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Cefazolin vs. alternative beta-lactams for prophylaxis in lower extremity fracture surgery: A target trial emulation

Takaki Yoshiyama [a,b], Toshiki Fukasawa [a,c], Soichiro Masuda [a,d], Shuichi Matsuda [b], Koji Kawakami [a,*]

[a] Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan
[b] Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[c] Department of Digital Health and Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan
[d] Department of Orthopaedics, Kyoto City Hospital, Kyoto, Japan

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ABSTRACT

Background: Cefazolin is the primary antibiotic for surgical prophylaxis in orthopedic procedures. The cessation of cefazolin supply in approximately 60 % of Japanese hospitals from 2019 to 2020 provided an opportunity to evaluate the effectiveness of alternative beta-lactams for preventing surgical site infection (SSI). Given the global potential for antibiotics shortages, confirming the effectiveness of alternative beta-lactams is critical.
Purpose: This study aims to evaluate the differences in risk of reoperation for SSI between cefazolin and alternative beta-lactams in patients undergoing lower extremity fracture surgeries.
Methods: We emulated a target trial to compare the effectiveness of cefazolin with alternative beta-lactams—specifically broad-spectrum penicillins and cephalosporins—in preventing SSI using a Japanese hospital administrative database provided by JMDC Inc. We included patients undergoing initial open reduction and internal fixation for closed lower extremity fractures between March 1, 2019, and February 29, 2020. The outcome was reoperation for SSI within 30 days after surgery. Risks were estimated using pooled logistic regression with adjustment for confounders via inverse probability weighting. Sensitivity analyses extended the follow-up period to 90 and 365 days.
Results: Of the 16,602 patients analyzed, 35 patients (0.30 %) in the cefazolin group (11,538 patients) and 16 patients (0.32 %) in the alternative beta-lactam group (5,064 patients) underwent reoperation for SSI within 30 days. The estimated 30-day risk was 0.31 % in the cefazolin group and 0.37 % in the alternative beta-lactam group, resulting in a risk difference of −0.06 % (95 % confidence interval [CI], −0.33 to 0.14) and a risk ratio of 0.82 (95 % CI, 0.50 to 1.52). In sensitivity analyses, the estimated 90-day risk was 0.67 % in the cefazolin group and 0.57 % in the alternative beta-lactam group, with a risk difference of 0.10 % (95 % CI, −0.15 to 0.32) and a risk ratio of 1.19 (95 % CI, 0.80 to 1.62). The 365-day risk was 1.02 % and 0.90 %, respectively, with a risk difference of 0.12 % (95 % CI, −0.29 to 0.39) and a risk ratio of 1.13 (95 % CI, 0.78 to 1.51).
Conclusions: In surgeries for lower extremity fractures, substituting cefazolin with alternative beta-lactams did not result in substantial differences in the risk of reoperation for SSI.

Introduction

Surgical site infection (SSI) is a critical complication in orthopedic surgeries, with incidence ranging from 0.1 % to 17.3 %. This complication can result in prolonged hospital stays, increased mortality, and higher medical costs [1–3]. In particular, most lower extremity fracture surgeries involve the use of metal implants, and the infection rate tends to be higher than surgeries for upper extremity fractures, highlighting the importance of effective prophylactic strategies [4–8].

Cefazolin, a first-generation cephalosporin effective against gram-positive cocci, including *Staphylococcus aureus* and *Staphylococcus epidermidis*, has been the standard antibiotic for perioperative SSI

* Corresponding author at: Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshidakonoe-cho, Sakyo-ku, Kyoto 606-8501, Japan.
E-mail addresses: yoshiyama.takaki.45a@st.kyoto-u.ac.jp (T. Yoshiyama), fukasawa.toshiki.4a@kyoto-u.ac.jp (T. Fukasawa), smat522@kuhp.kyoto-u.ac.jp (S. Matsuda), kawakami.koji.4e@kyoto-u.ac.jp (K. Kawakami).

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prevention [1,2,9]. Starting in March 2019, however, the supply of cefazolin by Nichi-Iko Pharmaceutical Co., Ltd. was halted for about a year, resulting in its unavailability in approximately 60 % of hospitals in Japan [10]. During this period, alternative antibiotics were used for perioperative SSI prophylaxis, following guidelines and the approved list of antibiotics issued by the Ministry of Health, Labour and Welfare [11]. This situation created a natural experiment to compare cefazolin with alternative beta-lactams in real-world clinical settings.

Some observational studies suggest that cefazolin is superior to alternative beta-lactams for upper limb surgery and spine surgery [12, 13]. These studies suffer from a number of limitations, however, including small sample sizes, limited generalizability from studies conducted at one to four centers, and insufficient confounding adjustment. Further, we are unaware of any study which has compared the effectiveness of cefazolin and other antibiotics in lower extremity fractures. It therefore remains unclear whether alternative beta-lactams are as effective as cefazolin.

Here, we aimed to emulate a target trial using large observational data to compare the effectiveness of cefazolin and alternative beta-lactams—namely, broad-spectrum penicillins and cephalosporins—in preventing perioperative SSI in patients undergoing open reduction and internal fixation (ORIF) for lower extremity fractures. We aimed to evaluate whether the effectiveness of cefazolin differs from that of alternative beta-lactams in preventing SSIs.

Methods

Data source

We used a Japanese hospital administrative database provided by JMDC Inc. [14]. As of 2023, the database contains data on a cumulative total of 34.25 million inpatients and outpatients treated at 937 hospitals. The database includes information on demographics, admission diagnoses, comorbidities at admission, complications during hospitalization, procedures, prescriptions, and discharge summaries. Each patient is assigned a unique identifier within the hospital, allowing follow-up as long as treatment continues at the same hospital. This database has been used in numerous studies across various medical fields [15,16]. The database covers the period from April 1, 2014, to December 31, 2023; for this study, we extracted data from March 1, 2019, to May 28, 2020. The study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (approval number: R4555). Informed consent was waived in accordance with Japanese ethical guidelines due to the anonymized nature of the data.

Specification and emulation of the target trial

We used the target trial emulation approach, in which we first specified the protocol of a hypothetical pragmatic randomized trial and then emulated the target trial using observational data [17,18]. A summary of the hypothetical target trial protocol and the emulation procedure, aimed at comparing cefazolin versus alternative beta-lactams for SSI prophylaxis in lower extremity fracture surgery, is provided in Supplementary Table 1.

Eligibility criteria

To be eligible, patients were requested to be aged 18 years or older and to have undergone their first ORIF for a fracture of the lower limbs, including proximal hip fractures, femoral fractures, tibia/fibula fractures, and foot fractures, between March 1, 2019, and February 29, 2020. We included patients who received cefazolin or other beta-lactams, including broad-spectrum penicillins and second- to fourth-generation cephalosporins, on the surgery date as having received prophylactic antibiotics. We excluded patients who underwent surgery for fractures at two or more sites during the same hospitalization, those with fractures where the surgical site (left or right) was unclear or indistinguishable, those prescribed any systemic antibiotics within the 7 days prior to the surgery date, those with open or pathological fractures, those receiving two or more beta-lactams (including both cefazolin and other beta-lactams) at the surgery date, those receiving non-beta-lactam systemic antibiotics at the surgery date, and those treated at hospitals that ceased providing data to the database during the follow-up period. Inclusion and exclusion criteria are detailed in Supplementary Table 2 and Supplementary Figure 1 [19].

Treatment strategies

The treatment strategies included (i) cefazolin administered on the surgery date and (ii) other beta-lactams, including broad-spectrum penicillins and second- to fourth-generation cephalosporins, also administered on surgery date.

Study outcomes

The effectiveness outcome was reoperation due to SSI, identified using a combination of International Classification of Diseases, Tenth Revision (ICD-10) codes and procedure codes (Supplementary Table 3). A validation study conducted in Japan suggests that operative information has a positive predictive value (PPV) approaching 100 % [20]. Total mortality was assessed as an additional outcome. We also evaluated the duration and dosage of prophylactic antibiotics used, the risk of blood transfusion within 30 days postoperatively and the duration of anesthesia.

Follow-up

For each eligible patient, follow-up began at the time of treatment assignment (i.e. date of surgery) and continued until either reoperation for SSI or 30 days post-surgery, whichever occurred first. Patients were not censored in the event of death during follow-up, as this approach is appropriate for estimating the total effect of treatment [21].

Causal contrast

Our emulation focused on an observational analog of the intention-to-treat effect, representing the effect of being assigned to cefazolin versus alternative beta-lactams at baseline.

Covariates

Based on clinical knowledge [15,22], we selected the following baseline covariates: age, sex, body mass index (BMI) category, smoking status (Brinkman index), comorbidities (diabetes, hypertension, hyperlipidemia, coronary artery disease, chronic heart failure, chronic pulmonary disease, cerebrovascular disease, hemodialysis, rheumatoid arthritis, malignant disease, Charlson comorbidity index), surgical site, anesthesia method, and hospital size as categorized by the number of beds (Supplementary Table 4).

Statistical analysis

We adjusted for confounders using inverse probability (IP) weighting, a propensity score method. Propensity scores were estimated by fitting a logistic regression model with cefazolin administration as the outcome variable, conditional on the covariates listed above, with age modeled using linear and quadratic terms. The model's predicted probabilities were used to calculate stabilized IP weights, which were then applied to fit an IP-weighted pooled logistic regression model to estimate 30-day risks and risk curves of reoperation for SSI, total mortality, and blood transfusion under each treatment strategy. This pooled logistic regression model included the treatment strategy indicator (i.e.,

cefazolin or other beta-lactams), a flexible function of follow-up days (linear and quadratic terms), and product terms between the treatment strategy indicator and all functions of follow-up days. 95 % confidence intervals (CIs) were derived from the 2.5th and 97.5th percentiles of estimates obtained through bootstrapping 500 samples from eligible patients. Anesthesia time was compared using the *t*-test.

To confirm the robustness of our findings, we assessed reoperation for SSI and total mortality within 90 and 365 instead of 30 days from the surgery date. Additionally, we conducted subgroup analyses, comparing outcomes by antibiotic type, including second- and third-generation cephalosporins, and broad-spectrum penicillins. Fourth-generation cephalosporins were excluded from the subgroup analyses due to a small sample size. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). The data codebook and the SAS codes for the primary analysis are available in the Supplementary Material.

Results

Descriptive data

We identified 21,911 potentially eligible patients and excluded 3790 patients for the following reasons (Fig. 1): 532 were aged under 18 years, 911 underwent surgery for two or more surgical sites, 241 had fractures where the surgical site (left or right) was unclear or indistinguishable, 102 had pathological fractures, 129 had open fractures, and 1875 were prescribed systemic antibiotics within 7 days prior to surgery. This left 18,121 patients confirmed to be eligible. Furthermore, we excluded 321 patients who did not receive cefazolin or an alternative beta-lactam for prophylaxis, 192 who received two or more beta-lactams on the surgery date, 552 who received non-beta-lactam systemic antibiotics at the surgery date, and 454 patients treated at hospitals that ceased providing data to the database during the follow-up period. The final analysis included 16,602 patients, with 11,538 in the cefazolin group and 5064 in the alternative beta-lactam group.

Baseline characteristics of the patients before and after IP weighting are presented in Table 1 (the complete table is available in Supplementary Table 5). Before IP weighting, mean age was 77.6 years (standard deviation [SD], 17.1) in the cefazolin group and 77.9 years

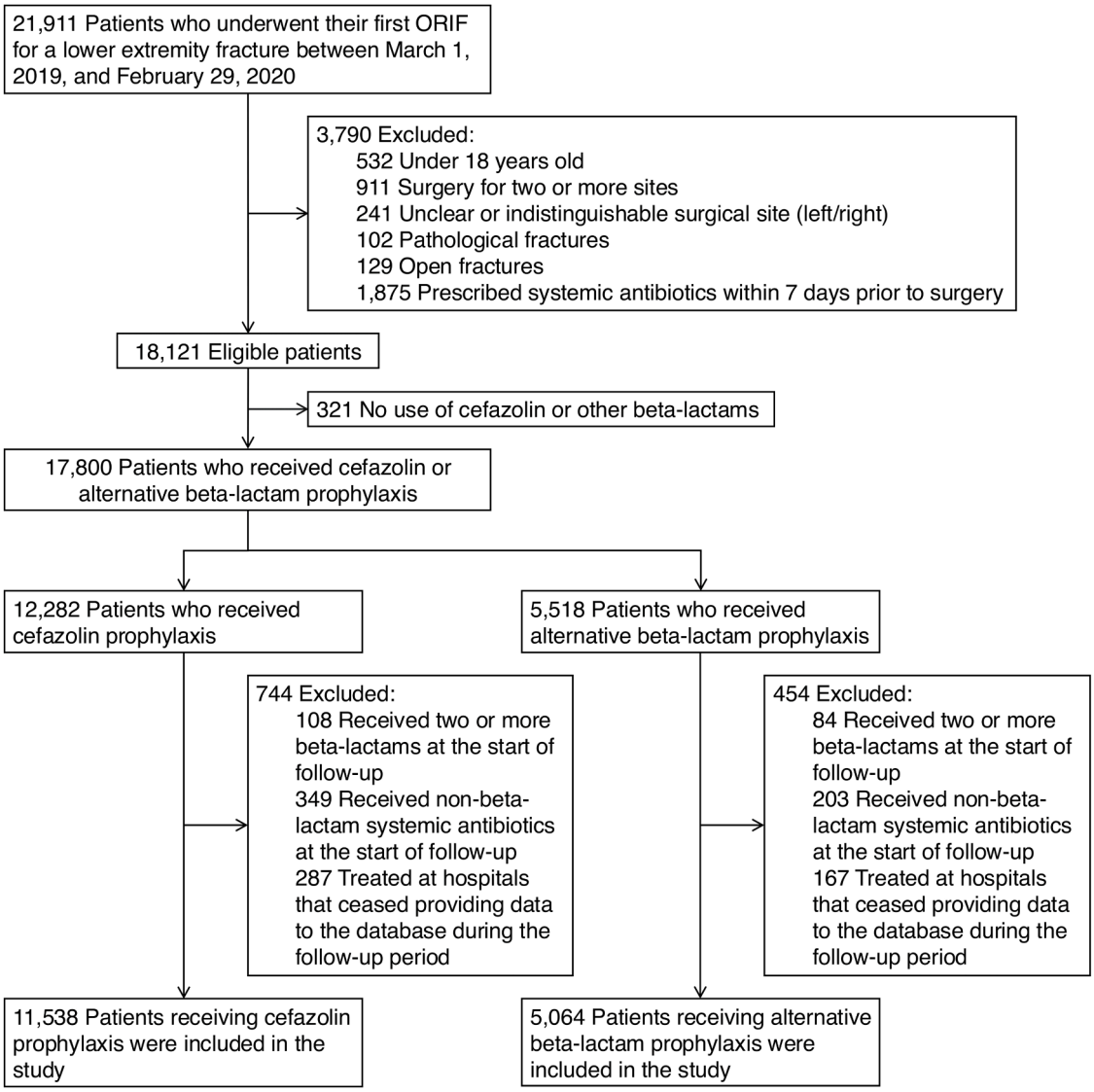

Fig. 1. Flow diagram illustrating the selection process of study participants. ORIF = open reduction and internal fixation.

Table 1
Selected baseline characteristics of patients receiving cefazolin versus alternative beta-lactams before and after inverse probability weighting.

	Before weighting			After weighting[a]		
	Cefazolin	Alternative beta-lactams	SMD	Cefazolin	Alternative beta-lactams	SMD
Characteristic	(n = 11,538)	(n = 5064)		(n = 11,541)	(n = 5059)	
Demographics						
Age (years), mean (SD)	77.7 (17.2)	77.9 (16.8)	0.02	77.7 (17.1)	77.7 (17.1)	0.00
Male sex	3228 (28.0)	1418 (28.0)	0.00	3234 (28.0)	1423 (28.1)	0.00
BMI (kg/m^2), mean (SD)	21.6 (3.4)	21.7 (3.4)	0.03	21.6 (3.4)	21.7 (3.4)	0.02
Comorbidities						
Diabetes	771 (6.7)	339 (6.7)	0.00	770 (6.7)	336 (6.6)	0.00
Hypertension	1300 (11.3)	557 (11.0)	0.01	1291 (11.2)	570 (11.3)	0.00
Hyperlipidemia	421 (3.6)	173 (3.4)	0.01	413 (3.6)	181 (3.6)	0.00
Coronary artery disease	162 (1.4)	75 (1.5)	0.01	165 (1.4)	72 (1.4)	0.00
Chronic heart failure	1328 (11.5)	547 (10.8)	0.02	1298 (11.2)	552 (10.9)	0.01
Chronic pulmonary disease	539 (4.7)	262 (5.2)	0.02	557 (4.8)	242 (4.8)	0.00
Cerebrovascular disease	1142 (9.9)	617 (12.2)	0.07	1226 (10.6)	543 (10.7)	0.00
Hemodialysis	193 (1.7)	77 (1.5)	0.01	187 (1.6)	80 (1.6)	0.00
Rheumatoid arthritis	192 (1.7)	88 (1.7)	0.01	194 (1.7)	85 (1.7)	0.00
Malignant disease	603 (5.2)	314 (6.2)	0.04	641 (5.6)	285 (5.6)	0.00
Surgical site			0.05			0.04
Femur	8295 (71.9)	3757 (74.2)		8321 (72.1)	3713 (73.4)	
Patella	627 (5.4)	252 (5.0)		624 (5.4)	258 (5.1)	
Tibia and fibula	1877 (16.3)	742 (14.7)		1868 (16.2)	762 (15.1)	
Foot	739 (6.4)	313 (6.2)		728 (6.3)	326 (6.4)	
Hospital size (No. beds)			0.32			0.00
20–99	653 (5.7)	194 (3.8)		587 (5.1)	253 (5.0)	
100–199	2599 (22.5)	626 (12.4)		2240 (19.4)	980 (19.4)	
200–299	2366 (20.5)	1213 (24.0)		2485 (21.5)	1088 (21.5)	
300–499	3771 (32.7)	2177 (43.0)		4140 (35.9)	1821 (36.0)	
≥500	2101 (18.2)	829 (16.4)		2037 (17.7)	895 (17.7)	
Missing	48 (0.4)	25 (0.5)		51 (0.4)	22 (0.4)	

BMI = body mass index; SD = standard deviation; SMD = standardized mean difference.
Note: Data are presented as the number (percentage) of patients unless otherwise indicated.
[a] Frequency numbers were rounded to integers based on weight. Adjusted for age, sex, BMI category, smoking status, diabetes, hypertension, hyperlipidemia, coronary artery disease, chronic heart failure, chronic pulmonary disease, cerebrovascular disease, hemodialysis, rheumatoid arthritis, malignant disease, Charlson comorbidity index, surgical site, and hospital size.

(SD, 16.8) in the alternative beta-lactam group, with males comprising 28.0 % of both groups. BMI, smoking status, comorbidities, and the distribution of surgical sites were well-balanced between the groups, as indicated by a standard mean difference (SMD) of <0.1. The only notable difference between the two groups before weighting was hospital size, with cefazolin being used more frequently in smaller hospitals. After applying IP weighting with stabilized weights, all baseline characteristics were well-balanced between the two groups. The distribution of propensity scores is shown in Supplementary Figure 2, and the unstabilized and stabilized IP weights computed from the propensity scores are detailed in Supplementary Table 6. The distribution of alternative beta-lactam antibiotics used is provided in Table 2. Among the 5064 patients who received alternative antibiotics, the most frequently administered were ampicillin-sulbactam (1450 patients, 28.6 %), cefotiam (1165 patients, 23.0 %), ceftriaxone (1143 patients, 22.6 %), flomoxef (488 patients, 9.6 %), cefmetazole (467 patients, 9.2 %), and piperacillin (173 patients, 3.4 %). Other antibiotics were used in fewer than 100 cases.

Table 2
Types of prophylactic antibiotic.

Antibiotic	Cefazolin (n = 11,538)	Alternative beta-lactams (n = 5064)
Cephalosporin	11,538 (100.0)	3390 (66.9)
1st generation	11,538 (100.0)	0
Cefazolin	11,538 (100.0)	0
2nd generation	0	2120 (41.8)
Cefotiam	0	1165 (23.0)
Cefmetazole	0	467 (9.2)
Flomoxef	0	488 (9.6)
3rd generation	0	1267 (25.0)
Ceftriaxone	0	1143 (22.6)
Cefotaxime	0	80 (1.6)
Cefoperazone-Sulbactam	0	44 (0.9)
4th generation	0	3 (0.1)
Cefepime	0	2 (0.0)
Cefozopran	0	1 (0.0)
Broad-spectrum penicillin	0	1674 (33.1)
Ampicillin	0	38 (0.8)
Ampicillin-Sulbactam	0	1450 (28.6)
Piperacillin	0	173 (3.4)
Piperacillin-Tazobactam	0	13 (0.3)

Note: Data are presented as the number (percentage) of patients.

Main outcomes

Within 30 days after surgery, reoperation for SSIs was performed in 35 of 11,538 patients (0.30 %) in the cefazolin group and in 16 of 5064 patients (0.32 %) in the alternative beta-lactam group. Total mortality within 30 days occurred in 86 of 11,538 patients (0.75 %) in the cefazolin group and 54 of 5064 patients (1.07 %) in the alternative beta-lactam group. All mortality cases occurred among patients with femoral fractures (Supplementary Table 7). The risk curves of reoperation for SSI are shown in Fig. 2. The estimated 30-day risk was 0.31 % (95 % CI, 0.20 to 0.42) in the cefazolin group and 0.37 % (95 % CI, 0.25 to 0.66) in the alternative beta-lactam group, resulting in a risk difference of −0.06 % (95 % CI, −0.33 to 0.14) and a risk ratio of 0.82 (95 % CI, 0.50 to 1.52) (Table 3). The estimated 30-day risk of total mortality was 0.75 % (95 % CI, 0.58 to 0.94) in the cefazolin group and 1.04 % (95 % CI, 0.80 to 1.28) in the alternative beta-lactam group, resulting in a risk difference of −0.29 % (95 % CI, −0.53 to 0.08) and a risk ratio of 0.72 (95 % CI, 0.53 to 0.83).

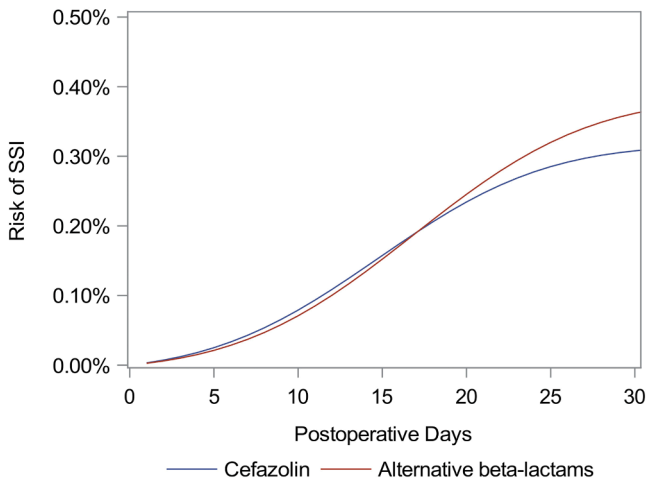

Fig. 2. Risk curves for reoperation due to surgical site infection. SSI = surgical site infection. Note: Color should be used for FIG. 2 in print.

Table 3
Risk of reoperation for surgical site infection and total mortality.

Outcome	Cefazolin		Alternative beta-lactams		Risk difference, % (95 % CI)	Risk ratio (95 % CI)
	Events[a]	Risk, % (95 % CI)	Events[a]	Risk, % (95 % CI)		
Reoperation for surgical site infection						
Within 30 days	37	0.31 (0.20 to 0.42)	17	0.37 (0.25 to 0.66)	−0.06 (−0.33 to 0.14)	0.82 (0.50 to 1.52)
Within 90 days	79	0.67 (0.52 to 0.86)	27	0.57 (0.40 to 0.87)	0.10 (−0.15 to 0.32)	1.19 (0.80 to 1.62)
Within 365 days	118	1.02 (0.84 to 1.16)	45	0.90 (0.69 to 1.25)	0.12 (−0.29 to 0.39)	1.13 (0.78 to 1.51)
Total mortality						
Within 30 days	86	0.75 (0.58 to 0.94)	54	1.04 (0.80 to 1.28)	−0.29 (−0.53 to 0.08)	0.72 (0.59 to 1.10)
Within 90 days	137	1.20 (1.06 to 1.42)	98	1.93 (1.49 to 2.17)	−0.73 (−1.01 to −0.27)	0.62 (0.53 to 0.83)
Within 365 days	163	1.43 (1.24 to 1.65)	107	2.10 (1.68 to 2.34)	−0.67 (−0.90 to −0.15)	0.68 (0.60 to 0.92)

CI = confidence interval; SSI = surgical site infection.
Note: Adjusted for baseline covariates. The alternative beta-lactams served as the reference group.
[a] Frequency numbers were rounded to integers based on weight.

Additional outcomes

The duration and dosage of prophylactic antibiotic administration from the surgery date were largely comparable between the groups. In the cefazolin group, 10,214 of 11,538 patients (88.5 %) and in the alternative beta-lactam group, 4501 of 5064 patients (88.9 %) received antibiotics for one or two days (Supplement Table 8). Similarly, 10,475 of 11,538 patients (90.8 %) in the cefazolin group and 4805 of 5064 patients (94.9 %) in the alternative beta-lactam group were administered a dosage of two vials or less of antibiotics at time 0 (Supplement Table 9). The risk of blood transfusion within 30 days postoperatively was 23.7 % (95 % CI, 23.3 to 24.6) in the cefazolin group and 23.1 % (95 % CI, 22.8 to 23.5) in the alternative beta-lactam group, resulting in a risk difference of 0.68 % (95 % CI, 0.36 to 1.66) and a risk ratio of 1.03 (95 % CI, 1.01 to 1.07) (Supplementary Table 10). The mean anesthesia time was 105 mins (SD, 51) in the cefazolin group and 104 mins (SD, 59) in the alternative beta-lactam group (P = 0.65). When stratified by anesthesia type, the mean duration for general anesthesia was 111 mins (SD, 55) in the cefazolin group and 112 mins (SD, 59) in the alternative beta-lactam group (P = 0.78), while the mean duration for spinal anesthesia was 94 mins (SD, 42) in the cefazolin group and 92 mins (SD, 46) in the alternative beta-lactam group (P = 0.12) (Supplementary Table 11).

Sensitivity analysis

The sensitivity analysis results, extending the follow-up period from 30 to 90 and 365 days, are summarized in Table 3, Supplementary Figure 3, and Supplementary Figure 4. At both 90 and 365 days, the risk of reoperation for SSI was about 0.1 % higher in the cefazolin group, while the mortality rate was about 0.7 % lower compared to the alternative beta-lactam group. These findings were consistent with the results of the main analysis at 30 days.

Subgroup analysis

Subgroup analyses comparing cefazolin with second- and third-generation cephalosporins and broad-spectrum penicillins are summarized in Table 4. The risks of reoperation for SSI at 30, 90, and 365 days were 0.31 % (95 % CI: 0.20–0.42), 0.67 % (0.52–0.86), and 1.02 % (0.84–1.16) for cefazolin; 0.30 % (0.15–0.75), 0.41 % (0.28–0.73), and 0.70 % (0.50–1.23) for second-generation cephalosporins; 0.53 % (0.09–1.46), 1.03 % (0.49–2.17), and 1.45 % (0.73–1.76) for third-generation cephalosporins; and 0.19 % (0.00–0.50), 0.37 % (0.12–0.65), and 0.72 % (0.41–1.25) for broad-spectrum penicillins. Across all groups and time periods, 95 % CIs for risk differences crossed zero, indicating no substantial differences.

Discussion

After emulating a target trial using a hospital administrative database, we found that the risk of reoperation due to SSI after surgery was consistently low regardless of whether cefazolin or alternative beta-lactams were used. This result was confirmed in the main analysis and sensitivity analyses with extended follow-up to 90 and 365 days. In the subgroup analyses by antibiotic type, the 95 % CIs crossed zero in all subgroups and time periods, suggesting no substantial differences between the two groups.

Although the effectiveness of prophylactic antibiotics has been reported in numerous studies [23–25], few have compared the effectiveness of alternative beta-lactams with cefazolin in orthopedic lower extremity fracture surgeries [26]. Our study is characterized by its large-scale, real-world setting, providing a direct comparison between cefazolin and alternative beta-lactams for closed lower extremity fractures. In our study, the estimated 30-day risk of reoperation was around 0.3 % in both groups. Several previous studies have estimated the risk of SSI in lower limb fractures. Some retrospective cohort studies have reported deep SSI risks of 1.2 % to 1.3 % for hip fractures [27,28], 1.6 % to 4.5 % for tibial or knee fractures [7,8,29], and 1.4 % to 6.8 % for ankle fractures [30–32]. The SSI risks reported in these previous studies were slightly higher than our findings, possibly because our study focused solely on reoperation for SSI. Supporting this, a retrospective cohort study of 74,711 patients with hip fractures reported that the risk of reoperation due to SSI was 0.53 % within 30 days and 0.95 % within 90 days after surgery, which is consistent with our findings [33].

Previous studies comparing cefazolin with alternative antibiotics have primarily focused on patients with penicillin allergies, in which

Table 4
Risk of reoperation for surgical site infection: subgroup analyses.

Outcome	Cefazolin		Alternative beta-lactams		Risk difference, % (95 % CI)	Risk ratio (95 % CI)
	Events[a]	Risk, % (95 % CI)	Events[a]	Risk, % (95 % CI)		
Cefazolin vs. second generation cephalosporins						
Within 30 days	37	0.31 (0.20 to 0.42)	7	0.30 (0.15 to 0.75)	0.01 (−0.48 to 0.25)	1.00 (0.30 to 2.82)
Within 90 days	79	0.67 (0.52 to 0.86)	10	0.41 (0.28 to 0.73)	0.26 (−0.06 to 0.47)	1.64 (0.91 to 2.69)
Within 365 days	118	1.02 (0.84 to 1.16)	17	0.70 (0.50 to 1.23)	0.32 (−0.09 to 0.52)	1.45 (0.90 to 2.06)
Cefazolin vs. third generation cephalosporins						
Within 30 days	37	0.31 (0.20 to 0.42)	5	0.53 (0.09 to 1.46)	−0.22 (−1.24 to 0.35)	0.59 (0.15 to 3.72)
Within 90 days	79	0.67 (0.52 to 0.86)	9	1.03 (1.49 to 2.17)	−0.36 (−0.70 to 0.26)	0.65 (0.47 to 1.62)
Within 365 days	118	1.02 (0.84 to 1.16)	14	1.45 (0.73 to 1.76)	−0.43 (−0.79 to 0.29)	0.70 (0.55 to 1.36)
Cefazolin vs. broad-spectrum penicillins						
Within 30 days	37	0.31 (0.20 to 0.42)	4	0.19 (0.00 to 0.50)	0.12 (−0.19 to 0.37)	1.59 (0.60 to 1908.73)
Within 90 days	79	0.67 (0.52 to 0.86)	8	0.37 (0.12 to 0.65)	0.30 (−0.03 to 0.59)	1.82 (0.96 to 6.10)
Within 365 days	118	1.02 (0.84 to 1.16)	14	0.72 (0.41 to 1.25)	0.30 (−0.17 to 0.62)	1.42 (0.86 to 2.37)

CI = confidence interval; SSI = surgical site infection.
Note: Adjusted for baseline covariates. The alternative beta-lactams served as the reference group.
[a] Frequency numbers were rounded to integers based on weight.

comparisons were made between cefazolin and non-beta-lactams rather than beta-lactams. Some studies reported that non-beta-lactams were not associated with a higher risk of SSI compared with cefazolin [34,35], whereas others found that non-beta-lactams were associated with a higher risk of SSI than cefazolin [36–40]. Regarding the effectiveness of beta-lactams, a few reports comparing them with cefazolin have shown inconsistent results [12,13,41,42]. For instance, in esophageal and pancreatic surgeries, which involve the presence of anaerobic bacteria, ampicillin-sulbactam and ceftriaxone have been reported to potentially reduce the risk of SSI compared with cefazolin [41,42]. This may be because the effectiveness of beta-lactams varies depending on the surgical site. To our knowledge, only two retrospective cohort studies have compared the effectiveness of cefazolin monotherapy with alternative beta-lactams in orthopedic surgeries [12,13]. One was a single-center study on upper extremity surgeries which reported a 90-day deep SSI incidence of 0.08 % in the cefazolin group and 1.12 % in the ceftriaxone group [13]. The other was a multicenter study on various spinal surgeries which reported an incidence of reoperation due to deep SSIs within 30 days of 0.31 % with cefazolin and 2.2 % with alternative beta-lactams [12]. Both studies suggested a higher risk of SSIs with alternative beta-lactams, in contrast with our results. We speculate that these differences might be due to variations in surgical sites, sample size, outcome definitions, and confounding adjustment. In terms of sample size, our study is the largest to date, with approximately five times more participants than the spinal surgery study, thereby enhancing generalizability and contributing to narrower CIs and accordingly providing greater precision. With regard to outcome definitions, our reliance on claims data may have introduced a risk of outcome misclassification, potentially underestimating the overall SSI incidence compared with studies using disease registry data [12]. In terms of confounding adjustment, we used a propensity score method to sufficiently adjust for confounding. IP-weighted pooled logistic regression allowed us to estimate absolute risk, risk differences, and risk ratios, which strengthened the reliability of our findings [43]. Additionally, our use of target trial emulation represents an advanced and relatively novel approach for causal inference [18,44]. While still uncommon in orthopedic research, this methodology is gaining recognition in other surgical fields [45,46]. Finally, a common strength of studies focused on cefazolin shortages is that patient characteristics have minimal influence on treatment assignment, resulting in limited confounding by indication. This could be an advantage over other observational studies [12,13].

This study has several limitations. First, while propensity score methods balance measured confounders, they cannot account for unmeasured confounders, such as local antibiotic resistance patterns, radiologic findings, malnutrition, prolonged Foley placement, use of negative pressure wound therapy, surgery type (plate, intramedullary device), variability in facility-level practices, and individual surgeon preferences. Although we cannot rule out the possibility of imbalance in these factors, all measured confounders were well-balanced after applying IP weighting—and indeed most were balanced even before weighting. We believe that major bias is unlikely because the nationwide cefazolin shortage, driven by a single major manufacturer supplying about 60 % of the market, affected hospitals regardless of size or region, reducing the risk of skewed distributions in patient severity or treatment patterns. Additionally, Japan's universal healthcare system and minimal variation in physician compensation or patient expenses also help ensure relatively uniform guideline adherence. As shown in Supplementary Tables 8 and 9, approximately 90 % of patients received antibiotic prophylaxis for only one or two days, with little variation in dosing—reflecting the recommended 24–48-hour prophylaxis window. Nonetheless, unmeasured confounders cannot be fully excluded, and readers should therefore interpret these findings with caution. Given that cefazolin is more frequently used in smaller hospitals, patients in the cefazolin group may have had less severe fractures than those in the alternative beta-lactam group. However, we believe that the similar risk of blood transfusion, duration and dosage of antibiotics used, and comparable duration of anesthesia suggest that the groups did not substantially differ by fracture severity (Supplementary Table 8). The cefazolin group also had approximately 0.3 % lower 30-day and 0.7 % lower 90-day and 365-day mortality risks than the alternative beta-lactam group. This may be because more patients with comorbidities were treated at larger hospitals, where alternative beta-lactams are more commonly used, and potentially unmeasured confounders may have affected mortality. Second, our outcome measure focused solely on "reoperation for SSI," which primarily captures deep SSIs and may have missed some superficial SSIs, potentially underestimating the overall incidence of SSIs. By using both ICD-10 and procedure codes to identify reoperations, we aimed to enhance the specificity of SSI identification and reduce the risk of coding inaccuracies [20]. Nevertheless, this approach may have resulted in lower sensitivity for detecting all SSIs. Superficial SSIs, which often do not require reoperation, can be managed with wound irrigation or antibiotics alone and are less clinically important than deep SSIs. The distinction between deep SSIs requiring surgical intervention and superficial SSIs managed with simpler procedures underscores the clinical relevance of our outcome definition. This definition has been used not only in our study but also in the prior literature informing our methodology [12,13,33]. Third, the database tracks events only within the same hospital, meaning that reoperations performed at other hospitals could not be captured,

potentially underestimating the overall SSI risk. While most early surgical complications within 30 and 90 days are likely treated at the hospital where the primary surgery was performed, it is important to note that SSI risk and mortality within 365 days may also be underestimated, as only patients who underwent reoperations or died at the same hospital are included. Fourth, the limited number of outcome events may have affected the precision of our subgroup analyses by antibiotic type. Future studies with larger sample sizes, focusing on a single antibiotic as the control group, will be necessary to validate our findings. Finally, since our analysis was conducted on a relatively homogeneous population of Japanese patients, factors such as antibiotic resistance, healthcare access, and lifestyle (e.g., nutritional status) may differ in other countries, thereby limiting the transportability of our findings.

Conclusions

Substituting cefazolin with alternative beta-lactams did not result in substantial differences in the risk of reoperation for SSI in surgeries for lower extremity fractures. Given that antibiotic supply shortages can realistically occur anywhere in the world, confirming that alternative beta-lactams are as effective as cefazolin provides valuable insights for clinical practice. We expect that these findings will be confirmed by larger prospective studies focusing on a single antibiotic as the control group.

Ethical statement

Ethical approval for this study was obtained from the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (approval number: R4555).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used GPT-4o, an AI model developed by OpenAI, in order to improve the fluency of the text. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

CRediT authorship contribution statement

Takaki Yoshiyama: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Toshiki Fukasawa:** Writing – review & editing, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Soichiro Masuda:** Writing – review & editing, Supervision, Conceptualization. **Shuichi Matsuda:** Supervision. **Koji Kawakami:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2025.112215.

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