



Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Safety of administering cefazolin versus other antibiotics in penicillin-allergic patients for surgical prophylaxis at a major Canadian teaching hospital

Jennifer M. Grant, MDCM, FRCPC^{a,b,c,d}, Wendy H.C. Song^e, Salomeh Shajari, BSc^a,
Raymond Mak, MD, FRCPC^f, Andrew T. Meikle, MD, FRCPC^{g,h},
Nilufar Partovi, PharmD, FCSHP^{i,j}, Bassam A. Masri, MD, FRCSC^k,
Tim T.Y. Lau, PharmD, FCSHP^{a,c,i,j,*}

^a SPIRES (Antimicrobial Stewardship Programme), Medicine Quality and Safety, Vancouver Coastal Health, Vancouver, BC, Canada

^b Divisions of Medical Microbiology and Infection Control, and Infectious Diseases, Vancouver Coastal Health, Vancouver, BC, Canada

^c Division of Infectious Diseases, Department of Medicine, Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada

^d Division of Medical Microbiology, Department of Pathology and Laboratory Medicine, Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada

^e Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada

^f Division of Allergy and Immunology, Department of Medicine, Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada

^g Department of Anesthesiology and Perioperative Care, Vancouver General Hospital and UBC Hospital, Vancouver Coastal Health, Vancouver, BC, Canada

^h Department of Anesthesiology, Pharmacology & Therapeutics, Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada

ⁱ Pharmaceutical Sciences, Vancouver General Hospital, Vancouver Coastal Health, Vancouver, BC, Canada

^j Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, BC, Canada

^k Department of Orthopaedics, Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada

ARTICLE INFO

Article history:

Accepted 6 March 2021

Available online xxx

ABSTRACT

Background: Cefazolin surgical prophylaxis is associated with better patient outcomes; however, its use in penicillin-allergic patients is controversial. We evaluated the safety of cefazolin as surgical prophylaxis in penicillin-allergic patients, including those with anaphylaxis histories.

Methods: We conducted a pre and postintervention quality improvement evaluation of an institution-wide policy change at a tertiary-care hospital, before (October 2017–January 2018), during (February 2018–September 2018), and after (October 2018–October 2019) transition to routine cefazolin prophylaxis for penicillin-allergic patients, including those with anaphylaxis histories but excluding severe delayed reactions (eg, Stevens-Johnson syndrome).

Retrospective data was collected on all surgical prophylaxis patients with penicillin-anaphylactic histories between October 2017 and September 2018. From October 2018, we prospectively reviewed adverse events with cefazolin. Primary outcome was adverse events in penicillin-allergic patients receiving cefazolin perioperatively.

Results: From October 2017 to October 2019, 27,467 operations were performed. Of 220 patients with penicillin-anaphylactic histories reviewed prior to the full policy change, no statistically significant differences were reported in allergic reactions ($P = .70$), surgical site infections ($P = 1.00$), or adverse events ($P = .32$) with cefazolin compared to other antibiotics. Postpolicy implementation, cefazolin usage increased 18.2%, while vancomycin and clindamycin decreased by 11.4% and 62.0%, respectively. No anaphylaxis was documented in penicillin-allergic patients receiving cefazolin in either the review or quality assurance follow-up after the change. Of 3 patients developing reactions to cefazolin, none had histories of penicillin allergy. Surgical site infection rates were similar between pre and postpolicy time periods ($P = .842$).

Conclusion: Administration of cefazolin in penicillin-anaphylactic patients for surgical prophylaxis appears to be safe.

© 2021 Elsevier Inc. All rights reserved.

* Reprint requests: Tim T.Y. Lau, PharmD, FCSHP, Pharmaceutical Sciences, Vancouver General Hospital, 855 West 12th Avenue, Vancouver, BC, V5Z 1M9, Canada.

E-mail address: Tim.Lau@vch.ca (T.T.Y. Lau);

Twitter: @nikepartair, @Bas_Vancouver, @TimLauRx

Introduction

Cefazolin is often considered the drug of choice for surgical prophylaxis due to its excellent safety profile and bactericidal activity against common pathogens associated with surgical site infections (SSIs).^{1,2} Historically, surgeons and anesthesiologists have avoided cefazolin in penicillin-allergic patients for concern of potential cross-reactivity.^{2,3} Instead, clindamycin and vancomycin are commonly used as second-line antibiotics but are associated with increased risk of SSI and higher rates of *Clostridioides difficile* infections or vancomycin-resistant enterococci.^{2–7}

Although most clinicians are comfortable with the low risk of cross-reactivity between penicillin and cephalosporins, they are often uncomfortable using cefazolin in patients with penicillin-allergy histories compatible with anaphylaxis,^{8,9} as was the case at our hospital. Recent data suggest cross-reactivity between beta-lactam antibiotics is due to similarities between their side-chains and not the beta-lactam ring structure.^{10–12} Because cefazolin has a unique R1 side-chain, its cross-reactivity with other beta-lactams should be negligible.¹⁰ Moreover, although 10% of the population report histories of penicillin allergy, over 90% will test negative on skin test and tolerate all beta-lactam antibiotics,^{10–12} thus reducing the true penicillin allergy prevalence rate to 1%. Previous retrospective studies of cefazolin as surgical prophylaxis in non-immunoglobulin E (IgE)-mediated penicillin-allergic patients have reported minimal rates of allergic reactions.^{10,12–15} Given the advantages of cefazolin, disadvantages of alternatives, and practical and theoretical reasons for nonreaction, several institutions in Canada have adopted the policy of using cefazolin in penicillin-allergic patients.^{16,17}

At Vancouver General Hospital, the antimicrobial stewardship service in conjunction with pharmacy, anesthesiology, and surgery launched a program to transition to using cefazolin as drug of choice for surgical prophylaxis in all penicillin-allergic patients (including those with anaphylactic reactions to penicillin), excluding those with histories of severe delayed skin reactions (eg, Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], drug reaction with eosinophilia and systemic symptoms [DRESS]). This started with a voluntary period where physicians elected to use cefazolin in penicillin-allergic patients and finished with a policy change that updated all hospital-wide preprinted order (PPO) sets for surgical prophylaxis. We hypothesize cefazolin is safe to administer to patients who report a penicillin allergy (provided it is not a severe delayed skin reaction). Primary objectives of this study were to evaluate safety of cefazolin use in all penicillin-allergic patients and in those with anaphylactic reactions to penicillin compared to alternative antibiotics for surgical prophylaxis. Secondary aims were to assess changes in antibiotic usage patterns and incidence of SSIs following policy change.

Patients and methods

Study population

Vancouver General Hospital is a 750-bed tertiary care institution serving a population of 2.5 million people in Vancouver, British Columbia, Canada, where ~15,000 surgical procedures are performed annually in all major surgical subspecialties.

Study design

This was a retrospective, observational pre and postintervention study with 3 subphases. Precefazolin policy change

(preimplementation) consisted of 2 phases: phase 1a, “preimplementation” period (October 2017–January 2018), when cefazolin was considered contraindicated in penicillin-allergic patients; and phase 1b, “transition” period (February 2018–September 2018), when the prohibition on cefazolin was lifted and some physicians voluntarily administered cefazolin to penicillin-allergic patients. Postcefazolin policy change (postimplementation) had 1 phase: phase 2, “postimplementation” period (October 2018–October 2019), after cefazolin was formally approved on PPOs for use in all penicillin-allergic patients for surgical prophylaxis.

Policy change

The preexisting policy specified nursing staff were expected to check patient allergy status at the time of operation and withhold administration of any beta-lactam antibiotic in the presence of a penicillin allergy history. Practice change was introduced unofficially in February 2018, as a result of educational sessions to surgeons and anesthesiologists. In this phase 1b transition period (February 2018–September 2018), physicians who wished to prescribe cefazolin as surgical prophylaxis for penicillin-allergic patients would do so by indicating they were “aware of the penicillin allergy” on the order to ensure administration by nursing staff. Additional antibiotic prophylaxis for Gram-negative or anaerobic coverage were also administered based on the wound classification of the procedure (ie, clean, clean-contaminated, contaminated, dirty-infected), according to local protocols. During this time, antimicrobial stewardship worked with pharmacy and professional practice to develop a full hospital-wide implementation strategy, which included physician, nursing, and pharmacy education, communication through surgical specialties, and official approval of all PPOs by the Pharmacy and Therapeutics Committee and Medical Advisory Committee. All presurgical PPOs were altered to read: “Cefazolin can be safely administered to patients with history of allergy to penicillin including anaphylaxis EXCEPT in those with severe delayed skin reactions—eg, SJS, TEN, DRESS,” with alternative antibiotic therapies preceded by the statement: “If cefazolin allergic or severe delayed skin reaction to penicillin (eg, SJS, TEN, DRESS).” The hospital-wide cefazolin policy was launched in October 2018.

Chart review of patients with history of anaphylaxis to penicillin

Part of the safety checks before full implementation included a retrospective chart review to ensure safety of cefazolin use in penicillin-allergic surgical patients. All adults (≥ 18 years old) with documented anaphylactic reaction to penicillin who received preoperative prophylactic antibiotics were identified using the pharmacy database from October 2017 to September 2018—phases 1a preimplementation to 1b transition periods. Anaphylactic reaction was defined as “acute onset of illness (in minutes to several hours) with involvement of skin, mucosal tissue, or both, involving either respiratory compromise or reduced blood pressure.”¹⁸ Included patients had 1 of the following keywords in their allergy histories: “hives/urticaria,” “facial/tongue/throat/airway/lip/mouth/periorbital/eye swelling,” “angioedema,” “dyspnea/shortness of breath/difficulty breathing,” “anaphylaxis,” or “positive penicillin skin test.” Nonanaphylactic patients, duplicate perioperative antibiotic orders, cancelled operations, and prescriptions with incomplete information or confounding factors were excluded.

Demographic and clinical data were collected through the Patient Care Information System, medical charts, and medication

administration records, which included admission/discharge dates, duration of stay, age, sex, operation type/procedure, antibiotic prophylaxis, pre/postoperative antibiotic regimens, adverse drug events (ADEs), and whether the operation proceeded. Choice of antibiotic prophylaxis was classified as “cefazolin,” “clindamycin,” “vancomycin,” or “others.”

Four categories of ADEs were recorded: (1) “allergic reactions”: hypersensitivity experienced anytime during hospital stay; (2) “surgical site infection”: infection occurring within 30 days after operation or 1 year if implant is left in place¹⁹; (3) “antibiotic toxicity” (eg, red man syndrome); and (4) “other” (eg, intraoperative asystole). The Naranjo Adverse Drug Reaction Probability Scale was used to determine the likelihood of whether the ADE was due to the antibiotic or other factors.²⁰ Finally, readmissions were reviewed through the Patient Care Information System to search for cases of SSIs for 30 days after the operation.

Quality assurance

Before policy implementation, the antimicrobial stewardship team communicated with operating room personnel including nursing, surgery, and anesthesiology to ensure ADEs were reported. In addition, the National Surgery Quality Improvement Program (NSQIP) collected allergy documentation for all NSQIP-eligible procedures during the preoperative and 1-month postoperative follow-up periods. These NSQIP operations represented approximately 15% to 20% of all surgical procedures, which includes 100% of colorectal resections, proctectomies, liver resections, pancreatetectomies, abdominal hysterectomies, cystectomies and hip arthroplasties, and a sample of other operations. To capture ADEs missed by NSQIP, the Patient Safety Learning System (PSLS) and the intensive care unit (ICU) database were queried for “allergy” and “anaphylaxis” from February 2018 to October 2019. Additionally, the allergist and anesthesiologist in charge of the Perioperative Allergy Clinic identified any patients referred for assessment as a result of cefazolin anaphylaxis who may have been missed. Antimicrobial use was recorded from the pharmacy database. Numbers and types of operations were collected through the Operating Room Management Information System.

Outcomes

Primary outcomes were safety of cefazolin and other antibiotic regimens in penicillin-anaphylactic patients during the preimplementation and transition periods and the number of ADEs to cefazolin in the postimplementation period. Secondary outcomes included change in antimicrobial consumption of cefazolin, clindamycin, and vancomycin between the preimplementation and postimplementation periods. In addition, SSIs were monitored per routine hospital practice as a balancing measure.

Statistical analysis

All statistical analyses were completed using Microsoft Excel (Microsoft, Redmond, WA). Fisher exact test was used to compare categorical variables, such as rates of ADEs (allergic reactions, SSIs, other) between cefazolin and alternative antibiotics. Sex differences were not considered a factor in the analysis. χ^2 analysis was performed to determine whether there was a difference in prevalence of SSIs between the pre and postintervention groups.

Ethics

The University of British Columbia's Clinical Research Ethics Board and the Vancouver Coastal Health Research Institute

reviewed the study protocol. Retrospective chart review was approved by the ethics board without need for informed consent, since it was deemed to be within the acceptable threshold of minimal risk. Data routinely collected and reported for surveillance and quality assurance were included with approval for secondary publication, as this change in practice was considered standard of care.

Results

During the phase 1a preimplementation period (October 2017–January 2018), there were 4,566 operations; in the phase 1b transition (February 2018–September 2018), 8,982 operations; and in phase 2 postimplementation (October 2018–October 2019), 13,919 operations.

Chart review

In the retrospective chart review (October 2017–September 2018), of 1,073 preoperative antibiotic orders from penicillin-allergic patients, 220 (20.5%) orders met inclusion criteria of anaphylaxis to penicillin. A total of 171 unique patients (70 men, 101 women) were analyzed with mean age of 60.8 ± 16.8 years (Fig 1). Cefazolin was most frequently prescribed ($n = 77$), followed by clindamycin ($n = 63$), other antibiotics (ie, ciprofloxacin, fluconazole, gentamicin, meropenem, metronidazole, and tobramycin) ($n = 47$), and vancomycin ($n = 33$) (Fig 2).

Patients with a history of penicillin anaphylaxis reported no cases of life-threatening anaphylactic reactions to any preoperative antibiotics, including cefazolin (Table 1). Minor allergic reactions (pruritus, rash, hives) were observed with all antibiotics; 3 cases of allergic reactions (3.9%) were seen with cefazolin, 2 with clindamycin (3.2%), 1 with vancomycin (3.0%), and 1 with other antibiotics (2.1%). Although the cefazolin group had 3 cases of allergic reactions (2 cases of full-body pruritus, 1 of rash), there was no significant difference between proportions of allergic reactions with cefazolin compared to all other antibiotics ($P = .70$). Additionally, 1 case of infusion-related reaction (red man syndrome) occurred during preoperative infusion of vancomycin. All allergic reactions resolved without need for treatment other than diphenhydramine administration for symptomatic management. The Naranjo score was 4 for all antibiotics and their corresponding reactions, which indicated a possible association between the drug and the ADE.

Two cases of SSIs were reported with cefazolin (2.6%), 2 with clindamycin (3.2%), none with vancomycin, and 1 with other antibiotics (2.1%) (Table 1). Two cases of these SSIs resulted in readmissions (1 case of cellulitis with cefazolin and 1 of sepsis with clindamycin). There was no significant difference between proportions of SSI with cefazolin use compared to all other antibiotics ($P = 1.00$).

Other adverse events included nonsurgically related infections, such as urinary tract infections, pneumonia, intraoperative asystole, and nausea or vomiting (Table 1). Overall, there was no significant difference between proportion of ADEs with cefazolin and all other antibiotics ($P = .32$).

Safety and adverse events

From October 2018 to October 2019 in the phase 2 postimplementation period, NSQIP surveillance followed 1,448 surgical cases administered cefazolin for surgical prophylaxis (which included procedures followed 100% by NSQIP, as well as a sample of other operations). Sixty-two (4.2%) of these had documented histories of penicillin allergy prior to the operation (46 rashes, 5 anaphylaxis, 5 nausea, 3 swelling, 1 convulsion, 1 urticaria, 1 dizziness). None of them had a reaction to cefazolin

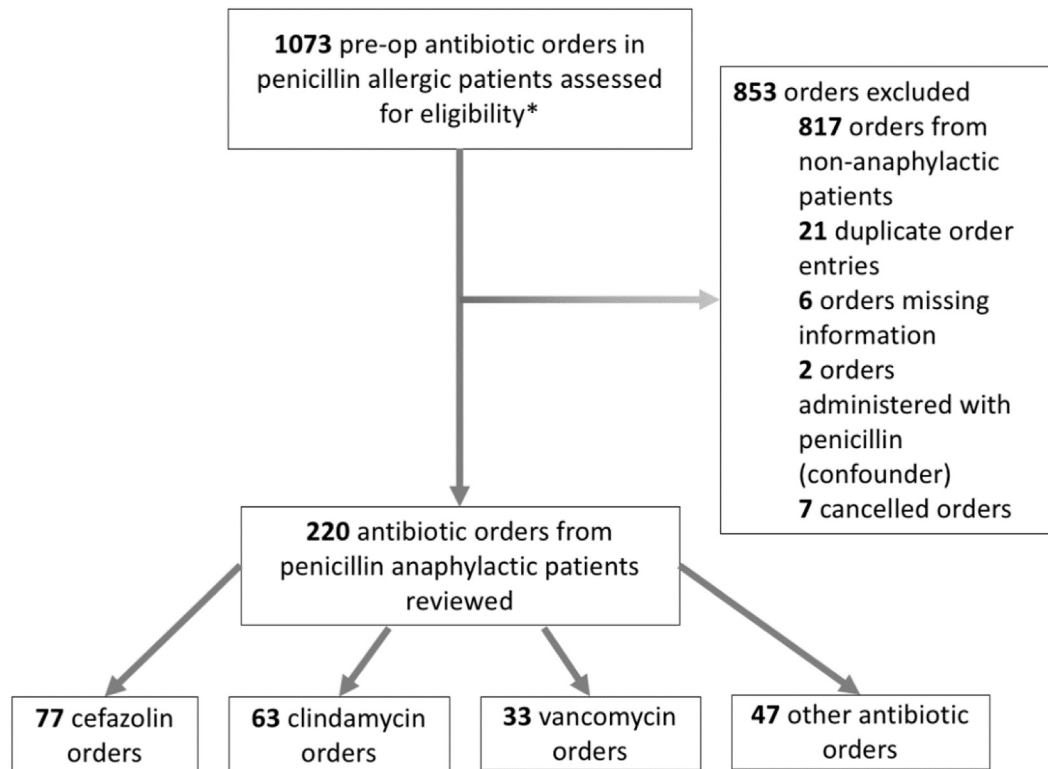


Fig 1. Identification of preoperative antibiotic orders eligible for inclusion in the quality assurance chart review of penicillin-anaphylactic patients (October 2017–September 2018).

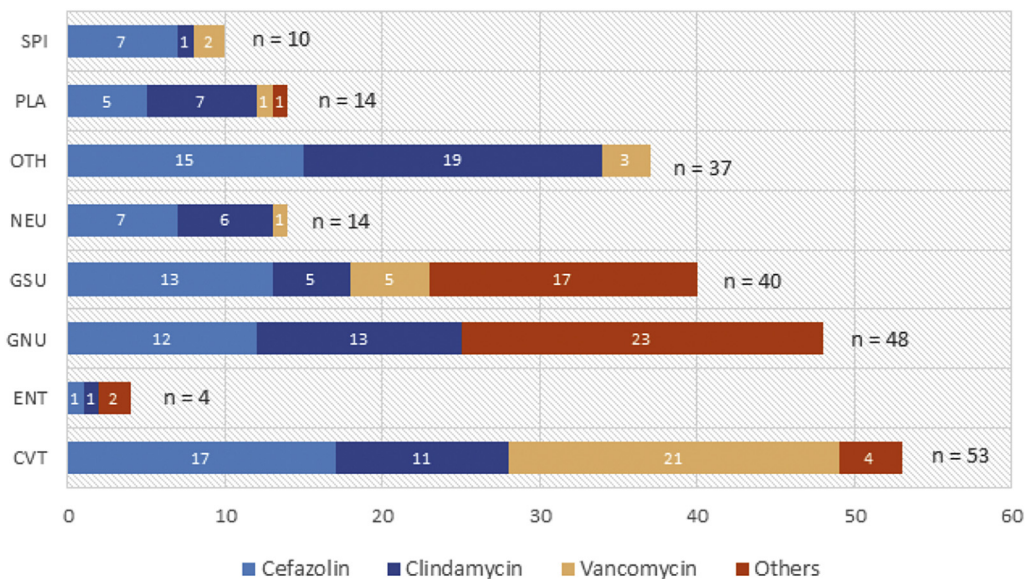


Fig 2. Preoperative antibiotics prescribed by operation type in the quality assurance chart review of penicillin-anaphylactic patients (October 2017–September 2018). CVT, cardiovascular and thoracic; ENT, ears, nose, throat; GNU, genitourinary; GSU, general surgery; NEU, neurology; OTH, orthotrauma; PLA, plastics; SPI, spinal.

postoperatively. Of the 3 patients who developed reactions to cefazolin within 72 hours, none had previous histories of penicillin allergies. No cefazolin allergies were noted in PSLS incident reports. During this period, no patients were referred to the Perioperative Allergy Clinic for suspected intraoperative cefazolin allergy. One case of possible anaphylaxis related to cefazolin was recorded in the ICU database; this occurred in a penicillin-allergic patient who was simultaneously administered penicillin and cefazolin. No additional

patients with anaphylaxis attributable to cefazolin were identified through any other source.

Antimicrobial use

Cefazolin usage increased by 18.2% from 91.2 defined daily doses (DDDs)/100 operations in the preintervention phase to 107.8 DDDs/100 operations in the postintervention period. This increase was

Table I

Reported adverse events in the quality assurance chart review of penicillin-anaphylactic patients (October 2017–September 2018)

	Allergic reactions				Surgical site infections		Other adverse events	
	Full body pruritus	Rash	Hives	Anaphylaxis*	Sepsis	Cellulitis	Asystole	Nausea/vomiting
Cefazolin (n = 77)	2 (2.6%)	1 (1.2%)	0	0	1 (1.2%)	1 (1.2%)	0	30 (39.0%)
Clindamycin (n = 63)	2 (3.2%)	0	0	0	1 (1.6%)	1 (1.6%)	1 (1.6%)	16 (25.3%)
Vancomycin (n = 33)	1 (3.0%)	1	0	0	0	0	0	16 (48.4%)
Others (n = 47)	0	0	1 (2.1%)	0	0	1 (2.1%)	1 (2.1%)	13 (27.7%)

Allergic reactions: cefazolin versus clindamycin versus vancomycin versus other antibiotics, $P = .70$.Surgical site infections: cefazolin versus clindamycin versus vancomycin versus other antibiotics, $P = 1.00$.Other adverse events: cefazolin versus clindamycin versus vancomycin versus other antibiotics, $P = .32$.* Anaphylaxis: acute onset of illness (in minutes to several hours) with involvement of the skin, mucosal tissue, or both, involving either respiratory compromise and/or reduced blood pressure.¹³

associated with a corresponding decrease of 11.4% in vancomycin use (21.1 DDDs/100 operations in the pre to 18.7 DDDs/100 operations postintervention period) and a 62.0% reduction in clindamycin during the same time period (7.1 DDDs/100 operations in the pre to 2.7 DDDs/100 operations postintervention).

Surgical site infections

Rates of SSIs for operations where NSQIP follows 100% of all cases appeared consistent and were not statistically different between prepolicy (October 2017–September 2018) and postpolicy (October 2018–October 2019) periods ($P = .842$) (Table II). General surgeries included colectomies, hepatectomies, pancreatectomies, and proctectomies, and SSI rates were as follows: colectomies 16.3% (36 of 221) and 12.2% (21 of 172); hepatectomies 14.6% (19 of 130) and 11.5% (13 of 113); pancreatectomies 42.5% (45 of 106) and 43.9% (43 of 98); and proctectomies 40.9% (9 of 22) and 62.5% (15 of 24) in pre and postpolicy periods, respectively.

Discussion

Penicillin allergies are commonly reported at an incidence of 10%, whereas cephalosporin allergies are relatively rare at ~1%.⁹ In the 1980s, cross-reactivity rates between penicillin and cephalosporins were as high as 10% to 20%, because some cephalosporin formulations were contaminated with traces of penicillin.²¹ More recently, estimated rate of cross-reactivity between penicillin and cephalosporins is ~1%,^{9,21} mainly attributable to similarities between the antigenic R1 side-chain on beta-lactam antibiotics.^{9,21–23} Cefazolin is a first-generation cephalosporin with a unique R1 side-chain and well-demonstrated safety profile in patients with non-IgE-mediated penicillin allergies. Goodman et al¹⁴ reported 413 penicillin-allergic orthopedic patients receiving cefazolin prophylaxis with only 1 potential allergic reaction (0.2%). Similarly, Haslam et al¹³ observed no adverse reactions in 54 orthopedic surgery patients with non-IgE-mediated penicillin allergies receiving cefazolin. Beltran et al¹⁵ observed only 1 allergic reaction (0.8%) out of 127 pediatric patients with both IgE- and non-IgE-mediated penicillin allergies receiving cefazolin.

Although the safety of cefazolin in penicillin-allergic patients is supported by literature, studies have found prescribers avoid using cephalosporins in favor of vancomycin or clindamycin whenever a penicillin allergy is documented, regardless of the accuracy of the history.^{2,3,24} This reluctance has direct consequences on treatment outcomes. Blumenthal et al⁷ reported penicillin-allergic patients were 8 to 16 times more likely to receive alternate antibiotics, which was associated with a 50% increase in SSIs. Another study²⁵ found patients not receiving beta-lactam therapy experienced 3 times more ADEs from another antibiotic and had higher

readmission rates. Furthermore, additional risks of second-line antibiotics were increased rates of *Clostridioides difficile* infections with clindamycin and vancomycin-associated nephrotoxicity.^{26,27} Our retrospective cohort data found no statistically significant differences between rates of ADEs and SSIs with cefazolin compared to other antibiotics. However, this observation could be due to the limited number of SSIs in our retrospective sample. In the larger NSQIP data set, there also did not appear to be any differences in infection rates and safety. We noted for general surgeries, our composite NSQIP SSI rates ranged from 11.5% to 62.5%, depending on the procedure. Approximately half of these were urgent cases, while a quarter were classified as contaminated or dirty-infected. Higher rates were mainly associated with pancreatectomies 43.1% (88 of 204) and proctectomies 52.2% (24 of 46). Many of these were referrals secondary to complicated underlying abnormalities and previously failed surgical attempts, which explains the high infection rates. Our standard prophylaxis regimen for intra-abdominal procedures is cefazolin and metronidazole; however, based on these surveillance findings and SSI cultures showing predominance of *Enterococcus*, *Enterobacter*, and *Klebsiella* in pancreatectomy cases, the surgical prophylaxis regimen for pancreatectomies has been revised to ampicillin and cefotaxime. For proctectomies, the higher SSI incidence was based on a smaller number of cases (~23 cases/year), so it is unclear whether this is due to complexities of the cases at a tertiary care center or other factors. These procedures will be closely monitored for continued quality assurance. At the very least, cefazolin's comparable safety outcomes to other agents should provide physicians with more confidence when prescribing it to penicillin-allergic patients.

Another advantage of cefazolin is its cost-effectiveness and convenience for surgical prophylaxis. When comparing cefazolin and vancomycin for surgical prophylaxis, provision of cefazolin to all penicillin-allergic patients was the least expensive strategy.²⁸ Cefazolin is also easy to administer as an infusion over 15 to 30 minutes, or if necessary, as an intravenous bolus in the operating room prior to incision, thus reducing preparation time prior to the operation and improving quality measures such as appropriate administration time with respect to surgical incision. Interestingly, during the transition period, some of our anesthesiologists adopted this new practice of cefazolin use early. Of 24 orders for alternative antibiotics prescribed by surgeons due to allergies, 11 were changed by anesthesiologists to cefazolin, which highlights the proactive role anesthesiologists can play in promoting antimicrobial stewardship in the perioperative setting.

An alternate strategy for promoting cefazolin use is through penicillin skin testing (PST).^{8,10} However, accuracy of PST to predict cross-reactivity with cephalosporins is debatable. In a study of 173 penicillin-allergic pediatric patients, 152 tested negative (87.9%) and 21 (12.1%) positive using PST.²⁹ Additionally, 1 ADE occurred

Table II

Reported surgical site infections for operations followed 100% by NSQIP during the preimplementation (October 2017–February 2018), transition (March 2018–September 2018), and postimplementation (October 2018–October 2019) periods

Operations	Period	n	Surgical site infections	Rate
Orthopedics	Preimplementation	107	1	0.9%
	Transition	169	2	1.2%
	Postimplementation	266	6	2.3%
General surgery Colectomy, hepatectomy, pancreatectomy, proctectomy	Preimplementation	194	51	26.3%
	Transition	285	58	20.4%
	Postimplementation	407	92	22.6%
Gynecology	Preimplementation	158	7	4.5%
	Transition	180	8	9.3%
	Postimplementation	284	19	6.9%
Urology	Preimplementation	40	2	4.5%
	Transition	57	14	9.3%
	Postimplementation	79	6	6.9%

Surgical site infections preimplementation/transition versus postimplementation, ($P = .842$).

NSQIP, National Surgery Quality Improvement Program.

(eye swelling) with cephalexin in a child who tested negative to penicillin, suggesting PST may not accurately predict cross-reactivity with cephalosporins. Moreover, other studies have shown cefazolin hypersensitivity may be selective and does not reflect tolerance of other beta-lactams.^{28,29} Both Uyttebroek et al³⁰ and Romano et al³¹ demonstrated in patients with anaphylaxis to cefazolin that penicillin and other cephalosporins showed negative skin tests, and these drugs were well-tolerated. These studies suggest PSTs have limitations and may not optimally rule out potential allergic reactions with cefazolin, as patients with true penicillin allergies do not appear to be more prone to cefazolin cross-reactivity.

Other groups have reported similar findings to ours.^{10,12} However, at our institution, rather than developing an algorithm for allergy assessment by physicians, we addressed the issue with an institution-wide policy change, which defaulted to cefazolin for surgical prophylaxis in penicillin-allergic patients. This tactic simplified the implementation process, while provided support to our allied health practitioners by highlighting rare instances where the policy would not be appropriate (ie, in cases of severe delayed skin reactions). In our experience, with ~15,000 operations after the policy change, rate of reaction to cephalosporins was low (0.2%), and not predicted by history of penicillin allergy. In our comprehensive case review of patients with anaphylaxis histories, rate of mild allergic reactions with cefazolin (3.9%) was slightly higher than the predicted 1%; however, this observed rate was comparable to reactions with other antibiotics. Cefazolin was not associated with a higher risk of hypersensitivity compared to alternative antibiotics, such as clindamycin and vancomycin. The overall increased rate of allergic reactions may be attributed to higher tendency of patients with IgE-mediated penicillin allergies to develop hypersensitivity reactions, so these may be *de novo* allergic reactions to cephalosporins and not cross-reactions.²³

Several limitations exist in our study. First, this is a retrospective study, so accuracy of the data is dependent on completeness in documentation of databases and health care records. In the postimplementation quality assurance review, we relied on both active surveillance of allergic reactions (NSQIP team) and passive (PSLS, ICU database, physician) reporting. Because active surveillance by NSQIP only reviewed a sample of surgical cases (15%–20%), it is possible to miss some cases as part of our safety review. However, for NSQIP operations where 100% of cases were followed, we reported the incidence of SSIs in the pre and postpolicy periods to ensure data consistency and to prevent oversampling of cases. We have remained vigilant to ADE reporting and to date have not identified any further cases of concern. In the case-control chart review, our initial screening depended on the pharmacy database

allergy profile and keywords associated with anaphylactic reactions. When determining safety of cefazolin, we were reliant on recording of adverse events by nurses and physicians. Presence of other confounding perioperative medications could have affected results, as it was not always straightforward to determine the causative agent for allergic reactions or ADEs. The Naranjo score was used to more objectively determine probability of preoperative antibiotics to cause ADEs, but most antibiotics had scores of 4, which indicated only a possible association. Therefore, it is unclear whether reported reactions are directly associated with the antibiotic itself or other confounders, such as opiates, which may cause postoperative pruritus,³² and neuromuscular blocking agents, which may be associated with immediate hypersensitivity reactions.³³ Nausea and vomiting were also a frequent ADE but can be a side effect of any of the perioperative medications, including anesthetic agents. Only patients readmitted to our hospital for SSIs or reported by NSQIP were followed up, since we were unable to capture SSI readmissions at another hospital. Furthermore, we did not have a reliable mechanism to identify superficial SSIs, which often present at outpatient clinics; therefore, we are unable to determine the comparable efficacy of cefazolin for surgical prophylaxis in this study.

Despite these limitations, the study holds merit in investigating the tolerance of cefazolin in a population previously thought to be contraindicated for its use, and these results should provide perioperative physicians assurance of cefazolin's safety profile for surgical prophylaxis in penicillin anaphylactic patients.

In conclusion, cefazolin appears to be a safe regimen in penicillin-anaphylactic patients for surgical prophylaxis. No significant differences were found between the proportion of allergic reactions, other ADEs, and SSIs with cefazolin as compared to other alternate antibiotics. Therefore, administration of cefazolin to penicillin-allergic patients, even those with true IgE-mediated allergies (except in those with histories of severe delayed-type reactions), can be safely recommended as surgical prophylaxis.

Funding/Support

No funding or financial support was received for this study.

Conflicts of interest/Disclosures

Dr. Raymond Mak reports having received lecture fees from PEDIAPHARM Inc and consulting fees from Sanofi. Dr Bassam Masri has received institutional support from Zimmer Biomet, Stryker Corp, Johnson & Johnson, and Smith & Nephew. All other authors have no related conflicts of interest or disclosures to declare.

Acknowledgments

We would like to acknowledge the contributions of our Medicine Quality and Safety Team including Ms Allison Muniak, Ms Julie Bedford, Mr Markus Zurberg, and Dr Donald Griesdale, the Medical Advisory Committee of the Vancouver Acute Community of Care at Vancouver Coastal Health, Dr Hamed Umedaly, Dr Juan Camillo Ruiz, and Dr William Bowie for their roles in supporting and executing this project. This study was nonfunded.

References

- Owens CD, Stoessel K. Surgical site infections: epidemiology, microbiology and prevention. *J Hosp Infect*. 2008;70(Suppl 2):3–10.
- Vorobeichik L, Weber EA, Tarshis J. Misconceptions surrounding penicillin allergy: implications for anesthesiologists. *Anesth Analg*. 2018;127:642–649.
- Epstein RH, Jacques PS, Wanderer JP, Bombulie MR, Agarwalla N. Prophylactic antibiotic management of surgical patients noted as “allergic” to penicillin at two academic hospitals. *A A Case Rep*. 2016;6:263–267.
- Branch-Elliman W, O'Brien W, Strymish J, Itani K, Wyatt C, Gupta K. Association of duration and type of surgical prophylaxis with antimicrobial associated adverse events. *JAMA Surg*. 2019;154:590–598.
- Bratzler DW, Dellinger EP, Olsen KM, et al, and the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Surgical Infection Society, the Society for Healthcare Epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health-Syst Pharm*. 2013;70:195–283.
- Kheir MM, Tan TL, Azboy I, Tan DD, 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;475:1767–1774.
- Blumenthal KG, Ryan EE, Li Y, Lee H, Kahlen JL, Shenoy ES. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis*. 2018;66:329–336.
- Hermanides J, Lemkes BA, Prins JM, Hollmann MW, Terreehorst I. Presumed β -lactam allergy and cross-reactivity in the operating theater: a practical approach. *Anesthesiology*. 2018;129:335–342.
- Zagursky RJ, Pichichero ME. Cross-reactivity in β -lactam allergy. *J Allergy Clin Immunol Pract*. 2018;6:72–81.e1.
- Kuruvilla M, Sexton M, Wiley Z, Langfitt T, Lynde GC, Wolf F. A streamlined approach to optimize perioperative antibiotic prophylaxis in the setting of penicillin allergy labels. *J Allergy Clin Immunol Pract*. 2020;8:1316–1322.
- McDaniel DL, Azar AE, Dowden AM, et al. Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplasty*. 2017;32:101–108.
- Albin S, Agarwal S. Prevalence and characteristics of reported penicillin allergy in an urban outpatient adult population. *Allergy Asthma Proc*. 2014;35:489–494.
- Haslam S, Yen D, Dvirnik N, Engen D. Cefazolin use in patients who report a non-IgE mediated penicillin allergy: a retrospective look at adverse reactions in arthroplasty. *Iowa Orthop J*. 2012;32:100–103.
- Goodman EJ, Morgan MJ, Johnson PA, Nichols BA, Denk N, Gold BB. Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. *J Clin Anesth*. 2001;13:561–564.
- Beltran RJ, Kako H, Chovanec T, Ramesh A, Bissonnette B, Tobias JD. Penicillin allergy and surgical prophylaxis: cephalosporin cross-reactivity risk in a pediatric tertiary care center. *J Pediatr Surg*. 2015;50:856–859.
- Sinai Health System and University Health Network Antimicrobial Stewardship Program. β -Lactam allergy. <https://www.antimicrobialstewardship.com/beta-lactam-allergy>. Accessed October 31, 2020.
- New Brunswick Provincial Health Authorities Anti-Infective Stewardship Committee. Management of penicillin and beta-lactam allergy; 2017. https://en.horizonnb.ca/media/927867/management_of_penicillin_and_beta_lactam_allergy.pdf. Accessed October 31, 2020.
- Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–397.
- Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control*. 1999;27:97–132.
- Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239–245.
- Pichichero ME. Use of selected cephalosporins in penicillin-allergic patients: a paradigm shift. *Diagn Microbiol Infect Dis*. 2007;57:135–185.
- Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients: a literature review. *J Emerg Med*. 2012;42:612–620.
- Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105:259–273.
- Kemp HI, Cook TM, Thomas M, Harper NJN. UK anaesthetists' perspectives and experiences of severe perioperative anaphylaxis: NAP6 baseline survey. *Br J Anaesth*. 2017;119:132–139.
- MacFadden DR, LaDelfa A, Leen J, et al. Impact of reported beta-lactam allergy on inpatient outcomes: a multicenter prospective cohort study. *Clin Infect Dis*. 2016;63:904–910.
- Vardakas KZ, Trigkidis KK, Boukouvala E, Falagas ME. *Clostridium difficile* infection following systemic antibiotic administration in randomised controlled trials: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2016;48:1–10.
- Flippone EJ, Kraft WK, Farber JL. The nephrotoxicity of vancomycin. *Clin Pharmacol Ther*. 2017;102:459–469.
- Phillips E, Louie M, Knowles SR, Simor AE, Oh PI. Cost-effectiveness analysis of six strategies for cardiovascular surgery prophylaxis in patients labeled penicillin allergic. *Am J Health Syst Pharm*. 2000;57:339–345.
- Ahmed KA, Fox SJ, Frigas E, Park MA. Clinical outcome in the use of cephalosporins in pediatric patients with a history of penicillin allergy. *Int Arch Allergy Immunol*. 2012;158:405–410.
- Uyttendaele AP, Decuyper II, Bridts CH, et al. Cefazolin hypersensitivity: toward optimized diagnosis. *J Allergy Clin Immunol Pract*. 2016;4:1232–1236.
- Romano A, Gaeta F, Valluzzi RL, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol*. 2015;136:685–691.
- Reich A, Ständer S, Szepietowski JC. Drug-induced pruritus: a review. *Acta Derm Venereol*. 2009;89:236–244.
- Mertes PM, Aimone-Gastin I, Guéant-Rodriguez RM, et al. Hypersensitivity reactions to neuromuscular blocking agents. *Curr Pharm Des*. 2008;14:2809–2825.