# Cefazolin Prophylaxis for Total Joint Arthroplasty: Obese Patients are Frequently Underdosed and at Increased Risk for Periprosthetic Joint Infection

Running Title: Cefazolin Dosing in TJA

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# Cefazolin Prophylaxis for Total Joint Arthroplasty: Obese Patients are Frequently Underdosed and at Increased Risk for Periprosthetic Joint Infection

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**ABSTRACT**

*Background:* One of the most effective prophylactic strategies against periprosthetic joint infection (PJI) is administration of perioperative antibiotics. Many orthopaedic surgeons are unaware of the weight-based dosing protocol for cefazolin. This study aimed to elucidate what proportion of patients receiving cefazolin prophylaxis are underdosed and whether this increases the risk for PJI.

*Methods:* A retrospective study of 17,393 primary total joint arthroplasties (TJA) receiving cefazolin as perioperative prophylaxis from 2005-2017 was performed. Patients were stratified into two groups (underdosed and adequately dosed) based on patient weight and antibiotic dosage. Patients that developed PJI within 1-year following index procedure were identified. A bivariate and multiple logistic regression analysis were performed to control for potential confounders and identify risk factors for PJI.

*Results*: The majority of patients weighing greater than 120 kg (95.9%, 944/984) were underdosed. Underdosed patients had a higher rate of PJI at 1-year compared with adequately dosed patients (1.51% vs. 0.86%, p=0.002). Patients weighing greater than 120 kg had higher 1-year PJI rate than patients weighing less than 120 kg (3.25% vs. 0.83%, p<0.001). Patients who were underdosed (odds ratio (OR) 1.665, p=0.006) with greater comorbidities (OR 1.259, p<0.001) were more likely to develop PJI at 1-year.

*Conclusion*: Cefazolin underdosing is common, especially for patients weighing more than 120 kg. Our study reports that underdosed patients were more likely to develop PJI.

Orthopaedic surgeons should pay attention to the weight-based dosing of antibiotics in the perioperative period to avoid increasing risk for PJI.

*Keywords:* Total Joint Arthroplasty; Periprosthetic Joint Infection; Perioperative Antibiotics; Obesity; Dosing; Risk

## INTRODUCTION

One of the most effective strategies for prevention of periprosthetic joint infection (PJI) has been the administration of perioperative antibiotics. The presence of antibiotics in the serum can eliminate the bacteria that gain access to the surgical site during total joint arthroplasty (TJA) and in turn reduce the incidence of surgical site infection [1]. Current practice is to administer first or second generation cephalosporin to all patients undergoing TJA, unless contraindicated [2]. Despite the widespread use of cefazolin as a perioperative antibiotic for TJA patients, many surgeons are unaware of cefazolin's weight-based dosing. Thus, the goals of the present study are (1) to ascertain what proportion of TJA patients receiving cefazolin are adequately dosed and (2) if under-dosing was associated with increased risk of subsequent PJI.

At our institution, the recommended dose of cefazolin has traditionally been 2 grams intravenously. Current guidelines for antimicrobial prophylaxis recommend weight-based dosing protocols starting the cefazolin dose at 1 gram (g) if a patient weighs less than 60 kilograms (kg), 2 grams if patient weights between 60 kg and 120 kg, and 3 grams if patient weight over 120 kg [2,3]. A previous study at our institution found the majority of patients receiving vancomycin as perioperative prophylaxis were underdosed according to weight-based dosage recommendations (15 milligrams/kg) [4].

Given the increasing prevalence of obesity [5,6] in the TJA population, many patients may be inadequately dosed for antibiotics. Thus, the effective drug concentration may not be met to provide bactericidal effects and subsequently may predispose patients to an increased risk for PJI. We hypothesis patients who are underdosed are at increased risk of adverse events and infection.

## MATERIALS AND METHODS

After Institutional Review Board approval, a retrospective review of 24,439 patients undergoing primary TJA at a single institution was performed from 2005-2017. All patients with primary TJA, with record of the perioperative antibiotic and dosage administrated were included in this study. Patients with aseptic revision TJA were excluded. The perioperative antibiotic and dosage were then obtained for the patient population, resulting in a cohort of 17,393 of patients receiving cefazolin as perioperative prophylactic antibiotic. Patients who received other types of perioperative prophylactic antibiotics (i.e. Vancomycin) other than Cefazolin were excluded from the study. Patients with a history of prior infection in the same joint or unavailable antibiotic information were excluded from the study. An electronic query and chart review was then performed to identify demographic information, height, weight, body mass index (BMI), joint, laterality, length of stay, operative time, time to incision from administration of cefazolin, and Charlson comorbidities. Demographic information of the cohort is presented in Table 1.

Using the generalized dosing protocol of 1 g for patients weighing below 60 kg, 2 g for patients weighing between 60 kg and 120 kg, and 3 g for patients weighing 120 kg or greater for cefazolin, proper dosage was calculated for each patient. These values were then compared to the actual dose given to the patients at time of surgery. Patients were assessed as either underdosed (< 1 g, if patient weighed between 60 kg-120 kg and was given <2g, or if patient weighed 120 kg or more and was given < 3 g) or adequately

dosed (if appropriately dosed based on weight). Cefazolin was administered within 60 minutes of incision in all cases.

The cohort was then cross-referenced with an institutional PJI database to identify patients with PJI. We defined PJI in patients based on the International Consensus Meeting criteria[7]. A subsequent manual chart review was undertaken to verify PJI outcomes and ensure the correct joint and laterality.

The primary endpoint was to assess the incidence of 1-year PJI following TJA in patients who were underdosed versus adequately dosed.

*Statistical Analysis*

All statistical analyses were performed with PJI rate analyzed among the two dosing groups and by weight class. Bivariate analyses were performed to compare demographics, perioperative variables between the two dosing groups and weight class. A multivariate logistic regression model was utilized to determine risk factors for PJI based on the following: antibiotic dosing, dosing status, age, patient weight, BMI, gender, joint, length of stay, and Charlson Comorbidity index. All statistical analyses were performed using R 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria) and an alpha level of 0.05 was used to evaluate significance. All analyses were conducted with Generalized estimating equations (GEE) to account for the clustering within patients who had multiple admissions. The GEE specified a binary distribution with a logit link for analyzing the dichotomous outcomes.

**RESULTS**

All patients included in the study received cefazolin preoperatively within 60 minutes as the main antibiotic prophylaxis. Of the 984 patients weighing 120 kg or greater, the majority were underdosed (95.9%, 944/984). For patients weighing less than 120 kg, most were adequately dosed (88.3%, 14,497/16,409). Overall, 83.6% (14,537/17,393) of patients were adequately dosed for cefazolin prophylaxis. Of note, 0.10% (18/17,393) patients were overdosed, however, none developed PJI at 1-year and all weighed between 60 and 120 kg.

Among primary TJAs, underdosed patients had a higher rate of 1-year PJI compared with adequately dosed patients (1.51% vs. 0.86%, p=0.002). When stratified by weight, patients weighing greater than or equal to 120 kg had higher 1-year PJI rate than patients weighing less than 120 kg (3.25% vs. 0.83%, p<0.001) (Table 1).

Bivariate analysis demonstrated that patients who were underdosed (adjusted odds ratio (OR) 1.762, p=0.002), male (OR 1.517, p=0.014), those with greater comorbidities (OR 1.251, p<0.001), and higher weight (OR 1.025, p<0.001) were more likely to develop PJI within 1-year (Table 2). Following multivariate regression analyses, these trends remained significant with underdosed (OR 1.665, p=0.006) and patients with greater comorbidities (OR 1.259, p<0.001) having a higher rate of PJI at 1-year (Table 3).

## DISCUSSION

The efficacy and value of perioperative antibiotics for surgical prophylaxis has been proven in the literature [8]. Recent studies have supported current universal antibiotic prophylaxis versus providing treatment based on individual comorbidities[9]. The most appropriate antibiotic therapy recommended for patients undergoing TJA is a

first or second generation cephalosporin due to its broad spectrum of action, cost effectiveness, and ability to cover both gram positive and gram negative organisms [3,10,11]. Furthermore, cephalosporins are bactericidal and have excellent distribution profiles in synovium, muscle, hematomas, and bone [12]. The current American Academy of Orthopaedic Surgeons (AAOS) guidelines recommend patients receive prophylactic antibiotics within one hour prior to surgical incisions and be discontinued within 24 hours following the end of surgery [13].

The literature has previously reported on the necessity for weight-based dosing of perioperative antibiotics. While the current guidelines from the Center for Disease Control and Prevention, World Health Organization, and National Institute for Healthcare and Excellence do not provide dosing recommendation, the Society for Healthcare Epidemiology of America and the International Consensus Meeting (ICM) on PJI strongly agreed that preoperative antibiotics weight-based dosing is valid and warranted [2,14,15,3,16]. However, for adult patients, standard antibiotic dosing remains a common practice as it is safe, effective, and conveniently avoids the need for calculations, thus reducing the potential for medication errors[17]. Different ranges for perioperative cefazolin dosing protocols has been reported from standard adult dose of 2 g [18] to weight-based dosing of 1 g for patients weighing less than 80 kg or 2 g for patients weighing greater than 80 kg [19]. The American Society of Health-System Pharmacists (ASHP) recommends a weight-based protocol of 1 g from patients weighing less than 60 kg, 2 g for patients weighing 60-120 kg, and 3 g for patients weighing 120 kg or more [3]. Our institution follows these weight-based guidelines utilizing both 60 kg and 120 kg cutoffs, however, as illustrated by the results of the present study, the majority of patient

148 weighing above 120 kg were underdosed by recieving 2 g of antibiotics. Similar to our
149 5.7% rate of patients weighing greater than 120 kg, the prevalence of extreme obesity
150 (BMI > 40) in the United States has been reported at 7.7% [5,20]. When assuming
151 estimates of 1,000,000 TJA performed annually and an underdosing rate of greater than
152 90% for the extreme obese population, fifty thousand TJA patients are likely underdosed
153 each year [21]. Given the significant rise in obesity and morbid obesity, increased
154 scrutiny with respect to perioperative antibiotic prophylaxis is warranted to ensure that
155 this population is not underdosed [5,6].

156 The literature has previously reported on factors affecting the dosing of
157 perioperative antibiotics, specifically patient weight. One study demonstrated that 2 g of
158 cefazolin provided 5 hours of adequate levels of prophylactic protection for patients
159 regardless of their BMI [18]. Edminston et al. reported on cefazolin serum concentrations
160 in morbidly obese undergoing gastric bypass, concluding that 2 g of cefazolin may not be
161 sufficient for patients with a BMI of 50 $Kg/m^2$ or greater [22]. A prospective randomized
162 controlled trial (RCT) of morbidly obese patients undergoing gastroplasty reported
163 decreased wound infection rate from 16.5% to 5.6% when cefazolin dosed was increased
164 from 1 g to 2 g [23]. In contrast to our study, Kheir et al. found a comparable PJI rate
165 among stratified vancomycin dosage groups (underdosed 2%, adequately dosed 2%,
166 overdosed 2%, p=0.995), however reported that 64% of patients receiving vancomycin as
167 prophylaxis were underdosed and overall patients receiving vancomycin prophylaxis
168 were at an increased risk of PJI (OR 1.587, p=0.048) compared to patients receiving
169 cefazolin prophylaxis [4]. Sharareh et al. found no difference in cefazolin concentration
170 in trabecular bone with respect to patient weight [24]. Additionally, Manrique et al.

reported that patients undergoing total knee arthroplasty (TKA) who were underweight had a higher likelihood of surgical site infection compared to other weight groups [25]. However, we do recognize that the majority of these studies report results by BMI as opposed to weight, which may create confusion as dosing is based on weight not BMI. The present study reports data by weight category as opposed to BMI.

The present study has several limitations. First, the retrospective nature of the study is subject to the inherent bias of retrospective work. Second, underdosed patients weighing greater than 120 kg may have been predisposed to adverse conditions due to morbidity associated with obesity rather than inadequate dosing of cefazolin. Third, despite having more than 17,000 patients, we may still be underpowered given the low rate of PJI. Fourth, the present study encompasses a large time-period and there may be protocol changes over this time-period that may not be accounted for. Fifth, while our study primarily focuses on weight, other factors that influence antibiotic dosing such as liver and kidney function, gender, and fat distribution were not considered. However, despite the aforementioned limitations, the present study does bring to light important dosing considerations when treating patients weighing 120 kg or more.

Perioperative antibiotics remain an important strategy in protection against PJI, one of the most devastating complications following TJA. While the majority of patients remain adequately dosed, underdosing of cefazolin in the obese patient is common. We suggest orthopaedic surgeons incorporate proper weight based antibiotic dosing in their preoperative planning. Orthopaedic surgeons must be vigilant when treating patients weighing 120 kg or greater as failure to adequately dose their perioperative antibiotics can unnecessarily predispose this population to PJI.

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**Table 1:** Demographic information and dosing information

| **Cohort (n= 17,393)** | | | |
|---|---|---|---|
| | **Adequately Dosed (n=14,537)** | **Underdosed (n=2,856)** | ***P value*** |
| **Age (year)** | 63.5 (0.09) | 63.5 (0.22) | 0.849 |
| **Gender (male)** | 6417 (44.1%) | 1736 (60.8%) | <0.001 |
| **BMI** | 29.55 (0.04) | 32.11 (0.13) | <0.001 |
| **Weight (kg)** | 84.41 (0.14) | 97.17 (0.49) | <0.001 |
| **CCI** | 0.391 (0.01) | 0.386 (0.02) | <0.001 |
| **Joint (knee)** | 6895 (47.4%) | 1320 (46.2%) | 0.235 |
| **LOS** | 2.67 (0.02) | 3.05 (0.05) | <0.001 |
| **90 day Readmission** | 555 (3.8%) | 128 (4.5%) | 0.113 |
| **1-year PJI** | 125 (0.86%) | 43 (1.51%) | 0.002 |
| **Stratified by Weight** | | | |
| | **< 120 kg (n=16,409)** | **≥ 120 kg (n=984)** | ***P value*** |
| **Age (year)** | 63.9 (0.09) | 57.8 (0.29) | 0.039 |
| **CCI** | 0.387 (0.01) | 0.441 (0.03) | 0.100 |
| **Joint (knee)** | 8047 (46.6%) | 567 (57.8%) | <0.001 |
| **LOS** | 2.71 (0.02) | 3.11 (0.08) | 0.618 |
| **90 day Readmission** | 614 (3.7%) | 69 (7.0%) | <0.001 |
| **Underdosed** | 1912 (11.7%) | 944 (95.9%) | <0.001 |
| **1-year PJI** | 136 (0.83%) | 32 (3.25%) | <0.001 |

Data presented in table as mean (standard error) or number (percentage)
Abbreviations: BMI, Body Mass Index; kg, kilogram; CCI, Charlson Comorbidity index; LOS, Length of Stay; PJI, Periprosthetic Joint Infection

**Table 2:** Bivariate analysis of Cefazolin and 1-year PJI

| | **Adjusted Odds Ratio** | ***P Value*** |
|---|---|---|
| **Underdosed** | 1.762 | 0.002 |
| **Gender (male)** | 1.517 | 0.014 |
| **Joint (knee)** | 0.900 | 0.512 |
| **Younger Age (year)** | 1.010 | 0.174 |
| **Weight (kg)** | 1.025 | <0.001 |
| **BMI** | 1.080 | <0.001 |
| **CCI** | 1.251 | <0.001 |

Abbreviations: PJI, Periprosthetic Joint Infection; kg, kilogram; BMI, Body Mass Index; CCI, Charlson Comorbidity index

**Table 3:** Multivariate analysis for weight-based dosing of Cefazolin and likelihood of PJI

| **Regression** | | |
|---|---|---|
| | **Adjusted Odds Ratio** | ***P Value*** |
| **Underdosed** | 1.665 | 0.006 |
| **Gender (male)** | 1.372 | 0.067 |
| **Younger Age (year)** | 1.011 | 0.130 |
| **CCI** | 1.259 | <0.001 |

Abbreviations: PJI, Periprosthetic Joint Infection; kg, kilogram; CCI, Charlson Comorbidity index