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MAJOR ARTICLE

Safety and Effectiveness of High-Dose Cefazolin in Patients With High Body Weight: A Retrospective Cohort Study

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Background. Cefazolin is a commonly used antibiotic for the treatment of mild to severe infections. Despite the use of higher dose of cefazolin (3 g/dose) for surgical prophylaxis in patients with obesity, there is currently a paucity of data identifying the optimal dose to treat infections in this specific patient population.

Methods. This was a multicenter, retrospective cohort study of patients who received cefazolin at weight-based (up to 9 g/day) or standard doses (up to 6 g/day) for the treatment of bacteremia or skin and soft tissue infection (SSTI). Study groups were stratified by body weight and cefazolin dose received. Primary outcome was the composite of treatment-emergent adverse events (TEAEs) and secondary outcome was treatment failure rate.

Results. A total of 208 patients were included for study analysis. Fifty-nine patients had body weight >120 kg. Of these, 33 received high-dose cefazolin while 26 received standard doses. The remaining 149 patients had body weight of ≤120 kg and received standard doses. The occurrence of TEAEs did not differ across the 3 groups. The study also did not find any difference between the rate of treatment failure between groups.

Conclusions. High-dose cefazolin (9 g/day) for the treatment of bacteremia or SSTIs in patients with high body weight was safe and well tolerated. Larger studies are needed to further explore the benefit of high-dose cefazolin in improving clinical outcomes.

Keywords. cefazolin; obesity; safety; dose optimization.

Cefazolin is a first-generation intravenous (IV) cephalosporin with indications for perioperative prophylaxis and treatment of various types of infections [1]. Guideline-recommended cefazolin dosing for bacteremia is 2 g every 8 hours [2], and 1 g every 8 hours for skin and soft tissue infection (SSTI) [3]. Despite being a commonly used antibiotic for multiple infections in clinical practice, there is a lack of evidence identifying the optimal dose to treat infections in patients with obesity.

There have been several studies investigating adipose tissue concentration and efficacy of higher doses of cefazolin in patients with obesity receiving perioperative prophylaxis [4–6]. A study compared cefazolin's unbound concentrations in the interstitial fluid of the subcutaneous adipose tissue of patients with and without morbid obesity and found that cefazolin tissue distribution was lower in patients with morbid obesity [4]. Increasing body weight further reduced the tissue concentration, highlighting the need for dose adjustment in patients with morbid obesity. Two other small prospective studies of cefazolin as perioperative prophylaxis in patients with obesity and morbid obesity demonstrated higher tissue concentrations at target sites (ie, surgical incision sites) with higher doses of cefazolin [5, 6]. Furthermore, Forse and colleagues also reported a significant reduction of surgical site infections, from 16.5% to 5.6%, in patients with morbid obesity when given perioperative cefazolin at higher dose of 2 g compared to 1 g (standard dose at the time) [5]. Moreover, a multicenter retrospective cohort study of adults hospitalized with gram-negative bacilli infections found patients with obesity treated with β-lactam antibiotics had higher rates of treatment failure and longer hospitalization periods compared with patients without obesity [7]. In a retrospective analysis, Simpson and colleagues assessed the safety and efficacy of cefazolin at a higher dose compared with traditional doses in patients with obesity (BMI >30 kg/m^2) [8]. The authors found no statistically significant difference in rates of adverse events between the 2 dosing strategies; however, they found higher rates of treatment failure in the traditional dosing group [8]. The mechanism behind the

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observed increased treatment failure in patients with obesity treated with standard doses of cefazolin is not clearly understood. One possible explanation may be alterations in cefazolin pharmacokinetic and pharmacodynamic (PK/PD) properties associated with obesity.

The changes in cefazolin PK/PD observed in patients with obesity, its frequent use as a major anti-infective agent, and limited data to support alternative dosing regimens outside surgical prophylaxis in patients with obesity prompt a need for studies to further explore this area. Therefore, the objective of our study was to evaluate the safety and effectiveness of higher doses of cefazolin (total of 9 g per day) in patients weighing >120 kg compared with standard doses of cefazolin (total of 3–6 g per day).

METHODS

Study Design and Population

This was a multicenter retrospective cohort study of patients treated with cefazolin for bacteremia or SSTI. The study sites included Robert Wood Johnson University Hospital (RWJUH) New Brunswick, a 620-bed academic medical center, and RWJUH Somerset, a 365-bed community teaching hospital. The data were collected using electronic medical record (EMR) reviews of inpatient encounters of adult patients admitted at the 2 hospitals. The EMR used at both sites was Sunrise Clinical Manager (Allscripts, Chicago, Illinois). The study protocol was reviewed and approved by the institutional review boards at each site.

Cefazolin Dosing

In October 2017, RWJUH Somerset implemented an institution-specific protocol for cefazolin dosing in adults according to actual body weight (ABW). This protocol recommends that patients weighing >120 kg receive cefazolin 3 g intravenously (IV) every 8 hours, while patients with ABW between 60 kg and 120 kg receive 2 g IV every 8 hours, and patients weighing <60 kg receive 1 g IV every 8 hours. Further dose adjustment is recommended in patients with renal impairment. Conversely, patients who received cefazolin at RWJUH New Brunswick were dosed according to standard dosing regimens, at doses of 1–2 g IV every 8 hours [1].

Inclusion and Exclusion

Hospitalized adult patients (aged ≥18 years) who received treatment for bacteremia or SSTI at our study sites between 1 January 2017 and 30 September 2020 were screened for eligibility. Of these patients, those who received at least 48 hours of cefazolin monotherapy met the study inclusion criteria. Patients were excluded from the study if they had calculated creatinine clearance <35 mL/minute using Cockcroft-Gault equation or were dialysis-dependent. Patients with no baseline laboratory tests available or those who left against medical advice were excluded. For patients with available microbiological data, patients were excluded if the bacteria attributed to the index infection were resistant to cefazolin.

Study Cohorts

Each patient was assigned to 1 of the following study cohorts: (1) high-dose cefazolin (HiDC); (2) standard-dose cefazolin in patients weighing >120 kg (SDC-120); or (3) standard-dose cefazolin in patients weighing ≤120 kg (SDC). The HiDC group included patients weighing >120 kg and treated with cefazolin 3 g. The SDC-120 group included those weighing >120 kg treated with standard doses of 1 or 2 g. The SDC group included those who weighed ≤120 kg and treated with standard doses.

Outcomes

The primary outcome was the composite of all treatment-emergent adverse events (TEAEs). TEAE was defined as any new event or any event already present that worsens in either intensity or frequency following cefazolin initiation. If cefazolin was discontinued prior to discharge, those occurring within 48 hours of the last cefazolin dose were also considered a TEAE. TEAEs were categorized as follows: (1) nephrotoxicity, defined as an increase in serum creatinine >0.5 mg/dL or 50% from baseline [9]; (2) leukopenia (white blood cell count <3000 cells/μL); (3) neutropenia (absolute neutrophil count <1000 cells/μL) [9]; (4) thrombocytopenia (platelets <100 000 cells/μL) [9]; (5) eosinophilia (eosinophil count >500 cells/μL) [9]; (6) neurotoxicity, defined as documented seizure or aseptic meningitis; (7) hepatotoxicity, defined using the National Institute of Health Drug-Induced Liver Injury Network criteria [10]; (8) gastrointestinal toxicity, defined as documented nausea, vomiting, diarrhea, or *Clostridioides difficile* infection; and (9) dermatologic/immunologic event, defined as documented phlebitis or rash. TEAEs that met our defined criteria were identified through evaluation of laboratory values and extraction of information from provider progress notes in the EMR. Patient charts were carefully reviewed to identify documented TEAEs that may have been associated with cefazolin. In addition, TEAEs that resulted in early discontinuation of cefazolin therapy were also identified.

Secondary outcome was treatment failure rates. Treatment failure was defined as meeting any 1 of the following criteria: worsening signs and symptoms of infection, changing antibiotic therapy due to the lack of clinical improvement, 30-day readmission due to the relapse or recurrence of the index infection, or death. Worsening signs and symptoms included persistent fever for >48 hours while on cefazolin, new hemodynamic instability, or transfer to intensive care unit (ICU). If the patient presented with bacteremia, having a persistent positive blood culture for ≥4 days since start of cefazolin was also included as treatment failure. For SSTI, documentation of worsening erythema or new onset of bacteremia secondary to SSTI was included as treatment failure.

Data Collection

Initial patient lists were extracted from each institution's EMR database. All adult patients with *International Classification of Diseases, Tenth Revision* diagnosis codes related to SSTI or bacteremia and charged for cefazolin (≥6 doses) were included for initial screening. Only patients' initial encounters were screened; duplicate records were removed. Records were then screened manually for study inclusion based on the established inclusion and exclusion criteria.

Collected data included patient demographics, comorbidities, medication use history, hospital length of stay, characteristic of baseline infection, antibiotic treatment, and laboratory and microbiological data as well as in-hospital death, readmission, and adverse events. Concomitant use of nephrotoxic drugs during cefazolin therapy was also collected; included nephrotoxic drugs were angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, loop diuretics, nonsteroidal anti-inflammatory drugs, IV contrast, and calcineurin inhibitors. Data were recorded and managed using REDCap (Research Electronic Data Capture), which is a secure, web-based application for research data collection [11].

Statistical Analysis

Continuous data were reported using medians with interquartile ranges and categorical data were reported using percentages. Analysis of variance and χ^2 or Fisher exact test were used to compare continuous and categorical data, respectively. Post hoc analysis was performed for statistically significant variables using Tukey honest significant difference test for continuous variables and Bonferroni correction for categorical variables. Data were analyzed using R software (version 1.4.1106). Results with P value <.05 were considered statistically significant.

RESULTS

Study Population

A total of 755 patients were eligible for screening, of whom 208 patients met inclusion criteria (Figure 1). Fifty-nine patients had ABW of >120 kg. Of these patients, 33 patients were treated with cefazolin 3 g (HiDC) and 26 were treated with standard doses (SDC-120). The remaining 149 patients had ABW of ≤120 kg and received standard doses of cefazolin 1–2 g every 8 hours (SDC).

Table 1 shows the baseline characteristics of the 3 groups. The majority of patients included in the study were male (64.9%) and identified themselves as White (75%). The median age of patients in the HiDC group was lower than that of patients who received standard doses (SDC-120 and

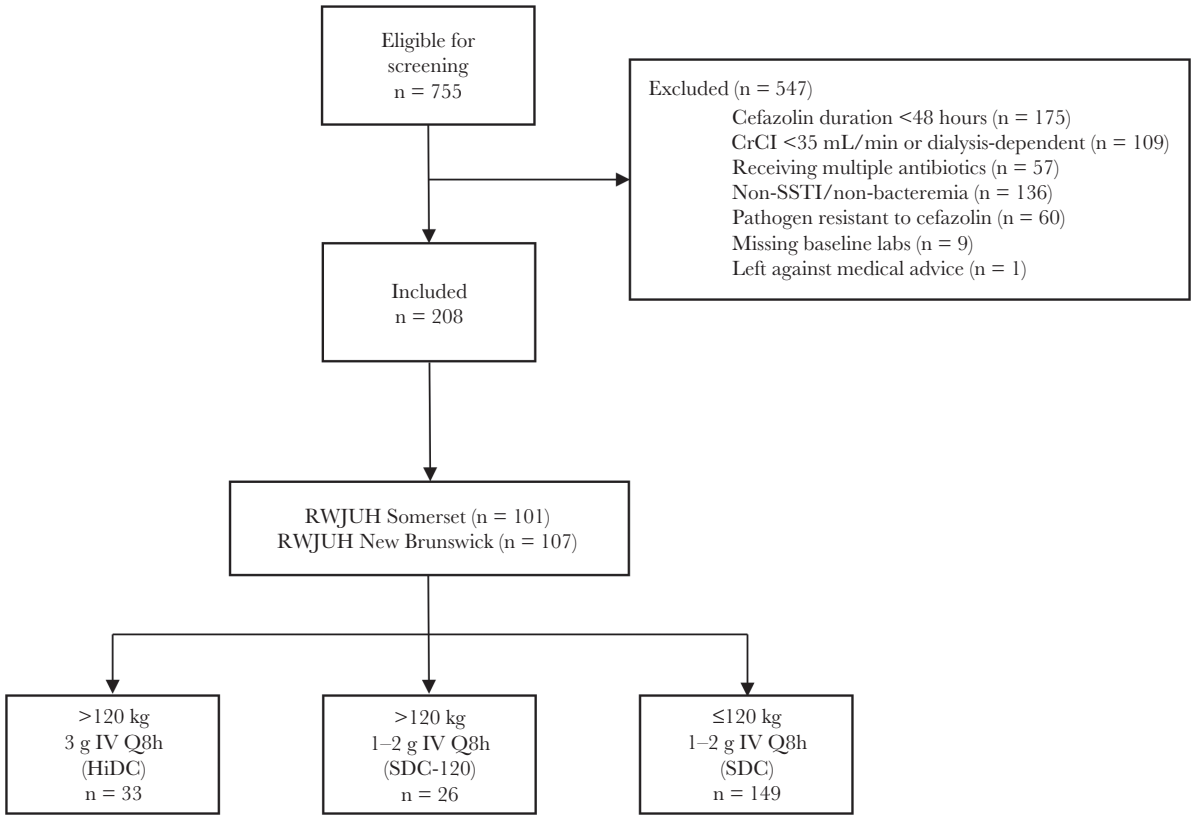

Figure 1. Flowchart of patient inclusion. Abbreviations: CrCl, creatinine clearance; HiDC, high-dose cefazolin; Q8h, every 8 hours; IV, intravenous; RWJUH, Robert Wood Johnson University Hospital; SDC, standard-dose cefazolin ≤120 kg; SDC-120, standard-dose cefazolin >120 kg; SSTI, skin and soft tissue infection.

Table 1. Summary of Patient Baseline Characteristics

Baseline Characteristic	HiDC (n = 33)	SDC-120 (n = 26)	SDC (n = 149)	*P* Value
Age, y, median (IQR)	58.0 (55–66)	65.5 (58.3–67.0)	69 (53–79)	.03
Sex, male	24 (73)	18 (69)	93 (62)	.47
Race				.03
White	31 (94)	23 (88)	102 (68)	
African American	2 (6)	2 (8)	19 (13)	
Asian	0	0	8 (5)	
Pacific Islander	0	0	0	
Other/unknown	0	1 (4)	20 (13)	
Weight, kg, median (IQR)	138.2 (127.5–170.0)	133.2 (123.2–149.5)	80.7 (67.9–96.5)	<.001
BMI, kg/m^2, median (IQR)	45.5 (41.5–52.3)	43.8 (38.7–48.0)	28.3 (24.1–33.0)	<.001
Cefazolin dose per weight, mg/kg, median (IQR)	21.7 (17.6–23.5)	11.8 (7.9–15.1)	20.4 (15.1–25.0)	.04
Infection type				
Bacteremia	6 (18)	1 (4)	47 (32)	.006
SSTI	26 (79)	21 (81)	84 (56)	.007
Concurrent bacteremia and SSTI	1 (3)	4 (15)	18 (12)	.24
Documented purulence (SSTI)[a]	6 (22)	2 (8)	24 (24)	.40
CCI score, median (IQR)	2 (1–3)	2 (1–4)	2 (1–4)	.57
Comorbidities				
Diabetes	15 (45)	16 (62)	57 (38)	.08
Malignancy	3 (9)	1 (4)	34 (23)	.02
Seizure disorder	1 (3)	0	7 (5)	.84
Stasis dermatitis	11 (33)	14 (54)	24 (16)	<.001
Lymphedema	8 (24)	5 (19)	7 (5)	<.001
No comorbidities	7 (21)	1 (4)	52 (35)	.003
Penicillin allergy	4 (12)	7 (27)	18 (12)	.13
Use of nephrotoxic drugs[b]	31 (94)	23 (88)	110 (74)	.02
ICU admission	1 (3)	0	21 (14)	.03
qSOFA score, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	.40
Source control achieved[c]	11 (92)	5 (63)	52 (63)	.42
ID consultation	28 (85)	19 (73)	123 (83)	.46
Duration of cefazolin, d, median (IQR)	5 (4–6)	5 (3–7)	6 (4–12)	.02

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

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; HiDC, high-dose cefazolin; ICU, intensive care unit; ID, infectious diseases; IQR, interquartile range; qSOFA, quick Sequential Organ Failure Assessment; SDC, standard-dose cefazolin ≤120 kg; SDC-120, standard-dose cefazolin >120 kg; SSTI, skin and soft tissue infection.

[a]Documented purulence in patients with SSTI includes those who presented with concurrent bacteremia and SSTI. Proportions are calculated using 27 patients in the HiDC group, 25 patients in the SDC-120 group, and 102 patients in the SDC group.

[b]Nephrotoxic drugs included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, loop diuretics, and intravenous contrast agents.

[c]Only includes patients who required source control and does not include cases of simple or mild SSTI. Proportions were calculated using 12 patients in the HiDC group, 8 patients in the SDC-120 group, and 83 patients in the SDC group.

SDC). Median cefazolin dose per weight, represented in milligrams per kilogram, was similar for the HiDC and SDC groups. However, the median dose per weight for patients in the SDC-120 group was significantly lower compared to the medians of the HiDC and SDC groups ($P = .04$). About one-fourth (26.0%) of all patients presented with bacteremia only as the index infection while more than half of the patients presented with SSTI only. The remainder of patients (11%) presented with both bacteremia and SSTI at baseline. The infection types were significantly different between the 3 groups, and post hoc Bonferroni analysis found that bacteremia was more common in the SDC group compared to SDC-120, and SSTI was more common in the SDC group compared to both SDC-120 and HiDC. The majority of bacteremia cases (43/77 [55.8%]) were caused by methicillin-sensitive *Staphylococcus aureus* while about one-fourth (20/77 [26%]) were caused by susceptible gram-negative organisms (Supplementary Table 1). The cohorts did not differ in their median Charlson Comorbidity Index scores. However, post hoc analysis indicated that stasis dermatitis and lymphedema were more common in patients weighing >120 kg (HiDC and SDC-120) than in those weighing ≤120 kg (SDC). Nephrotoxic drug use was also significantly different between groups,

with a higher percentage of patients in the HiDC group receiving nephrotoxic drugs than those in the SDC group, indicated by post hoc analysis. ICU admission at baseline was most common in the SDC group. Infectious diseases service was consulted for the majority of patients (81.7%).

Treatment Outcomes

TEAEs.

There were no statistically significant differences in the composite outcome of TEAEs between the 3 groups. There were 49 patients (23.6%) who experienced at least 1 TEAE, with a total of 60 TEAEs recorded (Table 2). Gastrointestinal adverse events were the most common, followed by renal and hematologic adverse events. There was no neurologic toxicity (aseptic meningitis or seizure) reported in any of the patients, and a very small proportion of patients in the SDC group (2%) experienced hepatic enzyme abnormalities. Of the 60 TEAEs, 19 (31.7%) were related to cefazolin as documented by the treating provider, and the occurrence of cefazolin-related TEAE was not different between groups. Cefazolin was discontinued in 4 patients (1 in HiDC and 3 in SDC) as a result of a TEAE.

Treatment Failure.

A total of 21 patients (10.1%) had treatment failure, without statistically significant difference between groups (Table 3). Three patients (9.1%) in the HiDC group and 18 patients (12.1%) in the SDC group experienced treatment failure while no patient in the SDC-120 had treatment failure. All 3 patients who failed treatment in the HiDC group had SSTI (11% of patients with SSTI). In the SDC group, treatment failure was more common in patients with bacteremia (10 of 65 patients [15%]) compared to those with SSTI (9 of 102 patients [9%]). One patient had both bacteremia and SSTI. Treatment failure due to worsening signs or symptoms of infection occurred in 9 patients (6%) in the SDC group, while none occurred in the HiDC group. Antibiotic escalation occurred in 1 patient (3%) in the HiDC

Table 2. Treatment-Emergent Adverse Event Outcomes

Outcome	HiDC (n = 33)	SDC-120 (n = 26)	SDC (n = 149)	*P* Value
Total No. of TEAEs	8	6	46	NR
No. of patients with TEAEs	7 (21)	6 (23)	36 (24)	.94
Renal[a]	3 (10)	0	8 (5)	.34
Hematologic	3 (9)	1 (4)	6 (4)	.38
Leukopenia[b]	0	1 (4)	1 (1)	.25
Neutropenia[c]	0	0	1 (1)	1.0
Thrombocytopenia[d]	1 (3)	1 (4)	2 (1)	.30
Eosinophilia[e]	2 (7)	1 (5)	5 (5)	.86
Hepatic[f]	0	0	3 (2)	.96
Neurologic	0	0	0	NR
Aseptic meningitis	0	0	0	NR
Seizure	0	0	0	NR
Gastrointestinal	1 (3)[g]	3 (12)	18 (12)	.36
Nausea/vomiting	1 (3)	0	7 (5)	.84
Diarrhea	1 (3)	3 (12)	13 (9)	.45
CDI	0	0	3 (2)	.55
Dermatologic/immunologic	0	0	3 (2)	1.0
Phlebitis	0	0	1 (1)	1.0
Rash	0	0	2 (1)	1.0
Cefazolin-related TEAE	1 (3)	2 (8)	16 (11)	.37
Cefazolin discontinued due to TEAE	1 (3)	0	3 (2)	.74

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

Abbreviations: CDI, *Clostridioides difficile* infection; HiDC, high-dose cefazolin; NR, not reported; SDC, standard-dose cefazolin ≤120 kg; SDC-120, standard-dose cefazolin >120 kg; TEAE, treatment-emergent adverse event.

[a]Two patients in the HiDC group and 3 patients in the SDC-120 group had missing data. The proportion of patients (%) is calculated using a denominator of 31 and 23 patients, respectively.

[b]Three patients in the HiDC group, 1 patient in the SDC-120 group, and 1 patient in the SDC group had missing data. The proportion of patients (%) is calculated using a denominator of 30, 25, and 148 for HiDC, SDC-120, and SDC, respectively.

[c]Three patients in the HiDC group, 6 patients in the SDC-120 group, and 40 patients in the SDC group had missing data. The proportion of patients (%) is calculated using a denominator of 30, 20, and 109 patients, respectively.

[d]Three patients in the HiDC group, 1 patient in the SDC-120 group, and 2 patients in the SDC group had missing data. The proportion of patients (%) is calculated using a denominator of 30, 25, and 147 patients, respectively.

[e]Three patients in the HiDC group, 7 patients in the SDC-120 group, and 39 patients in the SDC group had missing data. The proportion of patients (%) is calculated using a denominator of 30, 19, and 110 patients, respectively.

[f]Seventeen patients in the HiDC group, 15 patients in the SDC-120 group, and 78 patients in the SDC group had missing data. The proportion of patients (%) is calculated using a denominator of 16, 11, and 71 patients, respectively.

[g]One patient had both nausea and diarrhea.

Table 3. Treatment Failure Outcomes

Outcome	HiDC (n = 33)	SDC-120 (n = 26)	SDC (n = 149)	*P* Value
Worsening signs or symptoms of infection	0	0	9 (6)	.24
Bacteremia	0	0	5 (3)	.61
SSTI	0	0	4 (3)	.35
Antibiotic escalation	1 (3)	0	7 (5)	.84
30-day readmission	2 (6)	0	3 (2)	.29
Death	0	0	3 (2)	.55
Treatment failure	3 (9)	0	18 (12)	.14
Bacteremia[a]	0	0	10 (15)	.80
SSTI[b]	3 (11)	0	9 (9)	.30

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

Abbreviations: HiDC, high-dose cefazolin; SDC, standard-dose cefazolin ≤120 kg; SDC-120, standard-dose cefazolin >120 kg; SSTI, skin and soft tissue infection.

[a]Bacteremia patients who had treatment failure include patients who had concurrent bacteremia and SSTI. The proportion was calculated using the total number of patients with bacteremia (7 patients in HiDC, 5 patients in SDC-120, and 65 in SDC).

[b]SSTI patients who had treatment failure include patients who had concurrent bacteremia and SSTI. The proportion was calculated using the total number of SSTI patients (27 patients in HiDC, 25 patients in SDC-120, and 102 patients in SDC).

group and 7 patients (5%) in the SDC group. Additionally, 30-day readmission occurred in 2 patients (6%) in the HiDC group and 3 patients (2%) in the SDC group. In-hospital death occurred in 3 patients in the SDC group only.

DISCUSSION

Given that cefazolin's time-dependent antibiotic efficacy may be influenced by both clearance and volume of distribution, body size is an important factor to consider in determining an optimal dosing strategy for cefazolin in patients with obesity [12]. The goal of this study was to assess for overt safety signals with the use of high-dose cefazolin (9 g per day) in patients with high body weight. While our study cannot exclude less common adverse effects that would be detected with larger cohort studies, the goal was to conduct an initial pilot study to assess for obvious safety issues. This strategy is analogous to phase 1 clinical trials for new drugs in which smaller sample sizes are used initially to detect any overt safety issues with a novel compound. The lack of detection of obvious safety differences between high-dose and standard-dose groups leads to the conclusion that high-dose cefazolin may be safe to use in patients with high body weight. However, further larger studies are needed to validate this conclusion, particularly for detection of less common adverse effects. In our study, we found that the occurrence of TEAEs in patients exposed to higher daily doses of cefazolin for the treatment of bacteremia or SSTI did not differ from those receiving standard doses. This is similar to the findings of a published abstract that found no differences in TEAE in patients with obesity who received cefazolin 1–2 g every 8 hours compared to patients who received cefazolin 2 g every 4–6 hours [8]. Cefazolin is an overall safe and effective drug and the package insert lists a maximum dose of 12 g per day, but this is not common in clinical practice [1]. Therefore, our study adds valuable data to the limited body of literature that exists in using cefazolin doses >6 g per day in routine clinical practice.

There were no differences in treatment outcomes in patients who received cefazolin 3 g for bacteremia or SSTI, as demonstrated by the lack of difference in treatment failure rates across all 3 groups. This was an unexpected finding as we hypothesized that patients >120 kg who received cefazolin 3 g would be less likely to experience treatment failure compared to those weighing >120 kg who received standard doses of 1–2 g. This was also in contrast to the study by Simpson and colleagues, which found higher treatment failure rates in patients with obesity treated with traditional-dose, compared with high-dose cefazolin [8]. However, along with the small sample size, the relatively low overall treatment failure rate (occurring in only about 10% of patients) would make it difficult to detect statistically significant differences between groups. Furthermore, none of the 26 patients weighing >120 kg who received standard doses experienced treatment failure. The majority of these patients presented with SSTI and were likely treated for mild infections and, therefore, less likely to experience treatment failure. In addition, all 3 patients treated with high-dose cefazolin who failed treatment had SSTI rather than a more severe infection such as bacteremia. Weng and colleagues previously reported that lower-extremity cellulitis is commonly misdiagnosed and often confused with other conditions such as stasis dermatitis [13]. This raises an interesting question of whether or not the patients who experienced treatment failure in the high-dose group truly had a bacterial SSTI versus other mimicking conditions such as lymphedema or stasis dermatitis, which were present in approximately half of patients weighing >120 kg.

Our study has several limitations. First is the uneven distribution of baseline clinical severity of the index infection across our study cohorts. Patients in the SDC group appeared more ill with a higher proportion of patients presenting with bacteremia and ICU admission at baseline, compared to those weighing >120 kg. This difference alone may have contributed to the numerically higher rate of treatment failure observed in the SDC group. It would have been impractical to design our study to

only include patients with bacteremia given the small number of patients who received high-dose cefazolin. The effect of high-dose cefazolin on treatment failure rates in patients with severe infections such as bacteremia should be evaluated in future, larger studies. Second, this was an initial pilot study and was not powered to detect differences in less common adverse outcomes and the occurrence of treatment failure between groups. The safety and tolerability of cefazolin at standard doses have been consistently described in the literature [9, 14]. Even though our study did not find any major safety concerns with a higher dose of 9 g per day, the safety and tolerability of long-term use of cefazolin at the high dose needs to be evaluated in a future study as the median duration of cefazolin in our high-dose cohort was 5 days. As for treatment failure outcomes, we may not have captured all occurrences as the majority of our patients presented with SSTI, which is usually a less severe infection, and patients may have presented to their primary care provider or another healthcare facility for recurrence of infection. Last, our findings may not be generalizable to other dosing regimens that include more frequent dosing or a continuous infusion and results in doses >6 g per day.

A recent study reported that the treatment failure rate with β-lactam antibiotics, including cefazolin, was higher in patients with obesity than in those without obesity (most commonly a failure of resolution of leukocytosis) [7]. In that study, patients with obesity had higher disease burden compared to their counterparts and this difference alone could have contributed to the observed higher treatment failure. Nevertheless, the study authors acknowledged the lack of evidence for alternative dosing of β-lactam antibiotics in this population, which highlights the importance of further exploring alternative treatment dosing strategies of cefazolin in this population. Our institution-specific dosing regimen of 3 g administered IV every 8 hours in patients weighing >120 kg was designed to increase PK/PD target attainment by giving a higher dose without increasing dosing frequency (a practical consideration as well). Our institution agreed to this regimen to consider minimizing additional healthcare resource use that may occur with more frequent drug administration. In fact, the median dose per weight was very similar between the HiDC and SDC groups, showing that giving the higher dose of 3 g is crudely similar to giving standard doses of 1–2 g to those weighing ≤120 kg. To our knowledge, this study is one of the first evaluating the safety and effectiveness of such an alternative dosing regimen. Cefazolin is one of the most commonly used antibiotics in clinical practice. Despite the increasing prevalence of obesity, there is a paucity of information on the optimal dosing strategy in patients with obesity to improve clinical outcomes without increasing the risk of adverse events. The findings of our study demonstrate safety and tolerability of high-dose cefazolin but no difference in treatment failure rates. Larger studies are needed to further evaluate clinically relevant outcomes associated with high-dose cefazolin used for the treatment of infections in patients with obesity.

CONCLUSIONS

High-dose cefazolin in patients with high body weight appears to be safe and tolerable compared to standard dosing. Given the lack of overt safety signals observed in this study, we believe it is safe and feasible to conduct further clinical studies to test the safety and effectiveness of high-dose cefazolin for the treatment of infections in patients with high body weight.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Patient consent statement. The study design was approved by the local institutional review boards at each study site. Our study does not include factors necessitating patient consent.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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