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MAJOR ARTICLE

Association Between Estimated Pharmacokinetic/Pharmacodynamic Predictions of Efficacy and Observed Clinical Outcomes in Obese and Nonobese Patients With *Enterobacteriaceae* Bloodstream Infections

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Background. Evidence on pharmacokinetic/pharmacodynamic (PK/PD) alterations and clinical outcomes in obese patients with serious infections remains limited. This study aimed to evaluate predicted PK/PD indices of efficacy and observed clinical outcomes between obese and nonobese patients receiving cefepime or piperacillin-tazobactam for *Enterobacteriaceae* bacteremia.

Methods. This was a retrospective study of adult inpatients from 1/2012 to 9/2015 with *Enterobacteriaceae* bacteremia who received empiric cefepime or piperacillin-tazobactam. The primary outcome was clinical cure. First-dose free-drug exposure was estimated via predicted concentrations generated from population PK analyses and used to assess PD target attainment (>50% fT > minimum inhibitory concentration [MIC]) for the specific *Enterobacteriaceae* isolate. Multivariable logistic regression was utilized to identify independent predictors of clinical cure.

Results. One hundred forty-two patients were included, 57 obese and 85 nonobese. Clinical cure was achieved in 68.4% of obese and 62.4% of nonobese patients (P = .458). No significant difference in outcomes was observed when evaluated by World Health Organization (WHO) obesity classes. The PK/PD target was achieved in 98.2% of obese and 91.8% of nonobese patients (P = .144). Independent predictors of clinical cure were immunosuppression and a shorter duration of bacteremia. Obesity was not identified as a significant predictor of clinical outcomes.

Conclusions. Neither predicted PK/PD parameters nor clinical outcomes differed significantly between obese and nonobese patients treated with piperacillin-tazobactam or cefepime. As the majority of patients received extended-infusion piperacillin-tazobactam for bacteremia due to pathogens with low MICs, the potentially detrimental pathophysiologic derangements caused by obesity may not have been realized. Further studies are warranted to establish the optimal treatment of serious infections in obese patients.

Keywords. bacteremia; *Enterobacteriaceae*; obesity; pharmacodynamic; pharmacokinetic.

Obesity is an international health epidemic. According to the Centers for Disease Control and Prevention, more than one-third of American adults aged ≥20 years are obese [1]. Worldwide, over half a billion adults are currently classified as obese, and it is estimated that 75% of the US population and 70% of the UK population will be obese by 2030 [2, 3]. Obesity has been linked to both deleterious health outcomes and significantly increased health care costs [4–6]. Infections are more common in obese patients compared with nonobese patients, and obesity has been associated with poorer overall infection-related clinical outcomes [7–12]. Further, obese patients are more susceptible to developing infections in the intensive care unit (ICU), and obesity has been identified as an independent risk factor for developing bloodstream infections (BSIs) [13]. Specifically, the age- and sex-adjusted risk of BSI was shown to be 31% higher at a body mass index (BMI) of 30–34.9 kg/m^2 and 210% higher at a BMI ≥40 kg/m^2 compared with normal-weight patients, whereas BSI-related mortality was 37% and 120% higher among these BMI ranges, respectively [14]. Finally, obese patients have been shown to require more complex courses of antimicrobial therapy compared with nonobese patients [15].

The etiology behind the suboptimal infection-related clinical outcomes observed in obese patients is likely multifactorial,

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although physiological changes affecting the pharmacokinetic (PK) parameters of antimicrobials are well documented in this population, including derangements in volume of distribution and renal clearance [16]. Furthermore, patients with severe infections such as bacteremia have been shown to be less likely to achieve target antimicrobial PK/pharmacodynamic (PD) indices of efficacy and subsequently experience worse clinical outcomes [17]. Therefore, patients who are obese and have a life-threatening infection may be less likely to achieve adequate antimicrobial PK/PD end points required to treat serious infections. This is particularly true when patients are treated with antimicrobials that are not dose-adjusted based on body weight, like the β-lactams [18–20].

There is currently a paucity of data regarding the PK/PD alterations and associated clinical outcomes that occur in obese patients with serious infections. Given that antipseudomonal β-lactams such as cefepime and piperacillin-tazobactam are among the most commonly prescribed empiric antimicrobials in the United States [21] and that the population of Americans who are obese continues to rise, data examining the outcomes of obese patients treated with these agents for severe infections are urgently needed.

The objective of this study was to evaluate and compare predicted PK/PD indices of antimicrobial efficacy and observed clinical outcomes between obese and nonobese patients treated with cefepime or piperacillin-tazobactam for *Enterobacteriaceae* bacteremia.

METHODS

Study Design

This study was a retrospective, single-center cohort study conducted at the University of Illinois Hospital and Health Sciences System (UIHHSS), a 495-bed tertiary care academic medical center in Chicago, Illinois. The study was approved by the Office for the Protection of Research Subjects Institutional Review Board with a waiver of consent granted. Adult (≥18 years of age) inpatients admitted between January 2012 and September 2015 were included if they had documented bacteremia due to an *Enterobacteriaceae* spp. organism. Bacteremia was defined as ≥1 blood culture positive for *Enterobacteriaceae* spp. requiring antimicrobial treatment and not considered a contaminant by the treating medical team. Only the first episode of bacteremia per patient was included per study period. Only patients treated with either cefepime or piperacillin-tazobactam within 24 hours of index blood culture collection who were continued on treatment for at least 48 hours were included. Patients with an index blood culture obtained at an outside facility, those who died within 48 hours of index culture collection, those with an *Enterobacteriaceae* spp. isolate resistant to cefepime or piperacillin-tazobactam, and those requiring renal replacement therapies were excluded.

Data and Outcomes

Data were obtained from the UIHHSS electronic medical record (Cerner, North Kansas City, MO). Baseline was defined as the time of index blood culture collection. Patients with a BMI ≥30 kg/m^2 were considered obese, and patients with a BMI <30 kg/m^2 were considered nonobese [6]. Data obtained included baseline characteristics, Charlson Comorbidity Index [22], Pitt Bacteremia Score [23], immunosuppression (defined as administration of a cytotoxic agent within 90 days of bacteremia, corticosteroids at an equivalent daily dosage to prednisone ≥15 mg/d for >1 week within 4 weeks of bacteremia, antirejection medications within 2 weeks of bacteremia, absolute neutrophil count (ANC) <500 cells/mm^3, or CD_4 <200 cells/mm^3), antibiotics received in the previous 90 days, mechanical ventilation, source of bacteremia [24], antimicrobial susceptibilities, empiric (before susceptibility results; either cefepime or piperacillin-tazobactam) and definitive antimicrobial therapy (after susceptibility results), time to effective antibiotic therapy (defined as the time difference between index blood culture collection and the first administration of either cefepime or piperacillin-tazobactam), duration of inpatient antimicrobial therapy, infectious diseases (ID) consult, and time to ID consult.

The primary outcome was clinical cure, defined as resolution of baseline signs and symptoms of infection, white blood cell count <10 000 cells/mm^3, absence of oral temperature >38°C for 24 consecutive hours, and documented clearance of the causative pathogen from blood cultures. Clinical cure was assessed at the end of antimicrobial therapy or at hospital discharge, whichever was sooner. Secondary outcomes included achievement of PK/PD indices of efficacy, time to clinical cure, duration of bacteremia, hospital and intensive care unit (ICU) length of stay (LOS), all-cause in-hospital mortality, and 30-day readmissions for *Enterobacteriaceae* bacteremia. Time to clinical cure was defined as the time from index culture collection to achievement of clinical cure. Hospital and ICU LOS was calculated as the difference between admission and discharge dates.

PK/PD Analysis

The first-dose free-drug exposure to cefepime or piperacillin-tazobactam was simulated for each patient based on published population PK models in infected patients [25, 26], and predicted concentrations were generated every 6 minutes throughout the dosing interval via PKSolver in Excel (Microsoft, Redmond, WA). The relevant antibacterial PD parameter used was the percentage of the dosing interval during which free-drug concentrations remained above the minimum inhibitory concentration (MIC) against the specific *Enterobacteriaceae* isolate (%*f*T > MIC) [27, 28]. A target of 50% *f*T > MIC for both cefepime and piperacillin-tazobactam was considered, whereas 100% *f*T > MIC was also evaluated [29]. The %*f*T > MIC was determined for each patient from the MIC reported on the index

blood culture. Protein binding was accounted for by multiplying doses by drug-specific unbound fractions before calculating PD indices [30, 31].

Blood cultures were incubated using the BD BACTEC 9240 system (Becton-Dickinson, Sparks, MD), and organism identification and susceptibility were performed using the Vitek 2 system (bioMerieux, Inc, Hazelwood, MO). At UIHHSS, cefepime is administered as a standard 30-minute infusion, whereas piperacillin-tazobactam is administered as an extended infusion over 4 hours without an initial 30-minute intermittent infusion dose. The UIHHSS dosing guidelines for cefepime and piperacillin-tazobactam are presented in Supplementary Table 1.

Statistical Analysis

Continuous variables were compared using the Student *t* test if parametric and Mann-Whitney *U* test if nonparametric. Categorical variables were evaluated with the χ^2 or Fisher exact test as appropriate. Clinical cure was stratified by obesity as a binary variable and also by WHO obesity class: class 1 (BMI 30–34.9 kg/m^2), class 2 (BMI 35–39.9 kg/m^2), and class 3 (BMI ≥40 kg/m^2) [6]. A 2-tailed significance of ≤.05 was considered statistically significant. Multivariable logistic regression via a backwards-stepwise approach was utilized to identify predictors of clinical cure. Consideration for multivariable model inclusion was based on a *P* value ≤.20 on univariate analysis and biologic plausibility. Variables with a *P* value ≤.05 were retained in the final model. Model goodness of fit was assessed via the area under the curve of the receiver operating characteristic curve (AUC-ROC). Collinearity was assessed via tolerance and variance inflation factor. All analyses were performed using SPSS, version 24 (IBM Corporation, Armonk, NY).

RESULTS

Over the study period, 295 patients with an *Enterobacteriaceae* spp. BSI were identified for inclusion (Figure 1). Patients could have met multiple exclusion criteria, although the most common were empiric antibiotic selection other than piperacillin-tazobactam or cefepime (n = 85) and initiation of empiric antibiotic therapy >24 hours from or duration of therapy <48 hours from time of index culture collection (n = 37). After exclusion criteria were applied, 142 patients were included in the final analysis. Of these, 57 were obese and 85 were nonobese.

Baseline characteristics are presented in Table 1. Important demographic and severity of illness predictors, such as the Charlson Comorbidity Index and Pitt Bacteremia Score, were well balanced between nonobese and obese patients. Patients in the obese group weighed approximately 35 kg more on average than nonobese patients and had a BMI roughly 14 kg/m^2

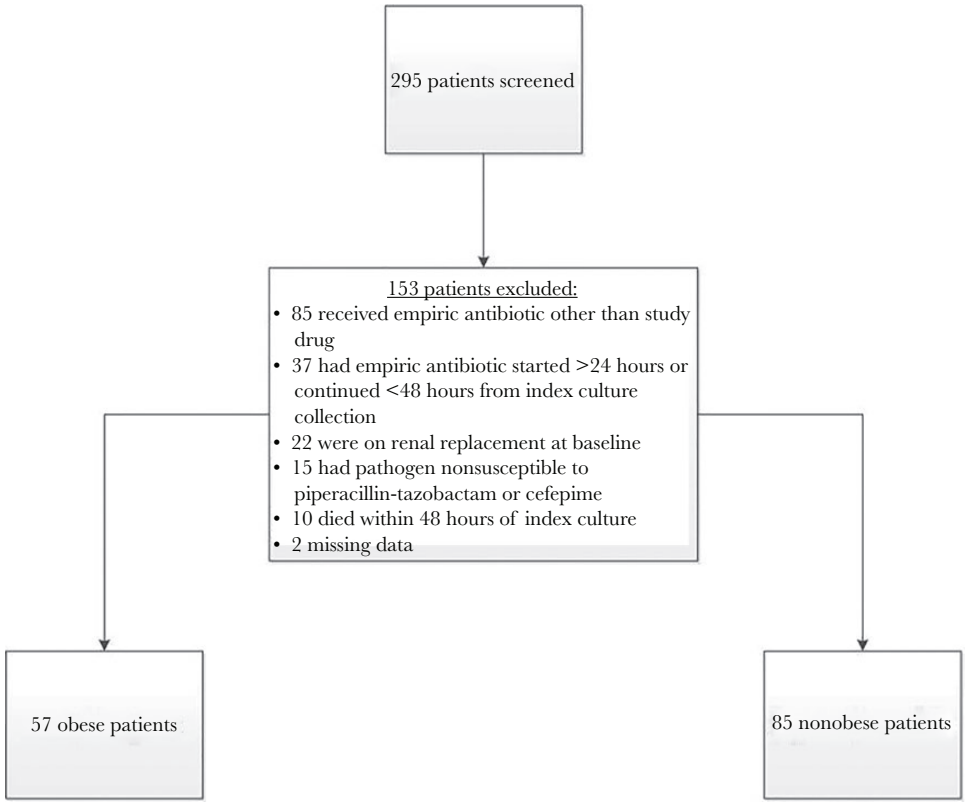

Figure 1. CONSORT diagram for development of study cohort.

Table 1. Comparison of Demographic and Baseline Characteristics Between Obese and Nonobese Patients With *Enterobacteriaceae* spp. Bacteremia

Characteristic	Obese (n = 57)	Nonobese (n = 85)	*P*
Male gender	27 (47.4)	38 (44.7)	.755
Age, y	57.8 ± 12	59.9 ± 17.6	.401
Actual body weight, kg	101.4 ± 21.6	65.8 ± 12.9	<.001
BMI, kg/m^2	37.6 ± 7.8	23.5 ± 3.9	<.001
WHO obesity class I	29 (50.9)	0 (0)	<.001
WHO obesity class II	14 (24.6)	0 (0)	<.001
WHO obesity class III	14 (24.6)	0 (0)	<.001
CrCl, mL/min	57.7 ± 33.5	61.6 ± 51.5	.835
Charlson Comorbidity Index	4 [0–14]	4 [0–11]	.647
Pitt Bacteremia Score	2 [0–8]	2 [0–5]	.261
Immunosuppression	18 (31.6)	28 (32.9)	.865
Hospitalization in last 90 d	29 (50.9)	41 (48.2)	.758
Antibiotics in last 90 d	28 (49.1)	41 (48.2)	.917
Time to index culture, d	2.8 ± 5.2	3.8 ± 6.8	.072
Polymicrobial bacteremia	6 (10.5)	9 (10.6)	.991
ICU admission	33 (57.9)	36 (42.4)	.069
Mechanical ventilation	3 (5.3)	3 (3.5)	.684
Duration of mechanical ventilation, d	5 [2–11]	2 [1–3]	.214
Infectious diseases consult	19 (33.3)	31 (36.5)	.701
Causative pathogen isolated from index blood culture			
E. coli	30 (52.6)	43 (50.6)	.865
K. pneumoniae	11 (19.3)	21 (24.7)	.541
P. mirabilis	4 (7)	5 (5.9)	1.00
S. marcescens	4 (7)	5 (5.9)	1.00
E. cloacae	2 (3.5)	5 (5.9)	.702
E. aerogenes	0 (0)	3 (3.5)	.274
C. freundii	1 (1.8)	2 (2.4)	1.00
K. oxytoca	3 (5.3)	1 (1.2)	.300
P. stuartii	1 (1.8)	0 (0)	.401
M. morganii	1 (1.8)	0 (0)	.401
Pathogen MIC, mg/L	4 [1–12]	4 [1–16]	.208
Initial β-lactam received			
Cefepime	10 (17.5)	20 (23.5)	.392
Piperacillin-tazobactam	47 (82.5)	65 (76.5)	.392
Time to effective therapy, h	8.8 ± 7.5	8.4 ± 7.0	.945
Duration of empiric treatment, d	5.4 ± 3.6	5 ± 3.0	.686
Definitive treatment			
Levofloxacin	29 (50.9)	42 (49.4)	.864
Ceftriaxone	14 (24.6)	26 (30.6)	.434
Other	14 (24.6)	17 (20)	.540
Total duration of inpatient antibiotic therapy, d	10.3 ± 6.7	8.7 ± 6.0	.242

Data are presented as mean ± SD, median [minimum–maximum], or No. (%).

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; ICU, intensive care unit; MIC, minimum inhibitory concentration; WHO, World Health Organization.

greater. Approximately one-quarter (24.6%) of obese patients fell into WHO obesity class II, and one-quarter into WHO obesity class III.

Approximately 50% of BSIs were due to *Escherichia coli* in each group, followed by *Klebsiella pneumoniae* (~25%) (Table 1). The predominant source of bacteremia was the genitourinary tract, observed in roughly 30% of isolates in each group (Figure 2). The median duration of bacteremia in the obese and nonobese patients was 1 and 2 days, respectively. More than three-fourths of the patients in each group received piperacillin-tazobactam as empiric therapy compared with cefepime. Effective therapy was administered within ~8 hours in each group, and the mean duration of empiric antimicrobial therapy was approximately 5 days. Roughly one-third of patients received an ID consult in either group. The most common definitive treatment was levofloxacin (71 patients; 50%), followed by ceftriaxone (40 patients; 28.2%). The mean duration of definitive antimicrobial therapy was ~5 days in the obese group and 4 days in the nonobese group.

The median (minimum–maximum) MIC among *Enterobacteriaceae* pathogens recovered in this study was 1 (1–1) mg/L for cefepime and 4 (1–16) mg/L for

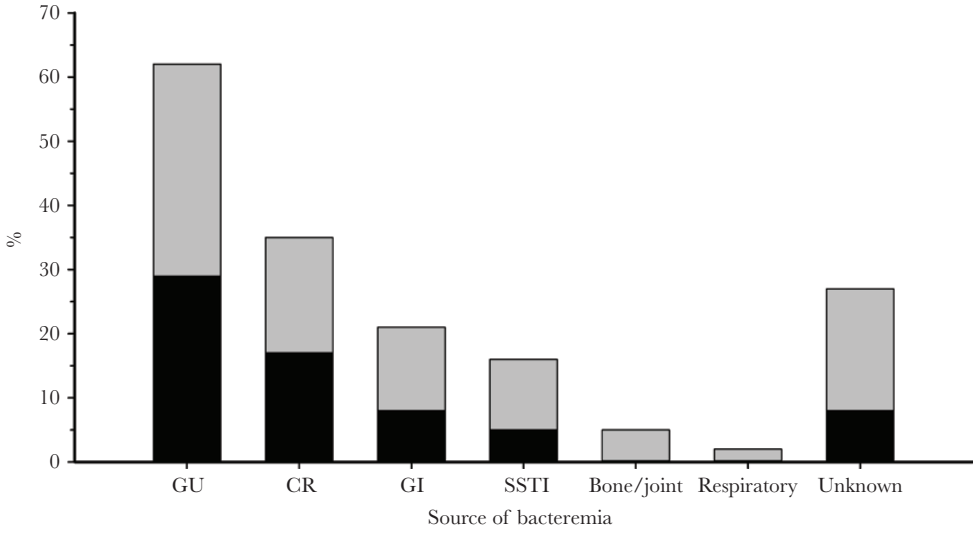

Figure 2. Source of Enterobacteriaceae spp. bacteremia among obese (n=57, black bar) and non-obese (n=85, gray bar) patients. Abbreviations: GU, genitourinary; CR, cather-related; GI, gastrointestinal; SSTI, skin and soft tissue.

piperacillin-tazobactam. The average %*f*T > MIC was not significantly different between obese and nonobese patients, and >90% of patients in each group achieved >50% *f*T > MIC. Approximately one-quarter of patients in both groups also achieved 100% %*f*T > MIC on average. Figure 3 displays the average estimated free concentration–time profiles of cefepime and piperacillin-tazobactam in relation to the median MIC for obese and nonobese patients.

Approximately two-thirds of obese and nonobese patients achieved a clinical cure, with no significant difference between the groups (Table 2). There were no statistically significant differences in any other observed clinical outcomes, including time to clinical cure, length of stay, or mortality between obese and nonobese patients. Supplementary Table 2 compares baseline characteristics and secondary outcomes between patients who achieved a clinical cure (n = 92) and those who did not (n = 50).

On univariate analysis, significantly more patients who were immunosuppressed achieved a clinical cure, as did patients who received an ID consult (Supplementary Table 2). Conversely,

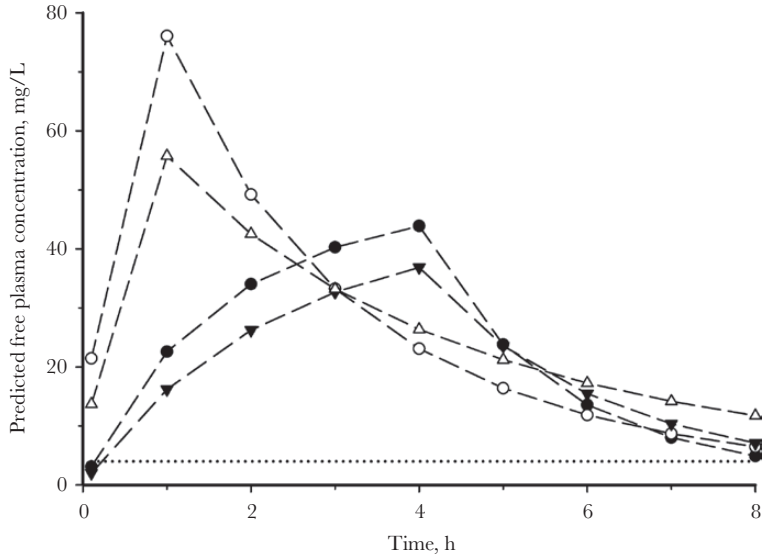

Figure 3. Mean predicted free concentration-versus-time profile of cefepime and piperacillin-tazobactam for obese and non-obese patients with *Enterobacteriaceae* bacteremia. Obese patients are shown as a dashed line with open triangles for cefepime and filled triangles for piperacillin-tazobactam. Non-obese patients are shown as a dashed line with open circles for cefepime and filled circles for piperacillin-tazobactam. The horizontal dotted line represents the overall median MIC of 4 mg/L. The y axis is in the linear scale.

Table 2. Comparison of PK/PD Predictions and Clinical Outcomes Between Nonobese and Obese Patients With *Enterobacteriaceae* spp. Bacteremia

Outcome	Obese (n = 57)	Nonobese (n = 85)	*P*
%*f*T > MIC	91.2 ± 13.1	85.5 ± 19.3	.381
%*f*T > 50	56 (98.2)	78 (91.8)	.144
%*f*T > 100	13 (22.8)	24 (28.2)	.470
Duration of bacteremia, d	1.8 ± 1.4	2.3 ± 2.3	.351
Clinical cure	39 (68.4)	53 (62.4)	.458
Time to clinical cure, d	7.0 ± 8.5	5.3 ± 6.3	.268
Hospital length of stay, d	13.3 ± 13.7	11.7 ± 11.6	.794
ICU length of stay, d	5.9 ± 7.7	5.1 ± 6.4	.833
In-hospital mortality	1 (1.8)	3 (3.5)	.646
30-d readmission for *Enterobacteriaceae* spp. bacteremia	3 (5.3)	4 (4.7)	1.00

Data are presented as mean ± SD or No. (%)

Abbreviations: ICU, intensive care unit; MIC, minimum inhibitory concentration; %*f*T > MIC, percentage of the dosing interval for which the estimated free-drug concentration remained above the organism's MIC; PK/PD, pharmacokinetic/pharmacodynamic.

significantly more patients who did not achieve a clinical cure were admitted to the ICU. Obesity, actual body weight, and BMI were not significantly different between those patients who achieved a clinical cure and those who did not. Additionally, %*f*T > MIC analyzed as a continuous variable or at thresholds of 50% or 100% *f*T > MIC was not significantly different between the groups. Finally, clinical cure rates were not significantly different among obese patients when stratified by WHO obesity classes.

After univariate analysis for clinical cure, there were 12 candidate independent variables with *P* values of ≤.2, which were entered into multivariable analysis. After multivariable logistic regression, the only independent predictors of clinical cure were immunosuppression (adjusted odds ratio [aOR], 3.05; 95% confidence interval [CI], 1.24–7.48; *P* = .02) and a shorter duration of bacteremia (aOR, 0.85; 95% CI, 0.68–1.00; *P* = .049). Neither weight, including having a BMI ≥40 kg/m^2, nor %*f*T > MIC was a significant independent predictor. Overall, the model was poorly discriminative, with an AUC-ROC of 0.278.

DISCUSSION

As the proportion of patients who are obese in the United States and worldwide continues to grow, more patients will be at risk for infections and will be likely to experience suboptimal clinical outcomes due to their body habitus. As such, data regarding appropriate antimicrobial dosing and its effect on clinical outcomes are urgently needed in this population. We evaluated the correlation between predicted PK/PD indices of efficacy and observed clinical outcomes among obese and nonobese patients with *Enterobacteriaceae* spp. BSIs. We did not observe significant differences in predicted PK/PD parameters or observed clinical end points between the groups, and we did not find an association between body weight or %*f*T > MIC and clinical cure rates. Notwithstanding poor multivariate model fit, as discussed, an association between being immunosuppressed or receiving an ID consult and an increased likelihood of clinical cure was observed, consistent with existing literature [32–35].

Our work is in agreement with previous studies, which have reported no difference in PK parameters and clinical outcomes in obese patients when β-lactams were administered as extended or continuous infusions [36–38]. A PK study examining piperacillin-tazobactam concentrations in obese and nonobese critically ill patients with severe sepsis or septic shock found no difference in piperacillin plasma concentrations [39]. Similarly, a case–control study found that serum concentrations and PK parameters of piperacillin-tazobactam were similar between obese and nonobese critically ill patients [18]. As such, it is plausible that the lack of observed effect of obesity on both PK/PD and clinical end points in our patients can be attributed to the fact that the vast majority (80%) of patients received extended-infusion piperacillin-tazobactam compared with intermittent-infusion cefepime. This optimized dosing, coupled with the relatively low median MIC observed in this study (4 mg/L), allowed >90% of patients to reach the PD target of at least 50% *f*T > MIC based on our estimations. This is supported by published PK/PD evaluations and Monte Carlo simulations of piperacillin indicating that higher doses and/or extended infusions are likely only needed when targeting higher MICs or treating extremely obese patients [36, 39].

The strengths of our study include inclusion of a narrow but clinically prevalent and relevant patient population in an effort to improve the validity of our findings. The limitations of this study include those inherent to its retrospective, single-center design. β-lactam concentrations were estimated and not directly measured, as therapeutic drug monitoring of the β-lactams is not routinely performed clinically in the United States. The population PK equations used in this study for both β-lactams were derived from studies in infected patients, but not specifically from those who were obese or had BSIs; though based on the height and weight demographics reported, there were obese subjects included in both studies [25, 26]. At the

inception of this work, no population PK analyses specific to obese patients were available for either drug, although subsequently 2 have been published evaluating piperacillin, both of which recommend extended-infusion dosing to overcome PK alterations in obese and/or critically ill patients [40, 41]. Additionally, first-dose PK profiles were utilized for PK/PD predictions as the most conservative estimation, although these may not be representative of steady-state estimations. Protein binding was assumed from the prescribing information and not directly measured, although the protein binding of the studied agents is negligible and preserved across clinical populations [42]. As this was a clinical study, MIC values were measured via Vitek 2, which could have introduced variability in PK/PD assumptions. Obtaining follow-up blood cultures for patients with *Enterobacteriaceae* bacteremia is standard practice within our institution, although the timing and frequency of collection was at the discretion of the provider. This lack of standardized follow-up blood cultures, along with the dependence on appropriate documentation of resolution of signs and symptoms of infection within the medical record, may have affected our ability to determine clinical cure. Finally, the relatively small patient population, high rate of PD target attainment, and high rate of clinical cure in obese and nonobese patients did not allow for adequate statistical discrimination between groups, which led to poor regression model fit.

CONCLUSIONS

Among patients in this study with *Enterobacteriaceae* spp. BSIs treated with either piperacillin-tazobactam or cefepime, there were no significant differences in either PK/PD predictions of efficacy or clinical outcomes between obese and nonobese patients. As the majority of patients received extended-infusion piperacillin-tazobactam for BSIs due to *Enterobacteriaceae* pathogens with low MICs, the potentially detrimental pathophysiologic derangements caused by obesity may not have been realized. Further studies are warranted to confirm these findings and establish the optimal treatment of serious infections in obese patients.

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.

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