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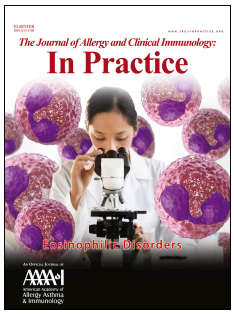

Penicillin allergy labels drive perioperative prophylactic antibiotic selection in orthopedic procedures

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Penicillin allergy labels drive perioperative prophylactic antibiotic selection in orthopedic procedures

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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 (PAL) in the United States is 8-20%, greater than 95% of PAL patients tolerate penicillins[1]. PAL is associated with adverse outcomes, including increased nosocomial infections, increased length of stay, and readmissions[2].

In surgical patients, PAL are associated with increased surgical site infections (SSI)[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 SSI[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 utilized to find patients who undergone at least one orthopedic surgery procedure. Age, gender, date of birth, perioperative antibiotics, PAL, and antibiotics received prior to the surgery were documented. Our definitions for orthopedic surgeries, perioperative antibiotics, and PAL can be found in the **EMethods in the Online Repository.** Manual chart review of non-PAL patients receiving clindamycin was performed, reviewing all drug allergy labels and physician notes around the time of surgery, when available.

Statistical comparisons (Stata 15.0) were performed between patients with or without a PAL. Fisher's exact test or Pearson's chi-squared were 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 ($P< 0.0005$), female ($P<0.005$), and white ($P<0.05$) **(Table 1)**.

Perioperative antibiotic selection data was available to review for 9,300 surgeries, of whom 1,412(15.2%) were PAL patients. Surgeries in PAL patients less frequently utilized cefazolin (28.4% vs. 80.4%) compared to non-PAL surgeries, and more frequently utilized clindamycin (66.9% vs. 5.6%) (both $P<$ 0.0005). 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 [0.08, 0.11], $P<0.0005$), including when adjusting for age, sex, and race (adjusted odds ratio [aOR] 0.10 [0.09, 0.11], $P<0.0005$). In the setting of a PAL, female sex was associated with decreased odds of receiving cefazolin (aOR 0.77 [0.69, 0.85], $P<0.0005$), and African American race was associated with increased odds of receiving cefazolin (aOR 1.30 [1.10, 1.52], $P<0.005$). A PAL greatly increased the odds of receiving clindamycin in unadjusted analysis (OR 34.6 [29.9, 40.1], $P<0.0005$), including when adjusting for age, sex, and race (aOR 33.7 [29.0, 39.1], $P<0.0005$)**.** In the setting of a PAL, female sex was also associated with increased odds of receiving clindamycin (aOR 1.45 [1.24, 1.68], $P<0.0005$)**.** PAL did not change the odds of receiving vancomycin (OR 1.13 [0.89, 1.45], $P=0.32$).

There was a statistically insignificant trend to an increased rate of SSI among PAL patients (1.49% vs. 1.15%, p-value 0.29), however we were underpowered to show a difference. Based on recent data showing increased SSI in PAL patients[3], future studies to analyze the relationship between SSI 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 non-PAL patients. After manual chart review, 550 of these cases were ultimately found to be PAL patients that mostly had PAL free-text inputs missed by our initial NLP protocol (**Figure E1 in the Online Repository**). 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 PAL patients, 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 prior to their scheduled surgery but still retained their PAL.

Overall, orthopedic PAL patients 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 non-PAL patients 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 PAL patients and required refinement of our algorithm to recapture 97% of them. We do not believe our conclusions would be significantly changed based on missing a few of these patients.

Some (7%) of the PAL patients 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 prior to surgery would result in appropriate reconciliation of the PAL.

We confirm that PAL drives selection of alterative antibiotics in orthopedic procedures, and in most cases, this is unnecessary and potentially harmful[3, 6]. Because most PAL is labeled in childhood and >80% of patients will undergo surgery after their penicillin index reaction[8], this avoidance affects most PAL patients. This information is helpful in guiding risk stratification for delabeling by history or testing[9] to improve perioperative antibiotic use and post-operative outcomes.

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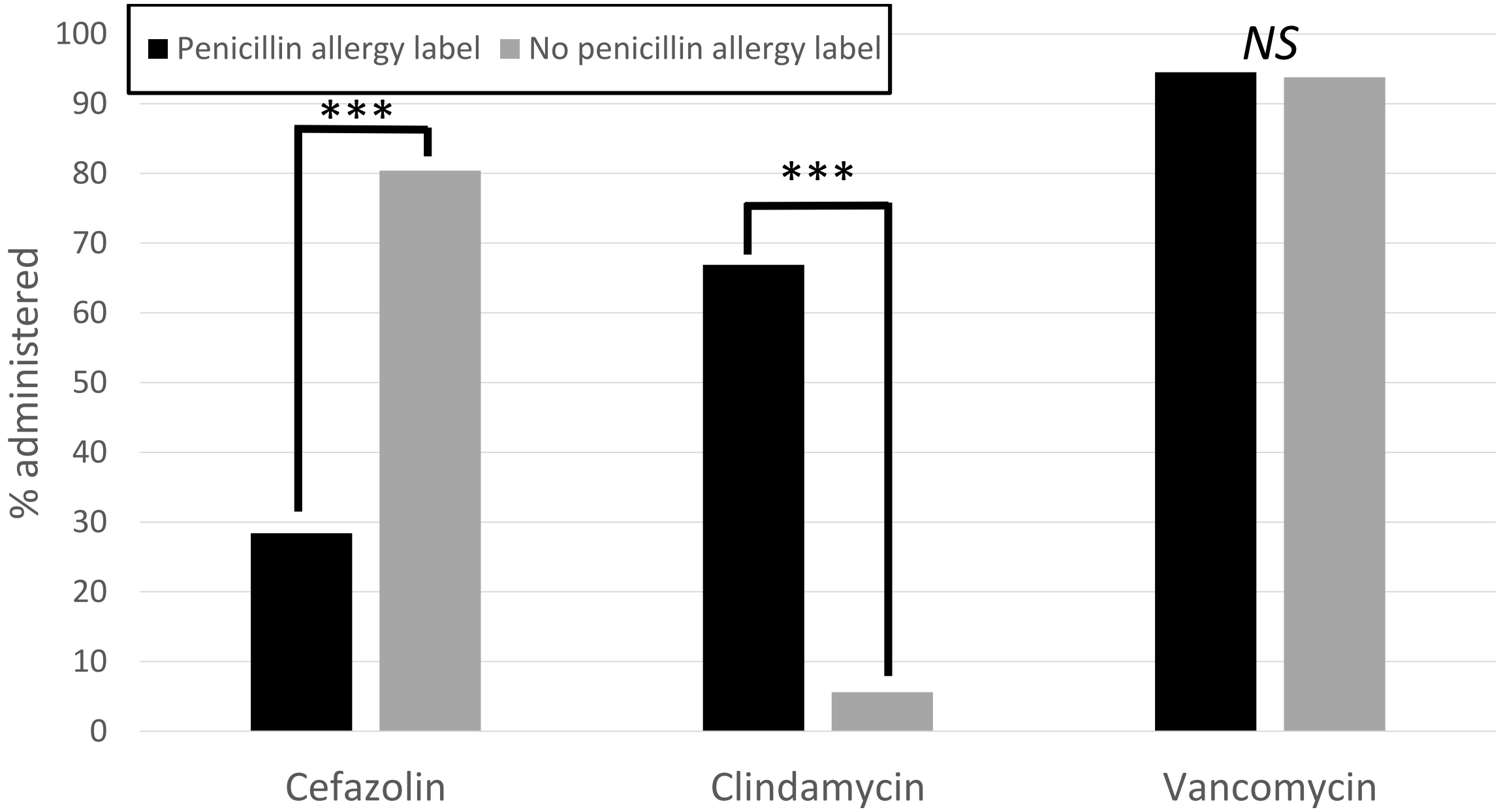
Figure Legend

Figure 1: Percentage of orthopedic surgeries utilizing 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 to patients with no penicillin allergy label. There was no difference in receipt of vancomycin (****P*<0.0005, *NS*= not significant).

Table 1: Demographics n=17,180			
	Penicillin Allergy Label (n=2,353)	No Penicillin Allergy Label (n=14,827)	*P*-value
Year of Birth Median [IQR]	1947 [1940, 1956]	1949 [1941, 1956]	<0.0005 (Wilcoxon rank sum)
Female Sex	1,615 (68.6%)	8,339 (56.2%)	<0.005 (Chi-Square test)
Race			<0.05 (Fisher's 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%)	


Penicillin allergy label
No penicillin allergy label
% administered
100
90
80
70
60
50
40
30
20
10
0
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NS
Cefazolin
Clindamycin
Vancomycin