant no. 1R01HL133786). E.J.P. receives funding from the National Institutes of Health (grant nos. 1P50GM115305-01, R21AI139021, R34AI136815, and 1 R01 HG010863-01) and the National Health and Medical Research Council of Australia. This project was supported by Clinical and Translational Science Award number 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.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 13, 2020; revised June 10, 2020; accepted for publication July 1, 2020.

Available online ■■

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

2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2020.07.007>

REFERENCES

1. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Curr Allergy Asthma Rep* 2014;14:476.
2. 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.
3. 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.
4. Kheir M, Tan T, Azboy I, Tan D, Parvizi J. Vancomycin prophylaxis for total joint arthroplasty: incorrectly dosed and has a higher rate of periprosthetic infection than cefazolin. *Clin Orthop Relat Res* 2017;475:1767-74.
5. Wyles C, Hevesi M, Osmon D, Park M, Habermann E, Lewallen D, et al. 2019 John Charnley Award: increased risk of prosthetic joint infection following primary total knee and hip arthroplasty with the use of alternative antibiotics to cefazolin: the value of allergy testing for antibiotic prophylaxis. *Bone Joint J* 2019;101-B:9-15.
6. Moussa Y, Shuster J, Matte G, Sullivan A, Goldstein R, Cunningham D, et al. De-labeling of beta-lactam allergy reduces intraoperative time and optimizes choice in antibiotic prophylaxis [published online ahead of print May 8, 2018]. *Surgery*, <https://doi.org/10.1016/j.surg.2018.03.004>.
7. Nadkarni P, Ohno-Machado L, Chapman W. Natural language processing: an introduction. *J Am Med Inform Assoc* 2011;18:544-51.
8. Coleman DT, Stone CA Jr, Wei W-Q, Phillips EJ. Readiness for PENicillin allergy testing: Perception of Allergy Label (PEN-PAL) Survey [published online ahead of print April 15, 2020]. *J Allergy Clin Immunol Pract*, <https://doi.org/10.1016/j.jaip.2020.03.049>.
9. Stone C Jr, Stollings J, Lindsell C, Dear M, Buie R, Rice T, et al. Risk-stratified management to remove low-risk penicillin allergy labels in the intensive care unit. *Am J Respir Crit Care Med* 2020;201:1572-5.

ONLINE REPOSITORY**METHODS**

Orthopedic surgery was defined by Current Procedural Technology (CPT) codes 27130, 27438, 27446, and 2744. Perioperative antibiotic was defined as any combination of antibiotics

among clindamycin, cefazolin, and vancomycin administered within 48 hours of surgery. PAL status was ascertained by the presence of PAL in the drug allergy box via NLP, or an *International Classification of Diseases, Ninth Revision, Clinical Modification* V14.0 or *International Classification of Diseases, Tenth Revision, Clinical Modification* Z88.0 code at the time of the surgery.

Examples of free text entries that were not initially captured by natural language processing

“PCN”

“Penicillin G Benzathine”

“Penicillins” (Rash)

“pcn”

“Penicillan” (sic), or other misspellings

FIGURE E1. Examples of PALs missed in our first bioinformatics pull. Abbreviated and shorthand PALs were initially missed via NLP and required modification of the NLP inputs.