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Comparison of immediate hypersensitivity reactions to preoperative antibiotics in patients labeled as penicillin allergic

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ABSTRACT

Background: Cefazolin is routinely recommended as the first-line agent for surgical antibiotic prophylaxis because it prevents more surgical site infections than second-line antibiotics. Clinicians often avoid administering cefazolin to patients who are labeled as penicillin allergic due to concerns of cross-reactivity. The aim of this study was to compare the incidence of hypersensitivity reactions between cefazolin and the second-line antibiotics vancomycin and clindamycin.

Methods: This retrospective study included patients who were labeled as penicillin allergic and received either cefazolin, clindamycin, or vancomycin as preoperative antibiotics. The primary outcome was intraoperative hypersensitivity reactions.

Results: A total of 734 surgical procedures in 690 patients were included. Fifteen immediate hypersensitivity reactions were identified. Probable hypersensitivity reactions occurred in 3 (0.9%) patients in the cefazolin group, 4 (1.4%) in the clindamycin group, and 1 (1.1%) in the vancomycin group. Seven of 8 patients reported allergies to additional medications beyond penicillin. There were seven cases of possible hypersensitivity reactions, 3 (0.9%) in the cefazolin group, 1 (1.1%) in the vancomycin group, and 3 (1.0%) in the clindamycin group.

Conclusion: Our data suggest that perioperative hypersensitivity reactions are uncommon in patients labeled as penicillin allergic. The frequency of immediate hypersensitivity reactions was not different between patients receiving cefazolin, clindamycin, or vancomycin. Avoiding cefazolin in patients labeled as penicillin allergic may not be warranted.

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Introduction

The guideline-recommended standard of care for surgical prophylaxis is cefazolin and second-line options include clindamycin and vancomycin.^{1–3} Guidelines identify that cefazolin is superior to vancomycin at preventing surgical site infections and possesses the narrowest spectrum of activity that still covers the most common causative pathogens. Use of second-line antibiotics among surgical patients not colonized by resistant organisms has been associated with higher rates of infection by vancomycin-resistant enterococci, *Clostridium difficile*, and methicillin-resistant *Staphylococcus aureus*.⁴ Additionally, beta-lactams like cefazolin have a favorable safety profile when compared with the second-line antibiotics.⁵

Approximately 10% of all surgical patients are labelled penicillin allergic.⁶ However, it is estimated that only 1% to 10% of reported allergies are confirmed to be type I, IgE-mediated reactions.⁷ Because of concern for cross-reactivity, patients labeled as penicillin allergic often do not receive cefazolin for surgical site infection prophylaxis. Studies have shown worse outcomes among penicillin allergic patients who receive second-line antibiotics rather than cefazolin. A recent retrospective study found that patients labelled as penicillin allergic were 1.6 times more likely to develop surgical site infections than non-penicillin-allergic patients, due to use of second-line antibiotics.⁸ SSIs are a major cause of morbidity and mortality among hospitalized patients, with an estimated 11% of intensive care unit deaths associated with surgical site infections.⁹ Therefore, all efforts should be made to prevent SSIs through optimal antimicrobial prescribing practices whenever possible.

The objective of this study is to compare rates of hypersensitivity reactions among patients who are labeled as penicillin allergic who received cefazolin, clindamycin, or vancomycin as preoperative antibiotics.

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Methods

Participants

Data from the electronic medical record were collected from adult male and female patients labeled as allergic to a penicillin antibiotic who had undergone a surgical procedure at University of Colorado Health (UCHealth) hospitals between August 2019 and September 2020. Potential participants were identified electronically from Health Data Compass Data Warehouse project (healthdatacompass.org), a comprehensive electronic health record database for the UCHealth system. Participants were included if they were ≥ 18 years, labeled as allergic to a penicillin antibiotic, and received either cefazolin, clindamycin, or vancomycin for perioperative antibiotic prophylaxis. Patients were excluded from the study if they received more than 1 perioperative antibiotic agent.

Study design

This retrospective chart review was performed to analyze rates of perioperative hypersensitivity reactions between patients receiving cefazolin, vancomycin, and clindamycin. It was reviewed and approved by The Colorado Multiple Institutional Review Board. Baseline characteristic data were gathered from the electronic medical record including admission and discharge problem lists, medications before admission, and allergy history. Information collected included demographic data, diseases of the immune system, immune modulating medications, comorbid conditions, and medications associated with increased risk of hypersensitivity reactions. Diseases of the immune system included cancer (active or resolved), transplant, rheumatoid arthritis, lupus, Crohn's and ulcerative colitis, asthma, psoriasis, multiple sclerosis, HIV, HSV, eczema, allergic rhinitis, seasonal allergies, and/or varicella. Immunomodulatory medications were defined as chemotherapy, B and T cell modulators, corticosteroids at a dose ≥ 20 mg of prednisone daily, and antihistamines. All allergy data were collected including source and reaction. Other allergies included in the medical record were also collected including medication, contact, environmental, and food. Patients were categorized based on receipt of either cefazolin, clindamycin, or vancomycin.

Outcomes

The primary outcome was intraoperative immediate hypersensitivity reaction. Immediate hypersensitivity reaction was defined as either probable or possible. Probable immediate hypersensitivity reaction was defined as the occurrence of flushing, urticaria, erythema, angioedema, acute hypotension (systolic blood pressure < 80 mmHg or 40% decrease in systolic blood pressure within 5 minutes), wheezing, increased vent pressures, bronchospasm, or respiratory distress⁹, or if allergic or hypersensitivity reaction was stated. Possible immediate hypersensitivity reaction was defined as receipt of intravenous epinephrine or diphenhydramine without a documented indication at doses and routes that were consistent with treatment for hypersensitivity reaction. Epinephrine given in association with anesthetics via a local, topical, or intrathecal route was not considered to be for the treatment of a possible immediate hypersensitivity reaction. Diphenhydramine administration was recorded if the dosing was 10 mg to 50 mg and given by intramuscular or intravenous route. The window of time in which patients were screened for hypersensitivity reactions started when preoperative antibiotics were administered through 60 minutes after the conclusion of the surgery.

The intraoperative flowchart was used to identify abnormal vital signs potentially associated with hypersensitivity reactions. Surgical and anesthesiology notes were read for any symptoms associated with hypersensitivity reactions including but not limited to swelling, edema, flushing, burning, shortness of breath, difficulty ventilating, bronchospasm, desaturation, throat tightness, hives, rash, fever, erythema, hypotension, itching, pruritis, arrhythmia, tachycardia, bradycardia, anaphylaxis, angioedema, anasarca, and laryngeal edema.⁵

Statistics

To detect a 4% difference between antibiotic groups, a sample size of 224 patients per group is needed. The sample size calculation is based on the following assumptions: hypersensitivity reactions frequency of 5% for cefazolin and 1% for vancomycin or clindamycin, an alpha of .05, and a beta of 20%. Baseline categorical variables were compared using a 2-tailed χ^2 test and z score to identify differences between patients receiving cefazolin, clindamycin, or vancomycin. Continuous variables were compared using an analysis of variance (ANOVA) and posthoc Tukey to identify differences between antibiotic groups. The primary outcome of hypersensitivity reactions between antibiotic groups was analyzed using a χ^2 test. Statistical significance was defined as a $P < .05$. Statistical analysis was performed using SPSS software, v. 27.0 (IBM, Armonk, NY).

Results

Cohort Characteristics

The final cohort included 734 surgical procedures performed on 690 patients, obtained by screening 9,782 surgical records. For each month screened, approximately 9% of surgical records were included in the final cohort. The primary exclusion reasons were use of multiple preoperative antibiotics or lack of beta-lactam allergy. The sample consisted of 480 females and 210 males. Cefazolin was used as preoperative prophylaxis in 350 (47.8%) cases, clindamycin in 295 (40.1%) cases, and vancomycin in 89 (12.1%) cases. Patients in the clindamycin and vancomycin groups were more likely to have a generic penicillin-allergy label, less likely to also have a cephalosporin allergy other than to cefazolin, and less likely to have a penicillin reaction history of anaphylaxis or edema. Patients who reported gastrointestinal distress as their index penicillin-associated symptom more often received cefazolin. All baseline characteristics can be found in [Table I](#).

Primary outcome: immediate hypersensitivity reactions

Among 734 surgical cases, immediate hypersensitivity reactions occurred in 15 patients ([Table II](#)). Probable immediate hypersensitivity occurred in 3 (0.9%) patients in the cefazolin group, 1 (1.1%) patient in the vancomycin group, and 4 (1.4%) patients in the clindamycin group. There were seven cases of possible hypersensitivity reactions in which patients received epinephrine and/or diphenhydramine at hypersensitivity reaction treatment doses but an indication was not documented, 3 (0.9%) in the cefazolin group, 1 (1.1%) in the vancomycin group, and 3 (1.0%) in the clindamycin group. Among the 8 patients with probable immediate hypersensitivity reactions, most common presentation was hypotension ([Table III](#)). Seven of 8 patients reported allergies to additional medications beyond penicillin and 6 were either receiving immunologic medications or had an immunologic disease. The most common sign of immediate hypersensitivity reactions was hypotension ($n = 4$) and respiratory dysfunction ($n = 3$). Four patients

Table I

Characteristics of patients labeled as allergic to penicillin receiving preoperative antibiotics

Variable	Cefazolin, N = 350	Vancomycin, N = 89	Clindamycin, N = 295	P value
Age, yr	56.8 ± 17.5	63.8 ± 14.6	52.3 ± 17.0	<.01 ^{*,†}
Sex, female	252 (72.0)	65 (73.0)	200 (67.8)	.43
Body mass index, kg/m ²	29.5 ± 6.9	30.2 ± 6.7	28.2 ± 6.6	.01
Penicillin allergy label				
Penicillin	253 (72.3)	75 (84.3)	241 (81.7)	<.01 ^{*,†}
Amoxicillin	64 (18.3)	17 (19.1)	55 (18.5)	.98
Amoxicillin/clavulanate	35 (10.0)	7 (7.9)	27 (9.2)	.81
Piperacillin/tazobactam	14 (4)	0 (0.0)	3 (1.0)	.01 [†]
Ampicillin	5 (1.4)	3 (3.4)	6 (2.0)	.48
Nafcillin	0 (0.0)	0 (0.0)	2 (0.7)	.23
Other antibiotic allergy label				
Cephalosporin	9 (2.6)	12 (13.5)	46 (15.5)	<.01 ^{*,†}
Clindamycin	11 (3.1)	16 (18.0)	0 (0.0)	<.01 [§]
Vancomycin	5 (1.4)	0 (0.0)	10 (3.4)	.08
Cefazolin	0 (0.0)	1 (1.1)	1 (0.3)	.19
Documented reaction history				
Rash	120 (34.3)	30 (33.7)	91 (30.8)	.64
Gastrointestinal	47 (13.4)	2 (2.2)	18 (6.1)	<.01 ^{*,†}
Hives	73 (20.9)	24 (27.0)	76 (25.8)	.25
Unknown	67 (19.1)	9 (10.1)	48 (16.3)	.12
Edema	19 (5.4)	10 (11.2)	37 (12.5)	<.01 ^{*,†}
Anaphylaxis	7 (2.0)	15 (16.9)	45 (15.3)	<.01 ^{*,†}
Erythema	1 (0.3)	2 (2.2)	4 (1.4)	.16
Organ toxicity	1 (0.3)	0 (0.0)	0 (0.0)	.58
SJS/TEN/DRESS	0 (0.0)	1 (1.1)	1 (0.3)	.19
Other	67 (19.1)	18 (20.2)	46 (15.6)	.41
History of non-antibiotic medication allergy	232 (66.3)	78 (87.6)	198 (67.1)	<.01 ^{*,†}

Data are presented as no. (%) unless otherwise indicated.

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; HSV, herpes simplex virus; HIV, human immunodeficiency virus; HTN, hypertension; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

^{*} Significant difference between cefazolin and vancomycin.[†] Significant difference between cefazolin and clindamycin.[‡] Significant difference between vancomycin and clindamycin.[§] Significant difference between all 3 groups.**Table II**

Frequency of immediate hypersensitivity reaction among patients labeled as allergic to penicillin receiving preoperative antibiotics

Variable	Cefazolin, N = 350	Vancomycin, N = 89	Clindamycin, N = 295	P value
Immediate hypersensitivity reaction	6 (1.7)	2 (2.2)	7 (2.4)	.83
Probable hypersensitivity reaction	3 (0.9)	1 (1.1)	4 (1.4)	.83
Acute hypotension	2 (0.6)	1 (1.1)	1 (0.3)	.68
Flushing	1 (0.3)	0 (0.0)	0 (0.0)	.58
Erythema	0 (0.0)	0 (0.0)	1 (0.3)	.48
Angioedema	0 (0.0)	1 (1.1)	0 (0.0)	.03 [*]
Wheezing	1 (0.3)	0 (0.0)	0 (0.0)	.58
Bronchospasm	0 (0.0)	0 (0.0)	1 (0.3)	.48
Respiratory distress	1 (0.3)	0 (0.0)	1 (0.3)	.86
Possible hypersensitivity reaction	3 (0.9)	1 (1.1)	3 (1.0)	.96
Receipt of epinephrine	3 (0.9)	0 (0.0)	1 (0.3)	.51
Receipt of diphenhydramine	0 (0.0)	1 (1.1)	2 (0.7)	.21

Data are presented as no. (%) unless otherwise indicated.

^{*} Significant difference between cefazolin and vancomycin.

received either intravenous epinephrine or diphenhydramine for hypersensitivity reaction symptoms.

Discussion

This study examined 734 surgical cases in which patients labeled as penicillin allergic received either cefazolin, clindamycin, or vancomycin, to assess the frequency of intraoperative hypersensitivity reactions. Of the 734 surgeries, 48% included the use of cefazolin, showing a promising trend toward increased prescribing of cefazolin among patients labeled as penicillin allergic. The remaining procedures utilized clindamycin (40%) and vancomycin (12%). The incidence of hypersensitivity reactions was low

regardless of which preoperative antibiotic was administered. The frequency of hypersensitivity reactions was approximately 1% for all antibiotic groups. Comparatively, 2 prospective studies reported an anaphylaxis frequency of 0.2% to 0.3%.^{10,11} However these studies were focused on anaphylaxis during induction and included all patients regardless of baseline allergy history. The frequency of hypersensitivity of 1% that was found in the present study is likely higher because all patients had a history of penicillin-allergy. Ideally a logistic regression would have been performed to identify risk factors for intraoperative hypersensitivity since antibiotic choice did not appear to be associated with hypersensitivity reactions. However, due to the low incidence of hypersensitivity reactions, logistic regression is inappropriate.

Table III
Characteristics of probable immediate hypersensitivity reactions among patients labeled as allergic to penicillin receiving preoperative antibiotics

Patient	Age/ Sex	Preoperative antibiotic	Penicillin allergy, reaction history	Other medication allergy, reaction	Contact allergies, reaction history	Medications and/or conditions of interest	Immediate hypersensitivity reaction presentation	Receipt of intravenous epinephrine	Receipt of diphenhydramine
1	31/F	Cefazolin	Pip/tazo, itching	Prochlorperazine, anxiety furosemide, flushing promethazine, malaise pantoprazole, nausea Iodine, airway obstruction None	None	Lisinopril, T2DM, HTN, renal disease	Wheezing, respiratory distress	Yes	Yes
2	82/F	Cefazolin	Amox/clav, gastrointestinal	None	Latex, blistering Adhesives, rash None	HTN, pancreatic cancer, allergic rhinitis None	Acute hypotension	Yes	No
3	64/M	Cefazolin	Penicillin, childhood reaction	Oxycodone, syncope	None	Tocilizumab, rheumatoid arthritis, seasonal allergies	Acute hypotension	No	No
4	72/F	Clindamycin	Penicillin, hives Amoxicillin, gastrointestinal	Oxycodone, nausea/vomiting	None	None	Acute hypotension	No	No
5	34/M	Clindamycin	Amoxicillin, rash	Cefazolin, rash	None	None	Erythema, rash Bronchospasm	No	Yes
6	41/F	Clindamycin	Penicillin, anaphylaxis	Cephalexin, anaphylaxis	Latex, hives Rubber, hives None	Asthma	Respiratory distress	No	No
7	38/F	Clindamycin	Penicillin, unknown	Metoclopramide, nausea, dizziness	None	Antihistamines	Respiratory distress	Yes	Yes
8	37/F	Vancomycin	Amox/clav, rash amoxicillin, rash	Oxycodone, nausea TMP/SMX, rash cefuroxime, rash clindamycin, rash	None	Asthma	Acute hypotension	No	No

Pip/tazo, piperacillin/tazobactam; amox/clav, amoxicillin/clavulanate; T2DM, type 2 diabetes mellitus; HTN, hypertension; TMP/SMX, trimethoprim/sulfamethoxazole.

Allergy history appeared to influence preoperative antibiotic choice. Specifically, patients with a history of anaphylaxis or edematous reactions to penicillin antibiotics were less likely to receive cefazolin. It is possible that hypersensitivity reactions would have been higher in the cefazolin group if more patients with a history of severe reactions, such as anaphylaxis, received cefazolin. However, out of the 67 patients who had a history of anaphylaxis to penicillins, only 1 had a probable hypersensitivity reaction in the perioperative period. This reaction occurred in a patient who received clindamycin, which is not structurally related to the natural penicillins, indicating that patients with a history of a hypersensitivity were equally as likely to react to non-beta-lactam antibiotics as they were to cefazolin. This hypothesis was investigated by Strom et al (2003) who analyzed the United Kingdom General Practice Research Database.¹² This large case-control study found that patients with no history of drug allergy had a lower frequency of allergic reactions to sulfonamide non-antibiotics (1.1%) compared with patients with history of allergic reactions to sulfonamide antibiotics (9.9%) but also to patients with history of penicillin allergy (14.2%). Since penicillins and sulfa drugs are not chemically similar, the authors concluded that the high rate of allergic reactions between sulfa antibiotics and sulfa non-antibiotics was due to a greater predisposition to allergic reactions in general among patients with a history of medication allergies.^{13,14}

There are a few possible explanations for the similarly low frequency of hypersensitivity reactions seen between antibiotic groups. Among a cohort of 400,000 patients who were evaluated for development of antibiotic allergy, a prevalence of 1.5% (excluding sulfonamide antibiotics) was found.¹⁵ Additionally, cefazolin is not cross-reactive with penicillin and true incidence of cross-reactivity between penicillins and cephalosporins is dependent on the side chain and not the shared beta-lactam ring.^{16,17} The historical cross-reactivity rate of approximately 10% between penicillins and cephalosporins has largely been debunked. Since cefazolin does not share a side chain with any other penicillins or cephalosporins cross-reactivity is unlikely.^{18–21} Studies utilizing skin testing have demonstrated that cefazolin is a unique allergy that should be classified separately from penicillins and other cephalosporins.²⁰ Another explanation for the similarity in hypersensitivity rates between groups could be the presence of multiple drug allergy/hypersensitivity syndrome, defined as a hypersensitivity to 2 or more medications with unrelated structures. Blumenthal et al reported an incidence of multiple drug allergy syndrome of 1.2%.²² The presence of multiple drug allergy could explain the similar low frequency of hypersensitivity reactions seen among patients receiving cefazolin, clindamycin, and vancomycin.

Inaccurate reporting of penicillin allergies by patients and clinicians may also have been a contributing factor to the low hypersensitivity rates seen in this study. In several previous studies, skin testing and diagnostic challenges revealed that very few patients who report a penicillin allergy have a true allergy. A study conducted by Cook et al examined the true incidence of penicillin allergy in patients who self-report with the use of penicillin skin testing and found the rate of true allergy to be low as 0.9%.²³ This over-reporting by patients could be due to lack of knowledge about what constitutes a 'true' penicillin allergy. This may lead to a patient self-identifying as penicillin allergic after experiencing a common adverse event like gastrointestinal upset. In addition to patient confusion regarding what constitutes a true allergy, clinicians often mislabel medication intolerances as allergies within the electronic medical record. Mislabeling of drug allergies within patient records leads to use of second-line antibiotics that are more toxic and/or less efficacious. Use of second-line antibiotics has been shown to result in undesirable patient outcomes, including

development of antibiotic-resistant infections, increased rates of *Clostridium difficile* infection, and increased adverse events from second-line antibiotics.²⁴ Chua et al (2020) initiated a penicillin allergy de-labeling service and concluded that appropriate labeling of antibiotic allergies may help distinguish between patients who could safely receive the offending drug again with appropriate monitoring and those who should avoid the medication completely.²⁵ Appropriate labeling of penicillin allergies could help prevent clinicians who are less familiar with antibiotic cross-reactivity from inappropriately avoiding first-line antibiotics.

Several studies have displayed similar findings to this study with regards to the incidence of hypersensitivity reactions observed. Butler et al (2018) examined the differences in surgical prophylaxis among children with and without a history of adverse reactions to penicillin.²⁶ The authors found only 1% of patients with a documented penicillin-allergy history who received cefazolin had perioperative adverse drug events. Beltran et al (2015) examined patients with penicillin allergy who received either cefazolin, vancomycin, clindamycin, or ciprofloxacin for surgical prophylaxis in pediatric surgical patients. The researchers found 0.7% of cefazolin patients and 2% of patients receiving clindamycin had an adverse reaction.⁵

Other studies have examined intraoperative hypersensitivity and reported a frequency of hypersensitivity reactions of less than 1%. Anstey et al (2019) examined perioperative use of antibiotics in patients with documented penicillin allergy finding a total of 9 out of 8770 (0.1%) hypersensitivity reactions in their cohort.²⁷ Goodman et al (2001) investigated rates of hypersensitivity reactions among patients labeled as penicillin allergic who had and had not received preoperative cephalosporin antibiotics.²⁸ The researchers found only 1 hypersensitivity reaction among the 300 penicillin allergic-patients who had received cephalosporin and point out that the rate seen in the study is similar to the 0.02% to 0.1% rate of anaphylaxis to cephalosporins seen in the general population. Epstein et al (2016) examined perioperative prescribing practices and hypersensitivity rates among prophylactic antibiotics in patients noted as penicillin allergic.²⁹ The researchers found only 1 suspected case of anaphylaxis in the intraoperative period across approximately 6,000 cases of patients with documented penicillin allergy receiving a cephalosporin.

This study has some important limitations. Due to the retrospective study design randomization to treatment groups did not occur, and the choice of preoperative antibiotic was at the discretion of the prescriber. Concern of cross-reactivity may have influenced antibiotic choice as patients with a history of severe reactions to penicillin antibiotics were less likely to receive cefazolin. Similarly, most patients with a history of cephalosporin allergies were also less likely to receive cefazolin. Additionally, patients receiving multiple preoperative antibiotics were excluded from the analysis. This was done to compare hypersensitivity reactions between patients receiving cefazolin, vancomycin, and clindamycin without confounding the groups with additional antibiotics. It is possible that patients who were indicated for multiple preoperative antibiotics would have differing rates of hypersensitivity reactions. Another limitation of this study was the inability to prove the index allergen. It is possible that the intraoperative hypersensitivity reaction was caused by a medication other than the preoperative antibiotic. Patients received a number of medications before and during surgery. Neuromuscular blocking agents, which are known to cause a high frequency of hypersensitivity reactions, were among the medications routinely given during surgery.^{30,31} Definitive identification of the culprit medication would have required allergy testing, which did not occur among the patients in this study. With these limitations, the outcome of this study

should be considered hypothesis-generating and validated with a prospective study. In conclusion, the present study demonstrated that perioperative hypersensitivity reaction rates are quite low in general, and that the rates do not differ with perioperative antibiotic choice. The large number of patients labeled allergic to penicillin who were still given cefazolin without an immediate hypersensitivity reaction indicates there is no cross reactivity between penicillins and cefazolin, suggesting that clinicians can safely prescribe first-line antibiotics within this patient population.

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Conflict of interest/Disclosure

Spencer Fosnot, Katelyn Currier, Jay Pendell, and Meghan Jeffres have no conflicts of interest to disclose.

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