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Original Article

Perioperative cefazolin prescribing rates following suppression of alerts for non-IgE-mediated penicillin allergies

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Abstract

Background: Cefazolin is the preferred antimicrobial for the prevention of surgical site infections (SSIs) in many procedures. The presence of penicillin allergies can influence prescribing of alternative agents like vancomycin. In April 2022, Nebraska Medicine implemented a suppression of alerts for non-IgE-mediated and nonsevere penicillin allergies in the electronic medical record (EMR) upon cephalosporin prescribing. The objective of this study was to evaluate changes in perioperative cefazolin for SSI prophylaxis.

Methods: This was a quasi-experimental study of patients undergoing procedures for which cefazolin was the preferred agent per institutional guidance. Education on the change was distributed via e-mail to surgical staff and pharmacists. Pre- and post-intervention data were collected from April 2021 through March 2022 and April 11, 2022, through October 2022, respectively. Chart review was performed on patients with reported penicillin allergies for the top surgical procedures with <50% cefazolin utilization pre-intervention. The primary outcome was the administration of perioperative cefazolin in patients with penicillin allergies, including unknown reactions.

Results: A total of 6,676 patients underwent surgical procedures (pre-intervention $n = 4{,}147$, post-intervention $n = 2{,}529$). Documented penicillin allergies were similar between the pre- and post-intervention group (12.3% vs. 12.6%). In individuals with documented penicillin allergies, cefazolin prescribing increased from 49.6% to 74.3% ($p < 0.01$). Chart review for safety outcomes identified no difference in new severe reactions, rescue medication, SSIs, acute kidney injury, postoperative *Clostridioides difficile* infection, or methicillin-resistant *Staphylococcus aureus* infections.

Conclusion: Following the suppression of EMR alerts for non-IgE-mediated and nonsevere penicillin allergies, cefazolin prescribing rates for SSI prophylaxis significantly improved.

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Introduction

Optimal use of antibiotics can lower the incidence of surgical site infections (SSIs), and beta-lactam antibiotics are recommended as prophylaxis for most procedures.[1,2] Cefazolin is a preferred agent due to its bactericidal activity against common skin flora such as *Staphylococcus* and *Streptococcus species*, plus favorable pharmacokinetics that allow for optimal concentration of the antibiotic in tissue.[1] The presence of penicillin allergies in the electronic medical record (EMR) can influence prescribers to choose non-beta-lactam alternatives such as vancomycin.[3–5] The use of second-line agents for individuals with penicillin allergies has been associated with a higher incidence of SSIs, methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridioides difficile* infections, and nephrotoxicity.[6–10]

Previous research indicates that 90%–99% of patients with reported reactions to penicillin do not currently have hypersensitivity to the drugs.[11,12] Furthermore, <3% of patients with true penicillin allergies will react to cefazolin due to its unique R-side chain.[13] Despite the low rates of cross-reactivity between penicillin and cephalosporins, prescribers are often influenced toward alternative therapies in the presence of penicillin allergies. Medication allergy information is typically highly visible in the EMR, but interruptive alerts are displayed at the time of ordering cross-reacting medications. Alerts to penicillin allergies in the EMR can influence provider decision-making as many alerts will default to severe warnings regardless of the documented allergy.[14,15] Recent literature suggests that removing these interruptive alerts for cefazolin prescribing in patients with penicillin allergies resulted in increased beta-lactam prescribing with no significant differences in anaphylaxis rates, treatment failure, or all-cause mortality.[16–18] In this study, we aimed to evaluate changes in cefazolin and vancomycin prescribing for SSI prophylaxis when alerts were suppressed in our EMR for nonsevere and non-IgE-mediated reactions to penicillin when any cephalosporin was ordered.

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Methods

Research design

This was a quasi-experimental study evaluating orders for cefazolin and vancomycin SSI prophylaxis before and after the suppression of allergy in the EMR (Epic OneChart®, Verona, WI) that went into effect in April 2022 at Nebraska Medicine, a 718-bed academic medical center in Omaha, NE. Prior to alert suppression, prescribers were given an interruptive upon prescribing a cephalosporin to patients with any form of a penicillin allergy. This interruptive alert required prescribers to acknowledge they were aware of the allergies and potentially document the reason for prescribing. Upon ordering cephalosporins after April 10, 2022, prescribers were only alerted to severe allergies to penicillins. Warnings were suppressed for all reactions to penicillin except anaphylaxis, angioedema, urticaria, wheals, hives, "throat swelling," shortness of breath, "trouble breathing," Stevens-Johnson syndrome (SJS), Toxic Epidermal necrolysis Syndrome (TENS), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Warnings were also suppressed if an individual had an unknown reaction to penicillin documented in the chart. Education was disseminated to surgical staff and all pharmacists via an e-mail prior to the intervention. Pre-intervention data included patients from April 1, 2021, to March 31, 2022. Post-intervention information was collected from April 11, 2022, to October 31, 2022.

Patients

Patients were included if they were ≥19 years old, underwent a surgical procedure where cefazolin was considered the preferred antimicrobial for SSI prophylaxis, and had a hospital length of stay 24 hours during the study period. Surgical procedures were categorized into 15 procedural categories (Table 1). Patients were excluded if they received both intravenous vancomycin and cefazolin. For individuals with multiple procedures during the study period, only the first surgery was included to avoid duplicative results.

Information on each surgical procedure performed, patient allergy history, and antibiotics administered for the indication of SSI prophylaxis were collected. All patient charts in the top five procedure categories with <50% cefazolin prescribing in patients with penicillin allergies were manually reviewed for data quality.

Outcomes

The primary outcome was the rate of cefazolin prescribing in patients with documented penicillin allergy. Secondary outcomes included vancomycin prescribing rates, the incidence of documented IgE-mediated or severe allergic reactions, utilization of medications for allergic reaction (diphenhydramine, steroids, and epinephrine), the incidence of SSIs based on documentation in surgical providers' notes, acute kidney injury as defined using RIFLE criteria, and detection of *C. difficile* or MRSA post-operatively within 30 days. SSIs were reviewed for up to one year after the procedure.

Statistical analysis

Fischer's exact test was used to analyze the primary outcome and to compare categorical variables for patients included in the manual chart review. Descriptive statistics were used for baseline patient characteristics. Statistical significance was defined as $p<0.05$. Statistical analysis was performed using SPSS software, version 29.0.

Table 1. Procedure classification and rates of penicillin allergies

Procedure category, *n* (%)	Pre-intervention	Post-intervention	Overall
All procedures	4,147 (100)	2,529 (100)	6,676 (100)
Penicillin allergies	507 (12.2)	318 (12.6)	825 (12.4)
Orthopedic	943 (22.7)	583 (23.1)	1,526 (22.9)
Penicillin allergies	99 (10.5)	73 (12.5)	172 (11.3)
Cardiac	624 (15.1)	359 (14.2)	983 (14.7)
Penicillin allergies	82 (13.1)	44 (12.3)	126 (12.8)
Spinal	512 (12.4)	339 (13.4)	851 (12.7)
Penicillin allergies	77 (15.0)	46 (13.6)	123 (14.5)
Neurologic	432 (10.4)	241 (9.5)	673 (10.1)
Penicillin allergies	59 (13.7)	38 (15.8)	97 (14.4)
Vascular	332 (8.0)	192 (7.6)	524 (7.8)
Penicillin allergies	52 (15.7)	24 (13.0)	76 (14.5)
Urologic	273 (6.6)	153 (6.0)	426 (6.4)
Penicillin allergies	38 (13.9)	17 (11.1)	55 (12.9)
Thoracic	235 (5.7)	144 (5.7)	379 (5.7)
Penicillin allergies	33 (14.0)	23 (16.0)	56 (14.8)
Abdominal	158 (3.8)	123 (4.9)	281 (4.2)
Penicillin allergies	20 (12.7)	17 (13.8)	37 (13.2)
Gynecologic	178 (4.3)	93 (3.7)	271 (4.1)
Penicillin allergies	11 (6.2)	8 (8.6)	19 (7.0)
Head & Neck	122 (2.9)	106 (4.2)	228 (3.4)
Penicillin allergies	4 (3.3)	7 (6.6)	11 (4.8)
Kidney transplant	98 (2.4)	62 (2.5)	160 (2.4)
Penicillin allergies	3 (3.1)	3 (4.8)	6 (3.8)
General	76 (1.8)	49 (1.9)	125 (1.9)
Penicillin allergies	14 (18.4)	8 (16.3)	22 (17.6)
Plastics	82 (2.0)	31 (1.2)	113 (1.7)
Penicillin allergies	6 (7.3)	3 (9.7)	9 (8.0)
Flap	46 (1.1)	28 (1.1)	74 (1.1)
Penicillin allergies	3 (6.5)	4 (14.3)	7 (9.5)
Gastroduodenal	33 (0.8)	21 (0.8)	54 (0.8)
Penicillin allergies	6 (18.2)	3 (14.3)	9 (16.7)
Radiation	3 (0.07)	5 (0.2)	8 (0.1)
Penicillin allergies	0	0	0

Results

Characteristics of patients

A total of 6,676 procedures were performed during the study period with 4,147 pre-intervention and 2,529 post-intervention. The characteristics of patients in both groups, before and after the intervention, were similar (Table 2). Penicillin allergies were reported in 508 (12.3%) individuals pre-intervention and 319 (12.6%) post-intervention.

Cefazolin was prescribed in 97.9% of procedures without a documented penicillin allergy and 49.6% of surgeries where a PCN allergy was present in the pre-intervention period. The top five

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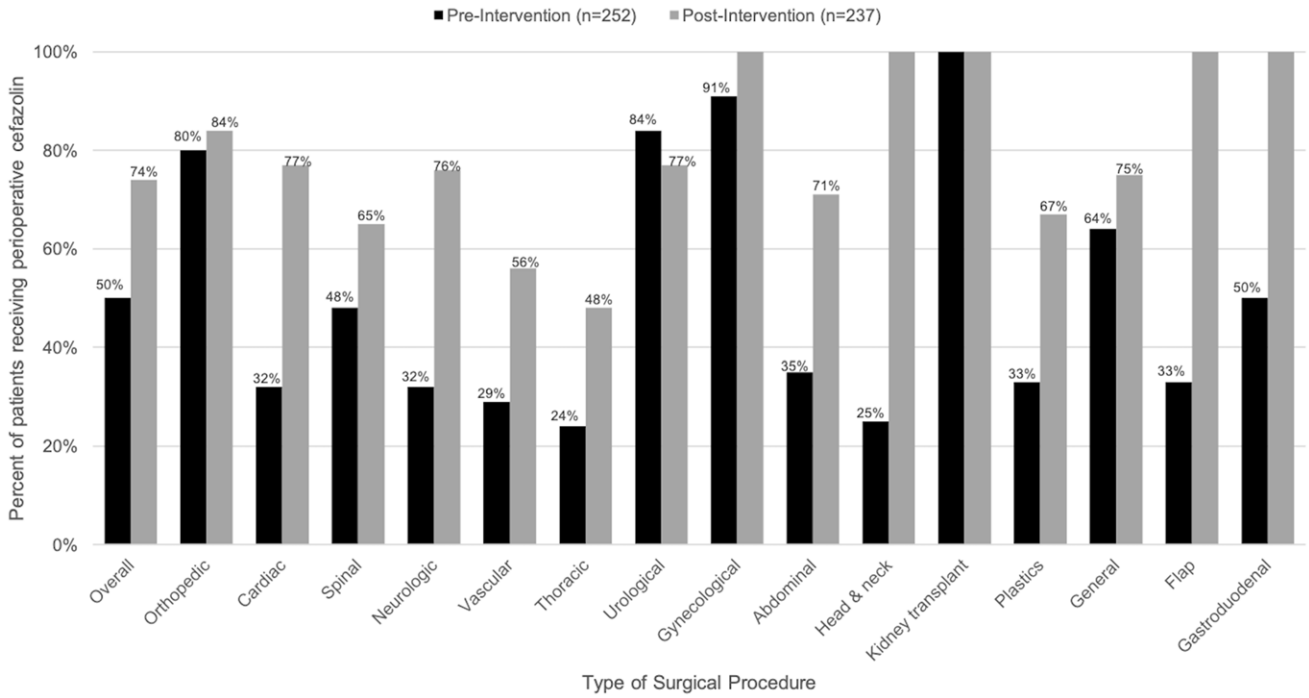

Figure 1. Perioperative cefazolin administration in patients with penicillin allergies by procedure type, in order of most procedures performed to least.

categories identified as having <50% cefazolin prescribing pre-intervention were cardiac, spinal, neurologic, vascular, and thoracic procedures (Figure 1). Patients undergoing procedures in these categories were identified as candidates for chart review.

A total of 478 patients were included in the chart review with 303 patients pre-intervention and 175 post-intervention. Patient characteristics were similar for all categories except for the rate of unknown penicillin allergy history (Table 2). More patients in the post-intervention cohort had an unknown reaction to penicillin charted in the EMR. When a penicillin allergy was documented in the EMR, it was more likely to be a nonsevere reaction. The most commonly documented IgE-mediated penicillin allergy was hives, wheals, or urticaria followed by anaphylaxis. Nonsevere reactions were most commonly identified as rash and then gastrointestinal symptoms.

Outcomes

Overall prescribing of cefazolin increased from 92% to 95% ($p < 0.01$). In individuals with a penicillin allergy, the rate of cefazolin prescribing increased from 49.6% pre-intervention to 74.34% post-intervention ($p < 0.01$). The rate of cefazolin prescribing in patients with penicillin allergy undergoing cardiac, spinal, neurologic, vascular, and thoracic procedures increased post-intervention (34.7% vs. 68.9%, $p < 0.01$). In addition, vancomycin prescribing rates decreased from 65.3% to 33.1% ($p < 0.01$) in patients with a reported penicillin allergy.

The frequency of reported severe allergic reactions in this cohort was <1% in each group (0.66% vs. 0.57%, $p = 0.90$). In the pre-intervention cohort, four individuals had reactions related to vancomycin and received diphenhydramine and two of these individuals also received a steroid. In the post-intervention group, one individual had a new reaction documented to cefazolin documented as lip swelling, but this is unlikely to be attributed to an allergic reaction based on the timing of over 72 hours after the completion of the antibiotic. The patient received diphenhydramine for the resolution of symptoms, and no additional action was needed. The rate of SSI was 1.7% between both groups ($p = 0.96$). The occurrence of acute kidney injury was lower in the post-intervention group but did not meet statistical significance (10.6% vs. 7.4%, $p = 0.26$). Postoperative *C. difficile* infections developed in five (1.7%) individuals pre-intervention and one (0.6%) post-intervention ($p = 0.42$). Similarly, the incidence of new postoperative MRSA infection developed in five (1.7%) patients pre-intervention and one (0.6%) patient post-intervention ($p = 0.52$).

Discussion

This study evaluated the rate of perioperative cefazolin prescribing in patients with reported penicillin allergy undergoing procedures where cefazolin was preferred after selectively suppressing an alert for penicillin allergies in the EMR. Overall, cefazolin prescribing rates significantly increased in patients with a documented allergy to penicillin without an increased risk of the use of rescue medications for allergic reactions or new documented reactions.

Following the suppression of the interruptive penicillin allergy alert in the EMR, there was a 50% increase in perioperative cefazolin prescribing. A similar result was seen in a study published by Macy et al, who evaluated the effects of a penicillin allergy alert suppression on dispensing or administration of all oral and parenteral antibiotics.[18] The authors demonstrated a 47% increase in cephalosporin administration among patients with penicillin allergies following a similar alert suppression (adjusted ratio of odds ratio, 1.47; 95% CI, 1.38–1.56). In addition to the increased utilization of cephalosporins among patients with penicillin allergies, there were also no significant differences in anaphylaxis, new allergies, or treatment failures.[18] Boesch et al. also evaluated a beta-lactam cross-allergy EMR alert suppression on patients with beta-lactam allergies.[19] A 91% relative increase in the number of

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Table 2. Baseline characteristics of patients with penicillin allergies undergoing procedures with <50% prescribing of cefazolin in procedures where it was the preferred agent for SSI prophylaxis

Variable, *n* (%)	Pre-intervention (*n* = 303)	Post-intervention (*n* = 175)
Age (years), mean ± SD	61.5 ± 15.6	61.8 ± 15.2
Female	181 (59.7)	104 (59.4)
Weight (kg), mean ± SD	87.6 ± 23.1	83.2 ± 24.0
Length of stay, mean ± SD	6.4 ± 20.6	8.19 ± 29.1
Prior MRSA infection	19 (6.2)	9 (5.1)
Procedure performed		
Cardiac	82 (27.1)	44 (25.1)
Spinal	77 (25.4)	46 (26.3)
Neurologic	59 (19.5)	38 (21.7)
Vascular	52 (17.2)	24 (13.7)
Thoracic	33 (10.8)	23 (13.1)
Non-penicillin beta-lactam allergy	40 (13.2)	45 (25.7)
Prior IgE-mediated or severe reaction	115 (38.0)	48 (27.4)
Hives, wheals, urticaria	77 (25.4)	35 (20.0)
Angioedema, "throat swelling"	9 (3.0)	5 (2.9)
Shortness of breath, "trouble breathing"	10 (3.3)	2 (1.1)
Anaphylaxis	19 (6.3)	6 (3.4)
SJS, TENS, DRESS	1 (0.3)	0 (0)
Prior nonsevere reaction	148 (48.8)	82 (46.9)
Rash	76 (25.1)	53 (30.3)
GI symptoms	41 (13.5)	21 (12.0)
Musculoskeletal symptoms	8 (2.6)	3 (1.7)
Itching	8 (2.6)	0 (0)
Altered mental status	4 (1.3)	3 (1.7)
Other	11 (3.6)	2 (1.1)

patients who received a beta-lactam agent was noted (26.6% vs. 51%, $p < 0.001$).[19]

Our study has several limitations to consider. First, this was a single-center review that lacked randomization which could limit the generalizability of the results. Determining the presence of adverse events, administration of rescue medications for new allergic reactions, and incidence of postoperative complications relied on accurate documentation in the health record. It is also possible that patients had postoperative complications, such as SSIs, and were assessed at outside facilities where data could not be collected. Additionally, the retrospective chart review of patients with penicillin allergies undergoing cardiac, spinal, neurologic, vascular, and thoracic procedures was performed 3 months after the end of the study period. Although this is a standard time frame for detecting healthcare-acquired infection, there is the potential that the rate of SSI may be underestimated. Next, we included patients in our study that had a hospital length of stay of at least 24 hours. Although we used this time frame to help ensure appropriate safety data could be collected from the EMR, not all adverse effects can be detected while patients are in the hospital or while presented to an affiliated clinic for follow-up. This study also did not evaluate other antibiotics such as clindamycin that could be used for surgical prophylaxis in patients with penicillin allergies, although it was not expected that the use of this agent would change substantially since it is not considered a preferred alternative to cefazolin at our institution.

Overall, this study demonstrates a statistically significant increase in cefazolin orders for SSI prophylaxis in surgical procedures where it is preferred following the suppression of alerts for nonsevere and non-IgE-mediated penicillin allergies upon cephalosporin prescribing. Allergy alert suppression was a safe and effective method to improve patient care through antimicrobial stewardship and increased prescribing of preferred antibiotics with minimal effort.

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