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Int J Spine Surg 2022, 16 (6) 1023-1028
doi: https://doi.org/10.14444/8326
https://www.ijssurgery.com/content/16/6/1023

The International Journal of Spine Surgery
2397 Waterbury Circle, Suite 1,
Aurora, IL 60504, Phone: +1-630-375-1432

International Journal of Spine Surgery, Vol. 16, No. 6, 2022, pp. 1023–1028
https://doi.org/10.14444/8326

Does a Reported Penicillin Allergy Affect Outcomes Following Elective Posterior Lumbar Fusions?

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ABSTRACT

Background: Patients with a reported penicillin allergy (PA) receive alternative antibiotics that may not be as effective as cephalosporins for surgical site infection (SSI) prophylaxis. While patient-reported PA has been correlated to increased complications in other fields, this has not been conclusively shown in spine surgery. We investigate the impact of PA on 90-day complications and inpatient charges/costs after elective posterior lumbar fusion between PA and non-PA cohorts.

Methods: The 2005 to 2014 SAF100 database was queried using International Classification of Diseases, Ninth Edition (ICD-9) procedure codes to identify patients undergoing elective posterior lumbar fusions. The reported PA ICD-9 code was used to divide the study sample into a PA cohort and non-PA cohort. Multivariate logistic regression analyses were used to assess significant differences in 90-day complications between PA and non-PA groups after controlling for confounding factors. Generalized linear regression modeling was used to assess for differences in inpatient charges and costs.

Results: A total of 286,042 patients, 7497 (2.6%) of whom reported a PA, who underwent elective posterior lumbar fusions were included. Following adjustment for confounding factors, patients in the PA group had significantly higher odds of experiencing SSIs (3.8% vs 3.1%, OR 1.20 [95% CI 1.07–1.36]; $P = 0.002$), urinary tract infections (12.3% vs 10.0%, OR 1.16 [95% CI 1.08–1.24]; $P < 0.001$), sepsis (1.5% vs 1.2%, OR 1.24 [95% CI 1.02–1.50]; $P = 0.026$), acute kidney injuries (3.8% vs 3.2%, OR 1.19 [95% CI 1.05–1.34]; $P = 0.006$), readmissions (9.8% vs 8.5%, OR 1.15 [95% CI 1.07–1.25]; $P < 0.001$), increased inpatient charges (+$4340; $P < 0.001$), and increased reimbursements (+$1221; $P < 0.001$).

Conclusions: Patients with a reported PA experienced significantly higher rates of 90-day complications and cost following elective posterior lumbar fusion. The findings of the study highlight the importance of preoperative PA testing to minimize the use of alternative antibiotics and potentially improve patient outcomes.

Clinical Relevance: Patients should be tested for penicillin allergy to minimize the use of alternative antibiotics among patients with a reported PA.

Level of Evidence: 3.

Complications

Keywords: penicillin allergy, B-lactam allergy, posterior lumbar fusion, spine surgery, outcomes

INTRODUCTION

Penicillin allergies (PAs) are commonly reported by patients. Approximately 7.9% to 12.8% of the US general population report a PA,[1–4] although only less than 5% of those who report a PA have a true PA.[5] While a true PA is rare, having a reported PA adversely affects patient outcomes in several fields of medicine. Patients who have a documented PA have higher rates of *Clostridium difficile* infections, methicillin-resistant *Staphylococcus aureus* infections, vancomycin-resistant enterococcus infections, and longer hospital stays.[3,6] Furthermore, after hip arthroplasty, knee arthroplasty, hysterectomy, colon surgery, and coronary artery bypass grafting, patients with a self-reported PA had a 50% increased chance of surgical site infection (SSI). This was attributed to the use of alternative, second-line antibiotics during the perioperative period for SSI prophylaxis.[7]

First-generation cephalosporins (eg, cefazolin) are the most common and typically recommended first-line agents for SSI prophylaxis in patients undergoing many types of surgery, including spine surgery.[8–11] When patients have a documented PA, they often receive alternative, second-line agents such as clindamycin or vancomycin due to the possible cross-reactivity between cefazolin and penicillin.[4,9,12,13] When patients receive a noncephalosporin antibiotic during spine surgery, there is conflicting evidence on the possible increased risk of an SSI.[14–16] There is no clear consensus on the superiority of one agent vs another for antibiotic prophylaxis in spine surgery as per the 2013 National American Spine Society guidelines.[17]

With inconclusive evidence on reported PA and outcomes following elective spine surgeries, this large database retrospective cohort study aims to investigate the impact of reported PA on 90-day outcomes

following elective posterior lumbar fusion. Primary outcomes assessed were the impact of a reported PA on rates of readmissions and complications: sepsis, SSI, urinary tract infection (UTI), acute kidney injury (AKI), and pneumonia. Secondary outcomes include inpatient charges and cost between PA and non-PA cohorts. Our hypothesis was that these patient outcomes will be adversely affected by a reported PA.

MATERIALS AND METHODS

Database and Patient Selection

This was a retrospective cohort study carried out using insurance claims from the 100% Medicare Standard Analytical Files (SAF100), accessed through the PearlDiver research software. The PearlDiver is a third-party subscription-based research program that houses multiple national sources of administrative claims from Medicare, private payers, and the National Inpatient Samples. The program allows researchers to query data for research/analytical purposes using a unique coding language that involves combinations of International Classification of Diseases, Ninth Edition (ICD-9) diagnosis codes, procedural codes, and Current Procedural Terminology codes. Further details about the PearlDiver program can be found on the official website (www.pearldiverinc.com).

The 2005 to 2014 Medicare SAF100 files were queried using ICD-9 procedure codes 81.07, 81.08, and 81.62 to identify patients undergoing elective 1- to 3-level posterior lumbar fusions for degenerative spinal pathology. Patients undergoing concurrent anterior fusions, combined anterior-posterior fusion, >3-level fusions, and fusions for deformity, trauma, and/or malignancy were excluded. The ICD-9 diagnosis code for patient-reported PA (V14.0) was used to identify patients who had a documented patient-reported PA on the day of surgery. The study sample was divided into 2 cohorts: (1) patients with PA and (2) patients without PA (non-PA).

Ninety-Day Outcomes and Costs

The 90-day outcomes that were assessed as part of the study included SSIs, UTIs, sepsis, AKI, pneumonia, and all-cause readmissions. All payments/reimbursements made from Medicare to acute/postacute care service providers associated with the inpatient episode of care were used to calculate inpatient costs. The term "costs" refers to actual reimbursements and is distinct from "charges," which is what the hospital or service provider bills for provision of services.

Statistical Analysis

Pearson χ^2 tests were used to compare differences in baseline demographics and clinical characteristics of the 2 groups. Multivariate logistic regression analyses were used to assess whether patients with PA had higher odds of experiencing 90-day complications and/or readmissions after controlling for age, gender, region, and Elixhauser Comorbidity Index (ECI). Generalized linear regression modeling that accounted for the skewness in cost-level data was used to assess the marginal cost impact of the presence of reported PA on costs after adjusting for age, gender, region, and ECI. Results from logistic regression models have been reported as adjusted ORs along with their 95% CIs and *P* values. Results from linear regression models have been reported as marginal cost impacts (in US dollars), along with their standard errors (SE) and *P* values. For all statistical purposes, a *P* value less than 0.05 was considered statistically significant. All statistical analyses were carried out through the PearlDiver research program, which makes use of *R* statistics to provide statistical output for users.

RESULTS

Summary Statistics

A total of 286,042 patients were included in the study: 7497 patients with a reported PA (PA cohort) and 278,545 without a reported PA (non-PA cohort). There was no significant difference in age between the study cohorts ($P = 0.410$), and most patients were older than 65 years (PA cohort: 77.8%; non-PA cohort: 77.4%). Regarding gender, 71.9% of patients in PA cohort were women, while 61.2% of patients in the non-PA cohort were women ($P < 0.001$). When allocating patients to their geographical region of the United States, there was a statistically significant difference between the 2 cohorts, with more PA patients from the south compared with the non-PA patients (49.0% vs 43.9%, $P < 0.001$). The patients in the PA cohort also had more medical conditions, as measured by the ECI (PA: 4.9 ± 2.0 vs non-PA: 4.7 ± 2.0; $P < 0.001$) (Table 1).

Ninety-Day Outcomes

Following adjustment for age, gender, geographical region, and comorbidity burden, 90-day outcomes between the PA and non-PA cohort were compared (Table 2). Patients in the PA cohort had significantly higher odds of SSIs (3.8% vs 3.1%, OR 1.20 [95% CI 1.07–1.36]; $P = 0.002$), UTIs (12.3% vs 10.0%, OR

Table 1. Baseline demographics of the study population.

Demographics	Patient-Reported Penicillin Allergy (n = 7497)	No Penicillin Allergy (n = 278,545)	P Value
Age, y			0.410
<65	1662 (22.2%)	63,023 (22.6%)	
65–69	2025 (27.0%)	76,403 (27.4%)	
70–74	1751 (23.4%)	63,639 (22.8%)	
75–79	1233 (16.4%)	44,822 (16.1%)	
80–84	598 (8.0%)	21,402 (7.7%)	
≥85	164 (2.2%)	6355 (2.3%)	
Gender			<0.001
Male	2041 (27.2%)	105,212 (37.8%)	
Female	5392 (71.9%)	170,432 (61.2%)	
Unknown	64 (0.9%)	2901 (1.0%)	
Region			<0.001
Midwest	1463 (19.5%)	72,523 (26.0%)	
Northeast	792 (10.6%)	36,314 (13.0%)	
South	3673 (49.0%)	122,287 (43.9%)	
West	1567 (20.9%)	47,406 (17.0%)	
Unknown	2 (<0.1%)	15 (<0.1%)	
Elixhauser Comorbidity Index, mean ± SD	4.9 ± 2.0	4.7 ± 2.0	<0.001

Note: Data presented as n (%) unless otherwise noted.

1.16 [95% CI 1.08–1.24]; $P < 0.001$), sepsis (1.5% vs 1.2%, OR 1.24 [95% CI 1.02–1.50]; $P = 0.026$), and AKIs (3.8% vs 3.2%, OR 1.19 [95% CI 1.05–1.34]; $P = 0.006$). Furthermore, the PA cohort had significantly higher all-cause readmissions (9.8% vs 8.5%, OR 1.15 [95% CI 1.07–1.25]; $P < 0.001$). Only the odds of having pneumonia showed no difference between the 2 groups (2.5% vs 2.5%, OR 0.99 [95% CI 0.85–1.14]; $P = 0.853$).

Inpatient Charges and Reimbursements

There were significant monetary implications associated with having a reported PA (Table 3). Patients in the PA cohort had significantly higher inpatient charges ($87,565 ± $53,290 vs $81,385 ± $51,222, $P < 0.001$) and inpatient reimbursements ($22,891 ± $8931 vs $21,587 ± $8827, $P < 0.001$). When a risk-adjusted marginal cost analysis was performed, the PA cohort had significantly higher inpatient reimbursements (additional $1221 [SE: 100]) and charges (additional $4340 [SE: 583]), as compared with the non-PA cohort.

DISCUSSION

SSIs after spine surgery can have dire consequences, such as an epidural abscess, osteomyelitis/discitis, and hardware failure, leading to loss of function and possibly life.[18] The optimal use of antibiotics for SSI prophylaxis is important to mitigate such risk. While a first- or second-generation cephalosporin is the most common first-line antibiotic, noncephalosporins (eg, clindamycin or vancomycin) are routinely used for patients with a reported PA.[8–11] With approximately 1 in 10 patients reporting a PA,[1–4] the use of a noncephalosporin for SSI prophylaxis is a common occurrence in spine surgery. When retrospectively comparing vancomycin vs cefazolin for SSI prophylaxis after neurosurgical procedures, including spine procedures, Nguyen et al found no significant difference in SSIs at their institution.[15] However, in an abstract published in the *European Spine Journal*, Kruse et al showed an increased rate of SSI when utilizing clindamycin after posterior lumbar fusions.[16] Overall, the effect of noncephalosporins for SSI prophylaxis in spine surgery is inconclusive. Thus,

Table 2. Ninety-day outcomes between PA and non-PA patient populations.

Factor	PA, n (%)	No PA, n (%)	OR (95% CI)	P Value
Surgical site infections	288 (3.8%)	8695 (3.1%)	1.20 (1.07–1.36)	**0.002**
Urinary tract infections	924 (12.3%)	27,968 (10.0%)	1.16 (1.08–1.24)	**<0.001**
Sepsis	109 (1.5%)	3253 (1.2%)	1.24 (1.02–1.50)	**0.026**
Acute kidney injury	283 (3.8%)	8931 (3.2%)	1.19 (1.05–1.34)	**0.006**
Pneumonia	185 (2.5%)	6919 (2.5%)	0.99 (0.85–1.14)	0.853
All-cause readmissions	735 (9.8%)	23,696 (8.5%)	1.15 (1.07–1.25)	**<0.001**

Abbreviation: PA, penicillin allergy.
Note: Boldface indicates statistically significant findings.

Table 3. Inpatient charges and reimbursements between PA and non-PA patient populations.

Factor	PA, Mean ± SD	No PA, Mean ± SD	Risk-Adjusted Marginal Cost (Ref: No PA)	*P* Value
Inpatient charges	$87,565 ± $53,290	$81,385 ± $51,222	+$4340 (SE: 583)	**<0.001**
Inpatient reimbursements	$22,891 ± $8931	$21,587 ± $8827	$1221 (SE: 100)	**<0.001**

Abbreviations: PA, penicillin allergy; SE, standard error.
Note: Boldface indicates statistically significant findings.

this large database retrospective cohort study aimed to investigate the impact of reported PA on 90-day outcomes following spine surgery.

A resoundingly negative effect of a reported PA on patient outcomes after elective posterior spine surgery was found in this study. The PA cohort had significantly higher rates of SSIs, AKIs, UTIs, sepsis, and readmissions. These findings are likely a reflection of the use of noncephalosporins for patients with a documented PA. After total hip/knee arthroplasty, total shoulder arthroplasty, general surgery procedures, and cardiac procedures, the use of noncephalosporin antibiotics for SSI prophylaxis has been shown to increase the risk of an SSI.[7,19–21] Our result of the PA cohort's increased risk of SSI is consistent with these findings. The increased rate of AKI is a known consequence of the use of vancomycin, as it is nephrotoxic;[22] thus, it is no surprise that our PA cohort had higher rates of AKIs and supports the likely use of noncephalosporins in the PA cohort. Our increased rate of UTIs in the PA cohort is similar to findings in the bariatric surgery literature. Helmen et al showed an increased incidence of UTIs after bariatric surgery when clindamycin was used instead of cefazolin.[23] The increased rate of sepsis and all-cause readmissions seen in our study population may reflect inferior treatment and/or the increased rate of other adverse outcomes (eg, UTIs and SSI).[24] Overall, this is the first spine surgery–specific study to show the increased risk of these adverse effects with a reported PA and emphasizes the need for antibiotic stewardship using first-/second-generation cephalosporins for SSI prophylaxis.

The American Association of Allergy Asthma & Immunology recommends routine PA testing in patients with a self-reported PA.[25,26] The gold standard for PA testing has traditionally been skin testing;[27,28] however, direct oral amoxicillin challenge without skin testing has been proven to be clinically and cost-effective for certain patient populations.[29–32] New recommendations by Shenoy et al state that low-risk individuals (eg, reported reaction not likely allergic or greater than 10 years unknown, nonanaphylactic reactions to a penicillin) can safely receive direct amoxicillin under supervision. Medium-risk individuals (eg, urticaria without anaphylaxis) should receive a penicillin skin test followed by oral amoxicillin challenge, and allergist/immunologist referral should be considered to perform this testing. High-risk individuals (eg, anaphylactic reaction) should be referred to an allergist/immunologist for consideration of desensitization.[4] For patients undergoing surgical procedures, including orthopedic procedures, preoperative penicillin testing has successfully and safely reduced the amount of patients receiving noncephalosporins for SSI prophylaxis.[19,33–35] The results of our study suggest patients undergoing spine surgery with a PA would similarly benefit from appropriate preoperative penicillin testing. Prospective studies evaluating preoperative PA testing on patients undergoing spine surgery would be beneficial and are ongoing at our institution.

Patients with a self-reported PA have been shown to have a higher financial burden on the health care system. Mattingly et al performed a systematic review of patient-reported PAs and associated inpatient costs; patients with a PA had higher inpatient costs from $1145 to $4254 per patient.[36] The increased cost seen in our cohort may be due to the significant increase in complications seen in the PA cohort due to noncephalosporin antibiotic use. This not only highlights the patient outcome benefit but also economic incentive of mitigating a potentially modifiable risk factor via preoperative PA testing. Blumenthal et al evaluated the cost of an outpatient PA evaluation by an allergist/immunologist, skin test, and direct oral challenge. They estimated the mean cost to be only $220, with the range from $40 to $537 under different models.[37]

Limitations

In addition to the inherent biases present for retrospective studies, this study is limited by the accuracies of administrative coding. Results of this study may be biased by potential incorrect coding or billing errors. The lack of granular clinical information, such as the exact antibiotics given, exact charges and reimbursement, and other relevant spinal parameters (eg, clinical symptoms and degree of spinal deformity), is a limitation of administrative databases. Given the

limitations, it is difficult to ascertain as to why costs in the PA cohort were significantly higher than the non-PA cohort; however, it is possible that the greater rate of infections seen with the use of alternative second-line antibiotics may have been an underlying factor. Future prospective studies would ideally include this clinically relevant information. Another limitation of our study is only 2.6% of patients had a reported PA, with the low end of published estimated prevalence of PA is 7.9%. While we adjust our results via the ECI to control for overall comorbidity difference between cohorts, there could theoretically be a more prevalent individual comorbidity in 1 cohort that cofounds the results. Estimates based on cost savings by implementing PA testing before posterior spinal fusion are theoretical and need further prospective studies to confirm.

CONCLUSIONS

Patients with reported PA experienced significantly higher rates of SSIs, AKIs, UTIs, sepsis, readmissions, and cost following an elective posterior lumbar fusion. These findings may be due to patients receiving alternative antibiotics for SSI prophylaxis that may not be as efficacious as first-line cephalosporins. The findings of the study call on the need for PA test to minimize the use of alternative antibiotics among patients with a reported PA to potentially improve patient outcomes and decrease hospital cost.

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Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of Conflicting Interests: The authors report no conflicts of interest or financial disclosures with respect to the research, authorship, and/or publication of this article.

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Published 12 July 2022