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# Cefazolin remains the linchpin for preventing acute periprosthetic joint infection following primary total knee arthroplasty

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## Aims

Despite recent literature questioning their use, vancomycin and clindamycin often substitute cefazolin as the preoperative antibiotic prophylaxis in primary total knee arthroplasty (TKA), especially in the setting of documented allergy to penicillin. Topical povidone-iodine lavage and vancomycin powder (VIP) are adjuncts that may further broaden antimicrobial coverage, and have shown some promise in recent investigations. The purpose of this study, therefore, is to compare the risk of acute periprosthetic joint infection (PJI) in primary TKA patients who received cefazolin and VIP to those who received a non-cephalosporin alternative and VIP.

## Methods

This was a retrospective cohort study of 11,550 primary TKAs performed at an orthopaedic hospital between 2013 and 2019. The primary outcome was PJI occurring within 90 days of surgery. Patients were stratified into two groups (cefazolin vs non-cephalosporin) based on their preoperative antibiotic. All patients also received the VIP protocol at wound closure. Bivariate and multiple logistic regression analyses were performed to control for potential confounders and identify the odds ratio of PJI.

## Results

In all, 10,484 knees (90.8%) received cefazolin, while 1,066 knees (9.2%) received a non-cephalosporin agent (either vancomycin or clindamycin) as preoperative prophylaxis. The rate of PJI in the cefazolin group (0.5%; 48/10,484) was significantly lower than the rate of PJI in the non-cephalosporin group (1.0%; 11/1,066) ( $p = 0.012$ ). After controlling for confounding variables, the odds ratio (OR) of developing a PJI was increased in the non-cephalosporin cohort compared to the cefazolin cohort (OR 2.389; 1.2 to 4.6);  $p = 0.01$ ).

## Conclusion

Despite the use of topical irrigant solutions and addition of local antimicrobial agents, the use of a non-cephalosporin perioperative antibiotic continues to be associated with a greater risk of TKA PJI compared to cefazolin. Strategies that increase the proportion of patients receiving cefazolin rather than non-cephalosporin alternatives must be emphasized.

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**Keywords:** knee, infection, prophylaxis, cefazolin, VIP, vancomycin powder, povidone-iodine lavage, organism profile

## Introduction

Periprosthetic joint infection (PJI) is one of the most devastating complications following total knee arthroplasty (TKA), representing substantial morbidity and increase in health-care costs.<sup>1,2</sup> Administration of perioperative prophylactic antibiotics remains the cornerstone of effective early PJI prevention,<sup>3</sup> with

current practice recommendations consisting of administering a first- or second-generation cephalosporin, unless contraindicated.<sup>4-6</sup>

The current guidelines from the American Academy of Orthopaedic Surgeons (AAOS)<sup>7</sup> cite limited evidence regarding superiority of cefazolin to non-cephalosporin alternatives as antimicrobial prophylaxis, and allows for

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**Table 1.** Demographics of patients by preoperative antibiotics given.

Variable	Non-cephalosporin (n = 1,066)	Cefazolin (n = 10,484)	Overall (n = 11,550)	p-value
Mean age, yrs (SD)	65.14 (10.2)	65.6 (9.6)	65.6 (9.6)	0.330*
Mean BMI, kg/m <sup>2</sup> (SD)	32.72 (7.0)	32.35 (6.4)	32.39 (6.5)	0.220*
Male sex, n (%)	243 (22.8)	3,438 (32.8)	3,681 (31.9)	< 0.0001 †‡
Diabetes mellitus, n (%)	107 (10.0)	996 (9.5)	1,103 (9.5)	0.570†
Rheumatologic history, n (%)	65 (6.1)	449 (4.3)	514 (4.5)	0.006†‡
Rheumatoid arthritis, n (%)	53 (5.0)	418 (4.0)	471 (4.1)	0.121†
Smoking, n (%)	67 (6.3)	737 (7.0)	804 (7.0)	0.363†
Age ≥ 65 yrs, n (%)	590 (55.3)	5,780 (55.1)	6,370 (55.2)	0.893†
BMI ≥ 35 kg/m <sup>2</sup> , n (%)	355 (33.3)	3,237 (30.9)	3,592 (31.1)	0.103†
Bilateral TKA, n (%)	66 (6.2)	650 (6.2)	716 (6.2)	0.991†
PJI, n (%)	11 (1.0)	48 (0.5)	59 (0.5)	0.012‡

\*Mann-Whitney U test.

†Chi-squared test.

‡Statistically significant.

PJI, periprosthetic joint infection; SD, standard deviation; TKA, total knee arthroplasty.

easy substitution to vancomycin or clindamycin when deemed appropriate. The emerging body of evidence, however, suggests higher incidence of PJI when vancomycin is used as the sole antimicrobial agent, highlighting the limits of this strategy.<sup>8–12</sup> Cephalosporins are bactericidal and have broad spectrum of action with the ability to cover both gram-negative and gram-positive organisms.<sup>5,13</sup> In contrast, clindamycin alone is only bacteriostatic, and vancomycin alone has reduced gram-negative coverage and may thus be associated with increased infection rates. Our institution (New York University Langone Orthopedic Hospital, USA) has two interventions in place to expand perioperative antimicrobial coverage. First, our standard antimicrobial prophylaxis broadens coverage to include a gram-negative agent when vancomycin is given. In addition, we perform a dilute povidone-iodine lavage of the surgical site and apply topical vancomycin powder prior to wound closure in an attempt to further reduce rates of PJI.<sup>14,15</sup>

The success of our institution's vancomycin povidone-iodine protocol (VIP) has been reported previously;<sup>14,15</sup> however, it remains unclear whether combining these adjunctive antimicrobial agents can mitigate the apparent superiority of cefazolin over non-cephalosporin alternatives in preventing PJI. Our study thus attempts to address these concerns by asking two questions: 1) in patients who received the VIP protocol, does the use of a non-cephalosporin perioperative antibiotic prophylaxis increase the odds of an acute PJI when compared to the use of cefazolin perioperative prophylaxis?; and 2) does the organism profile for early PJI differs between cefazolin and non-cephalosporin antibiotic administration? We hypothesized that first, there would be no difference in infection rates between the patients who received cefazolin versus those received a non-cephalosporin agent, and second, that the PJI organism profiles would be similar between the two cohorts.

## Methods

This study is a retrospective cohort study performed at a single large volume academic orthopaedic hospital. In accordance with our institutional guidelines, this study was considered a quality improvement intervention, and was thus exempt from our Institutional Review Board (IRB) process. All patients included in this study underwent primary TKA at our institution between January 2013 and December 2019 and had a minimum of 90-day follow-up. PJI cases were considered to be our primary outcome, and were identified by our infection control department by cross-referencing a prospectively collected database based on the criteria defined by the Centres for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN) criteria to screen for infections, which require that an infection occurs within the 90-day postoperative period.<sup>16</sup> All suspected PJIs were confirmed by manual chart review using the Musculoskeletal Infection Society (MSIS) criteria.<sup>17</sup>

All primary TKAs were performed in standard operating rooms with similar staffing and personnel requirements. All scrubbed personnel were required to wear a surgical helmet and body exhaust suit. Our institution's antimicrobial prophylaxis guidelines recommends that patients receive one of the following: 2 g of cefazolin given every eight hours for 24 hours, including initial dose within 60 minutes of skin incision; one preoperative dose of 15 to 20 mg/kg of vancomycin within 120 minutes of skin incision with a gram-negative agent (one dose of 2 g of aztreonam if aged 75 years and older; ≥ 120 kg, or creatinine clearance < 20 ml/min, or 3 to 5 mg/kg of gentamicin) if methicillin-resistant *Staphylococcus aureus* (MRSA) positive, or one preoperative dose of 900 mg of clindamycin if the patient reported a penicillin or cephalosporin allergy. Patients with a penicillin allergy did not undergo routine allergy testing. It was at the discretion of the anesthesia and surgical team in deciding whether a

**Table II.** Demographics of patients by periprosthetic joint infection (PJI) versus no PJI.

Variable	PJI (n = 59)	No PJI (n = 11,491)	Total (n = 11,550)	p-value
Male sex, n (%)	29 (49.2)	3,652 (31.8)	3,681 (31.9)	0.004*†
Diabetes mellitus, n (%)	4 (6.8)	1,099 (9.6)	1,103	0.468*
Rheumatologic history, n (%)	4 (6.8)	510 (4.4)	514	0.384*
Rheumatoid arthritis, n (%)	3 (5.1)	468 (4.1)	471	0.695*
Smoking, n (%)	6 (10.2)	798 (6.9)	804	0.332*
Mean age, yrs (SD)	63.5 (9.2)	65.4 (9.6)	65.6 (9.6)	0.139‡
Mean BMI, kg/m <sup>2</sup> (SD)	35.2 (8.0)	32.3 (6.5)	32.39 (6.5)	0.009‡†
Age ≥ 65 yrs, n (%)	33 (55.9)	5,154 (55.1)	6,370	0.904*
BMI ≥ 35 kg/m <sup>2</sup> , n (%)	23 (39)	3,569 (31.1)	3,592	0.190*
Bilateral TKA, n (%)	0 (0)	716 (6.2)	716	0.051*

\*Chi-squared test.

†Statistically significant.

‡Mann-Whitney U test.

PJI, periprosthetic joint infection; SD, standard deviation; TKA, total knee arthroplasty.

test dose of cephalosporin was administered in the operating room. All patients underwent MRSA colonization screening from their nares, and those who were MRSA positive underwent preoperative decolonization with povidone-iodine ointment to the nares one to six hours before surgery. All patients were advised to use 2% chlorhexidine gluconate wipes for skin decolonization the night before surgery, as well as the morning of surgery. Prior to prepping and draping, hair was removed from the incision site. The skin was prepped using 2% chlorhexidine gluconate in 70% isopropyl alcohol solution (ChlorPrep; Carefusion, USA). Unless contraindicated, tranexamic acid 1 g IV was administered to all patients prior to incision. During the study period, our institution did not extend the duration of postoperative antimicrobial prophylaxis for high-risk patients.

The VIP protocol, as described by Iorio et al,<sup>15</sup> was implemented at our institution in 2013, and consists of a 0.35% povidone-iodine (17.5 ml in 500 ml saline) solution lavage, which is left in place for three minutes after final prosthesis implantation. This is followed by pulsed irrigation with 1 l of sterile saline, placement of 1 g of vancomycin deep to the fascia, and another 1 g superficial to the fascia during wound closure.

Patients were stratified into two cohorts: received cefazolin (cefazolin cohort), or a non-cephalosporin agent (vancomycin or clindamycin). Demographics, including age, sex, BMI, the presence of diabetes mellitus or rheumatoid arthritis, American Society of Anesthesiologists (ASA) classification, as well as organism characteristics, were obtained for all confirmed PJIs via manual chart review.

**Statistical analysis.** All statistical analyses were performed using SPSS version 25 (IBM, USA). Demographics were compared using chi-squared tests for categorical variables and Mann-Whitney U tests for continuous variables. Infection rates and differences in offending microbiome between the two cohorts were performed using Fisher's

**Table III.** Multivariate analysis assessing risk of infection with non-cephalosporin alternatives.

Variable	OR (95% CI)	p-value
PJI risk without cefazolin	2.267 (1.2 to 4.4)	0.015*
PJI risk without cefazolin: adjusted	2.389 (1.2 to 4.6)	0.010†*

Adjusted for male sex, BMI, and rheumatologic history.

\*Statistically significant.

†Multivariate logistic regression.

CI, confidence interval; OR, odds ratio; PJI, periprosthetic joint infection.

exact tests. All significance was set to  $p < 0.05$ . Bivariate analyses identified variables associated with infection ( $p < 0.05$ ) that were subsequently entered into a multivariate logistic regression which was performed to control for identified independent risk factors for PJI and to determine the odds ratio for infection.

## Results

Our analysis included 11,550 knees in 10,834 patients with 10,484 (90.8%) and 1,066 (9.2%) knees in the cefazolin and non-cephalosporin cohorts, respectively. Our overall 90-day PJI incidence was 0.51% (59/11,550), with our data showing the PJI incidence in the non-cefazolin cohort to be significantly higher than the PJI incidence in the cefazolin cohort (1% (11/1,066) vs 0.5% (48/10,484);  $p = 0.012$ ) Additionally, there were significantly more males in the cefazolin cohort compared to the non-cephalosporin cohort (3,438 (32.8) vs 243 (22.8);  $p = < 0.001$ ), and significantly more patients with a rheumatologic history in the non-cephalosporin cohort compared to the cefazolin cohort (65 (6.1%) vs 449 (4.3%);  $p = 0.006$ ) (Table I).

Without controlling for antibiotic regimen, male sex and increasing BMI were identified as risk factors for PJI (Table II). A multivariate logistic regression controlling for these factors and rheumatologic history revealed a greater than two-fold increased odds ratio for PJI in the non-cephalosporin cohort compared to the cefazolin cohort (OR 2.389 (1.2 to 4.6);  $p = 0.009$ ) (Table III).

**Table IV.** Organism profile stratified based on preoperative antibiotics given.

Organism	Cefazolin (n = 10,484), n	Organisms/cefazolin population, %	Non-cephalosporin (n = 1,066), n	Organism/non-cephalosporin population, %	p-value
<b>Gram-positive organisms</b>					
<i>Actinomyces meyeri</i>	1	0.01	0	0.00	1.000
<i>Corynebacterium jeikeium</i>	2	0.02	0	0.00	1.000
<i>Cutibacterium acnes</i>	2	0.02	0	0.00	1.000
<i>Fingoldia magna</i>	0	0.00	1	0.09	0.092
MRSA	4	0.04	3	0.28	0.021*
MRSE	11	0.10	1	0.09	1.000
MSSA	17	0.16	2	0.19	0.693
MSSE	5	0.05	3	0.28%	0.031*
<i>Propionibacterium Granulosum</i>	0	0.00	2	0.19	0.009*
<i>Serratia marcescens</i>	2	0.02	0	0.00	1.000
<i>Staph. Lugdunensis</i>	1	0.01	0	0.00	1.000
<i>Strep. Agalactiae</i>	3	0.03	2	0.19	0.070
<i>Strep. Anginosus</i>	1	0.01	0	0.00	1.000
<i>Strep. Mitis</i>	0	0.00	1	0.09	0.092
<i>Strep. Pyogenes</i>	1	0.01	0	0.00	1.000
Total	50	0.48	15	1.41	0.00011
<b>Gram-negative organisms</b>					
<i>Acinetobacter calcoaceticus-baumannii</i> complex	1	0.01	0	0.00	1.000
<i>Citrobacter koseri</i>	1	0.01	0	0.00	1.000
<i>Enterobacter cloacae</i>	1	0.01	0	0.00	1.000
<i>Enterococcus faecalis</i>	1	0.01	0	0.00	1.000
<i>Eschericia Coli</i>	1	0.01	1	0.09	0.176
<i>Eschericia Hermanii</i>	1	0.01	0	0.00	1.000
<i>Klebsiella aerogenes</i>	0	0.00	1	0.09	0.092
<i>Klebsiella pneumoniae</i>	3	0.03	1	0.09	0.321
<i>Morganella morganii</i>	1	0.01	0	0.00	1.000
<i>Pasteurella multocida</i>	1	0.01	0	0.00	1.000
<i>Proteus Mirabilis</i>	2	0.02	0	0.00	1.000
<i>Pseudomonas aeruginosa</i>	4	0.04	1	0.09	0.384
Total	17	0.16	4	0.38	0.124

\*Statistically significant.

MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSE, methicillin-sensitive *Staphylococcus epidermidis*.

Table IV lists the microbiological profile of PJI organism in each cohort. The incidence of gram-negative and gram-positive isolates were higher in the non-cephalosporin cohort (1.41% and 0.38%) than the cefazolin group (0.48% and 0.16%); however, only the difference in the gram-positive isolates was statistically significant ( $p < 0.001$ ). The incidence of MRSA was also significantly higher in the non-cephalosporin group (0.28%) compared to the cefazolin group (0.04%) ( $p = 0.021$ ).

## Discussion

PJI remains one of the most devastating complications following TKA, and, as such, multiple strategies are in place to reduce its risk of occurrence. Perioperative antibiotic prophylaxis remains the most effective strategy to reduce infection, with recommendation for first- or second-generation cephalosporin agent or an alternate drug, such as vancomycin

or clindamycin in cases where cephalosporin is contraindicated<sup>4,5,13,18,19</sup> due to penicillin allergy or MRSA colonization. Multimodal antimicrobial strategies to decrease the risk of PJI include broadening antimicrobial coverage with drugs targeting gram-negative organisms, and the use of adjuvants such as dilute povidone-iodine lavage and topical vancomycin powder.<sup>20-22</sup> To the best of our knowledge, this investigation is the first to better elucidate the differences in risk of PJI in TKA patients receiving cefazolin compared to non-cephalosporin antibiotics in the setting of concomitant use of dilute povidone-iodine lavage and topical vancomycin powder.

Our data suggests the superiority of cefazolin over non-cephalosporin alternatives, even with the concomitant use of a VIP protocol. Patients receiving either vancomycin or clindamycin had a greater than two-fold increasing risk of developing a PJI compared to cefazolin. Cefazolin has a broad

spectrum activity that includes coverage for most gram-positive organisms (with the exception of MRSA) and in addition to having some gram-negative activity.<sup>13</sup> In contrast, vancomycin and clindamycin have narrower gram-positive antimicrobial activity which likely explains the superiority of ceftazidime in preventing PJI following primary TKA.

Interestingly, our data showed that patients receiving a non-cephalosporin agent had significantly higher rates of gram-positive organisms causing PJI than patients who received ceftazidime. Additionally, these patients had significantly higher rates of MRSA PJI, despite receiving agents such as IV vancomycin or topical vancomycin powder, which specifically target this organism. These findings suggest several limitations of non-cephalosporin agents: First, the non-cephalosporin agents used in this study, namely vancomycin and clindamycin, have a narrow spectrum of coverage for gram-positive organisms as shown by the increased rate of gram-positive organisms; and second, authors report that there are challenges in achieving therapeutic intravascular minimal inhibitory concentrations for vancomycin, which may limit its effectiveness in reducing PJI when used intravenously.<sup>10,23</sup> Kheir et al<sup>12</sup> highlighted the challenges of dosing vancomycin in their study, where they noted that only 28% of patients received the appropriate weight-based dosing for vancomycin when used for total joint prophylaxis, even with an institutional protocol in place. While their study failed to find higher PJI rates in under-dosed patients compared to appropriately and over-dosed patients, they did note that the two MRSA infections in their vancomycin monotherapy cohort occurred only in the under-dosed patients. Furthermore, vancomycin monotherapy used for prophylaxis had a 1.587 odds ratio of suffering a PJI compared to ceftazidime monotherapy.<sup>12</sup> Feder et al<sup>24</sup> similarly found that late (within 30 minutes of incision), incomplete administration of intravenous vancomycin prophylaxis had a greater than five-fold increased risk of PJI (OR 5.22;  $p = 0.112$ ). Notably, our institution used a weight-based dosing regimen for vancomycin started 120 minutes before skin incision, which mitigates confounding from potentially incomplete or inappropriately dosed vancomycin.

Our study adds to the growing evidence of clear superiority of cephalosporins over non-cephalosporin alternatives in preventing PJI following primary TKA.<sup>8,9,11</sup> For most individuals, the decision to provide appropriately dosed cephalosporin is easy, however, in patients with contraindications to cephalosporins, controversy regarding appropriate antimicrobial prophylaxis remains. There are several studies that suggest that the prevalence of penicillin allergies is grossly overexaggerated.<sup>8,25</sup> Wyles et al<sup>8</sup> performed allergy testing in 2,493 patients with a documented penicillin allergy and cleared 97% of those patients to use cephalosporins for their TJA prophylaxis. Further, Pagani et al<sup>25</sup> performed a cost-effectiveness

analysis of routine preoperative penicillin and cephalosporin allergy testing in arthroplasty patients and found both to be cost-effective. Their analysis showed that penicillin allergy testing needed to prevent one infection out of 123 suspected-allergy TKAs to be cost-effective.

The current practice at our institution is to perform a test dose of ceftazidime in patients with documented penicillin allergy. Anecdotally, we have found that an overwhelmingly large proportion of patients receive ceftazidime without any significant adverse effect. We believe either of the two strategies of preoperative testing or performing test dose are reasonable ways to increase the volume of patients who receive ceftazidime rather than non-cephalosporin alternatives as their primary perioperative antimicrobial prophylaxis. Patients with MRSA routinely receive vancomycin in addition to a gram-negative agent at our institution. While this combination does appear to reduce the incidence of gram-negative infections,<sup>22</sup> we did note a much higher proportion of infections with gram-positive organisms compared to ceftazidime. We recognize that this could also reflect a population at higher risk of infection. Studies have shown that vancomycin and ceftazidime act synergistically against MRSA and other gram-positive microbes,<sup>5,6</sup> perhaps explaining this discrepancy. A possible more evidence-based approach that some surgeons have begun to employ is to add ceftazidime to vancomycin in coverage for these patients.

There are several limitations to this study that are inherent in the retrospective nature of its design. Not all risk factors for PJI were analyzed including operative time, early wound complication, specific anticoagulation, prior infection, liver failure, and treatment with immunosuppressive agents. Additionally, this study did not have rigid criteria applied to the ultimate choice of perioperative antibiotics. While we do have an institutional protocol in place, it is still difficult to control for factors such as variation in surgeon practice, timing of antibiotic dosing, the choice of antibiotics, strict compliance with institutional practice, and characteristics that may be associated with an increased baseline risk for PJI. Nonetheless, these weaknesses were mitigated by the large sample size, despite all being performed at a single centre, very strong physician adherence to institutional protocols, and validated internal registries, which enabled assessment of potential confounders. Even after accounting for these potential confounders, non-cephalosporin agents continued to be associated with a greater risk for PJI.

In addition, this study reported only on PJI that occurred within the 90 day postoperative period, thus our data does not report on later PJI which could also be related to the perioperative infection control strategies being evaluated. Skin flora is often the microorganism source during the acute period, and thus perioperative antimicrobial interventions are most likely to modify the infection risk in this acute period. We believe including

infections from the 90-day postoperative period limits the chance of confounding from hematogenous infections, which are believed to be more common during lateral postoperative time periods. We therefore believe that our data does support a clear advantage of cefazolin over non-cephalosporin alternates.

Another limitation is that our dataset does not specify which non-cephalosporin antibiotic patients received, and thus we were unable to differentiate the specific PJI risks of vancomycin and clindamycin individually. Further, we were unable to confirm that patients received the VIP protocol, and thus must consider that aspect of our study an intention-to-treat analysis. While our data set is quite large, the incidence of PJI is extremely low, and it is possible that even with that data, our study would be underpowered to separate those two agents into additional cohorts for analysis. In addition, our institutional practice is similar to other centres: in cases where cefazolin is contraindicated, vancomycin is typically the first-choice alternative. Clindamycin is given only in situations of vancomycin allergy. Thus, the number of patients receiving clindamycin is likely quite low.

The main strength of this study is that it is a large series at a high-volume academic centre with multiple surgeons participating. The subtle variations in surgeon practices makes our conclusions more generalizable, while the clear protocols for perioperative antimicrobial treatment provides a more controlled and reproducible environment from which to evaluate our results.

In conclusion, despite the addition of local antimicrobial agents, the use of a non-cephalosporin perioperative antibiotic continues to be associated with a greater risk of infection compared to cefazolin. Strategies that increase the proportion of patients receiving cefazolin instead of non-cephalosporin alternatives, such as preoperative cephalosporin allergy testing or intraoperative test dosing for those with documented penicillin or cephalosporin allergies, or using both cefazolin and vancomycin when a patient is MRSA-positive, are strongly recommended.



### Take home message

- Non-cephalosporin perioperative antibiotic are associated with a greater risk of total knee arthroplasty periprosthetic joint infection compared to cefazolin.

- Strategies that increase the proportion of patients receiving cefazolin rather than non-cephalosporin alternatives must be emphasized.

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