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MAJOR ARTICLE

Effect of Obesity on Clinical Failure of Patients Treated With β-Lactams

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Background. Altered pharmacokinetics in obese patients raise concerns over worse clinical outcomes. This study assessed whether obese patients receiving a β-lactam have worse clinical outcomes compared to nonobese patients and to identify if therapeutic drug monitoring may be beneficial.

Methods. This multicenter, retrospective cohort included hospitalized adults admitted from July 2015 to July 2017 treated with a β-lactam as definitive monotherapy against a gram-negative bacilli for ≥72 hours. Patients were excluded if there was lack of source control or if polymicrobial infections required >1 antibiotic for definitive therapy. Patients were classified based on body mass index (BMI): nonobese (BMI ≤29.9 kg/m^2) and obese (BMI ≥30.0 kg/m^2). The primary outcome was clinical treatment failure, and secondary outcomes were hospital length of stay, inpatient all-cause mortality, and 30-day all-cause readmission.

Results. There were 257 (43.6%) obese patients and 332 (56.4%) nonobese patients included. The most common infections were urinary (50.9%) and respiratory (31.4%). Definitive treatment was driven by third-generation cephalosporins (46.9%) and cefepime (44.7%). Treatment failure occurred in 131 (51%) obese patients and 109 (32.8%) nonobese patients ($P < .001$). Obesity and respiratory source were independently associated with increased likelihood of treatment failure. Obese patients were hospitalized longer than nonobese patients ($P = .002$), but no differences were found for all-cause mortality ($P = .117$) or infection-related readmission (0 = 0.112).

Conclusions. Obese patients treated with β-lactams have higher rates of treatment failure and longer hospitalization periods than nonobese patients. Future studies are needed to assess the impact of therapeutic drug monitoring and specific dosing recommendations for targeted infection types.

Keywords. β-lactams; cephalosporins; clinical failure; gram-negative infections; obesity.

With the continued increase in obesity rates observed in the United States and worldwide, there has been a renewed interest in this population, particularly within the realm of infectious diseases and antimicrobial usage [1, 2]. Obese patients have higher risks of infections when compared to nonobese patients, primarily due to increased comorbidities, vascular complications, and slower wound healing. Altered pharmacokinetics, specifically increased volume of distribution and altered renal clearance, lead to concerns for worsened clinical outcomes in obese patients [3, 4]. Cefazolin underdosing for surgical site prophylaxis, particularly in obese patients, resulted in higher rates of postsurgical infections [5, 6]. This subsequently led to higher dosing recommendations based on patient weight within this population. Despite the risk of underdosing in the obese population, clinical outcomes data do not exist for most β-lactams.

One potential solution to the challenge of effectively treating obese patients with infections is therapeutic drug monitoring (TDM). TDM is routinely performed for certain antimicrobials, particularly those with narrow therapeutic windows or those that can be affected by variable pharmacokinetics or disease states [7, 8]. Historically, performance of β-lactam TDM has been infrequent. Therefore, the purpose of this study was to assess whether obese patients receiving a β-lactam have worsened clinical outcomes compared to nonobese patients and to identify if pursuing TDM may be beneficial in this patient population.

METHODS

This multicenter, retrospective cohort included hospitalized adult patients admitted from 1 July 2015 through 31 July 2017 who were treated with a β-lactam as definitive monotherapy for a gram-negative bacilli infection for at least 72 hours. Patients were excluded if source control was unable to be achieved within 72 hours and if polymicrobial infections were present that required >1 antibiotic for definitive therapy. If a patient

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had multiple occurrences of β-lactam monotherapy during the study period, only the first episode was included. Patients were classified into 2 groups based on body mass index (BMI): nonobese (BMI ≤29.9 kg/m^2) and obese (BMI ≥30.0 kg/m^2) [9]. The following data were extracted from the medical record: patient demographics, comorbidities, microbiological and antimicrobial treatment data, hospital length of stay, discharge disposition, hospital readmission within 30 days of discharge, and inpatient mortality within 30 days of administration of therapy. Sites of infection were categorized for definitive therapy based upon indication for the β-lactam, as well as notes within the medical record. The primary outcome was clinical treatment failure, defined as a composite of (1) change in definitive therapy >72 hours due to clinical worsening; (2) residual leukocytosis (white blood cell count >10 × 10^9 cells/L) >72 hours after treatment initiation; (3) presence of a fever (single temperature >38.3°C [100.9°F]) >72 hours after treatment initiation; or (4) readmission within 30 days due to reinfection with the same organism. Secondary outcomes were hospital length of stay, inpatient all-cause mortality, and 30-day all-cause readmission.

Categorical data were analyzed utilizing Pearson χ^2 or Fisher exact test; continuous data were analyzed utilizing the Mann-Whitney *U* test. A 2-sided *P* value of <.05 was considered statistically significant. A forward stepwise logistic regression analysis was conducted using the following variables: age, sex, race, obesity, serum creatinine, heart failure, chronic pulmonary disease, chronic kidney disease, dementia, cerebrovascular disease, complicated diabetes mellitus, cirrhosis, definitive antibiotic (first-, third-, or fourth-generation cephalosporins), definitive source (bloodstream, respiratory, urine), and causative organism. Variables that were significantly associated with treatment failure (*P* < .05) were included in the multivariable logistic regression model. A post hoc power analysis was conducted to determine if the effect size impacted the ability to detect a difference in the primary endpoint. The post hoc power was determined to be 99.4% with an α = .05 [10]. Statistical analyses were performed using SPSS (version 26.0, IBM, Armonk, New York). This study was approved by each respective institution's institutional review board (IRB). All methods were carried out in accordance with relevant guidelines and regulations. The IRBs granted a waiver of consent as this was a retrospective study.

RESULTS

There were 589 patients included in the study with 257 (43.6%) patients in the obese group and 332 (56.4%) patients in the nonobese group. There were 194 (32.9%) patients included from site 1 and 395 (67.1%) included from site 2. The median weight and BMI in the obese group were 102.2 (interquartile range [IQR], 91.9–116.1) kg and 35.3 (IQR, 32.1–40.3) m/kg^2, respectively. The median weight and BMI in the nonobese group were 68.1 (IQR, 59–80.1) kg and 24.4 (IQR, 21.4–27.2) m/kg^2, respectively. When examining the total population, the median age was 70 (IQR, 59–80) years, and almost half (n = 255 [43.0%]) of the patients were male. Most patients were either African American (n = 312 [53.0%]) or white (n = 271 [46.0%]). There are several notable differences in baseline characteristics (Table 1), including age, renal function, and comorbid conditions. Obese patients were younger than nonobese patients (67 years vs 74 years; *P* = .004), yet they had poorer renal function as measured by their baseline serum creatinine (1.24 mg/dL vs 1.06 mg/dL; *P* = .004). Additionally, obese patients had a higher Charlson comorbidity score than nonobese patients (3 vs 2; *P* < .001), which was primarily driven by the presence of hypertension, congestive heart failure, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, uncomplicated diabetes, and moderate-to-severe chronic kidney disease.

Common empiric suspected sites of infection included urinary tract (55.5%), respiratory tract (34.3%), and bloodstream (27.8%), with no differences seen between groups. The most commonly administered empiric antibiotics included intravenous vancomycin (n = 243 [41.3%]), third-generation cephalosporins (n = 230 [39.0%]), cefepime (n = 214 [36.3%]), and β-lactam/β-lactamase inhibitors (n = 90 [15.3%]). There were significant differences in the use of empiric cefepime (30.0% obese vs 41.3% nonobese; *P* = .005) and β-lactam/β-lactamase inhibitors (19.5% obese vs 12.0% nonobese; *P* = .013). Additionally, nonobese patients were more likely to receive cefepime at 1 g every 6 hours compared to obese patients (33.6% vs 14.5%; *P* = .003). With regard to duration of empiric therapy, obese patients received third-generation cephalosporins for a longer duration (3 days vs 2 days; *P* < .001), while nonobese patients received cefepime for a longer duration (4 days vs 2 days; *P* < .001).

Cultures were commonly obtained from the urine (48.7%), blood (19.5%), and sputum (14.6%), with more urine cultures obtained in the nonobese patients (53.0% vs 43.2%; *P* = .018). A breakdown of the cultured organisms can be found in Table 2. There were minimal differences in organisms cultured between groups. The most common final diagnoses made were urinary tract infection (50.9%), respiratory tract infection (31.4%), and bloodstream infection (9.3%), with no differences in infection location between groups. Additionally, 39 (6.6%) patients had multiple sites of infections, but there was no difference between groups (8.6% obese vs 5.1% nonobese; *P* = .096). The minimum inhibitory concentrations (MICs) for the cultured organisms against first-generation cephalosporins were mostly ≤8 mg/L (n = 23 [48.9%]) or not available (n = 20 [42.6%]) with no differences between groups. Most MICs for third-generation cephalosporins were ≤1 mg/L (n = 178 [64.5%]) with more organisms cultured

Table 1. Baseline Patient Demographics

Variable	Total (N = 589)	Obese (n = 257)	Nonobese (n = 332)	*P* Value
Age, y, median (IQR)	70 (59–80)	67 (57.5–75)	74 (61–83.8)	<.001
Sex, male	255 (43.4)	94 (36.7)	161 (48.6)	.004
Race				
White	271 (46)	95 (37)	176 (53)	<.001
African American	312 (53)	161 (62.6)	151 (45.5)	<.001
Hispanic	2 (0.3)	1 (0.4)	1 (0.3)	1.000
Other	1 (0.2)	0 (0)	1 (0.3)	1.000
Unknown	3 (0.5)	0 (0)	3 (0.9)	.261
Serum creatinine, mg/dL, median (IQR)	1.16 (0.80–1.96)	1.24 (0.88–2.09)	1.06 (0.78–1.79)	.004
Weight, kg, median (IQR)	83.1 (66.1–100.1)	102.2 (91.9–116.1)	68.1 (59–80.1)	<.001
BMI, mg/kg^2, median (IQR)	28.5 (23.7–34.2)	35.3 (32.1–40.3)	24.4 (21.4–27.2)	<.001
Comorbidities				
Hypertension	498 (84.6)	229 (89.1)	269 (81)	.007
History of myocardial infarction	91 (15.4)	25 (9.7)	66 (19.9)	.001
Congestive heart failure	155 (26.3)	88 (34.2)	67 (20.2)	<.001
Peripheral vascular disease	67 (11.4)	20 (7.8)	47 (14.2)	.016
Cerebrovascular disease	174 (29.5)	62 (24.1)	112 (33.7)	.011
Dementia	68 (11.5)	15 (5.8)	53 (16)	<.001
Chronic pulmonary disease	185 (31.4)	95 (37)	90 (27.1)	.011
Connective tissue disease	69 (11.7)	55 (21.4)	14 (4.2)	<.001
Peptic ulcer disease	59 (10)	44 (17.1)	15 (4.5)	<.001
Diabetes mellitus, uncomplicated	115 (19.5)	72 (28)	43 (13)	<.001
Diabetes mellitus, complicated	97 (16.5)	48 (18.7)	49 (14.8)	.204
CKD, moderate to severe	132 (22.4)	70 (27.2)	62 (18.7)	.013
Hemiplegia/paraplegia	24 (4.1)	11 (4.3)	13 (3.9)	.824
Leukemia	9 (1.5)	4 (1.6)	5 (1.5)	1.000
Malignant lymphoma	20 (3.4)	7 (2.7)	13 (3.9)	.428
Solid tumor, not metastatic	36 (6.1)	24 (9.3)	12 (3.6)	.004
Solid tumor, metastatic	23 (3.9)	10 (3.9)	13 (3.9)	.988
Liver disease, mild	12 (2)	5 (1.9)	7 (2.1)	.890
Liver disease, moderate to severe	13 (2.2)	4 (1.6)	9 (2.7)	.344
AIDS	2 (0.3)	0 (0)	2 (0.6)	.507
Charlson score, median (IQR)	3 (1–4)	3 (2–5)	2 (1–4)	<.001

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

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; IQR, interquartile range.

from nonobese patients having this MIC (70.3% vs 57.8%; $P = .031$). Most cultured organisms had a MIC ≤1 mg/L against cefepime (n = 77 [29.3%]) with no differences in MICs seen between groups.

A high percentage of patients (n = 276 [46.9%]) received a third-generation cephalosporin for definitive therapy, while 263 (44.7%) patients received cefepime, 47 (8.0%) patients received a first-generation cephalosporin, 2 (0.3%) received an anti-pseudomonal carbapenem, and 1 (0.2%) received a β-lactam/β-lactamase inhibitor combination. There were no differences in definitive doses for any β-lactam prescribed except for cefepime, with more patients in the obese group receiving 2 g every 8 hours (12.4% vs 5.3%; $P = .041$). A detailed breakdown of prescribed definitive β-lactam regimens is in Table 3. There was no difference between groups in duration of definitive therapy for any β-lactam.

Two hundred forty (40.7%) patients experienced treatment failure with 131 (51.0%) obese patients failing and 109 (32.8%) nonobese patients failing ($P < .001$; Table 4). A majority of patients failed due to unresolved leukocytosis (n = 181/240 [46.9%]); however, there were no differences between groups. Results of the logistic regression analysis are shown in Table 5. Only obesity (odds ratio, 2.3) and respiratory source (odds ratio, 3.1) were independently associated with treatment failure. There were no factors that were associated with reducing the odds of treatment failure.

The median hospital length of stay was 9 (IQR, 6–16) days; however, obese patients had a longer length of stay than nonobese patients (10 days vs 8 days; $P = .002$). Just under half the patients (n = 289 [48.7%]) were discharged home, with 206 (35%) patients discharged to a skilled nursing/rehabilitation facility, 25 (4.2%) patients discharged to hospice, 8

Table 2. Microbiological Characteristics

Variable	Total (N = 589)	Obese (n = 257)	Nonobese (n = 332)	*P* Value
Cultured organisms				
MRSA	2 (0.3)	2 (0.8)	0 (0)	.190
MSSA	10 (1.7)	3 (1.2)	7 (2.1)	.525
Staphylococcus spp	5 (0.8)	2 (0.8)	3 (0.9)	1.000
Streptococcus spp	16 (2.7)	8 (3.1)	8 (2.4)	.603
Escherichia coli	176 (29.9)	75 (29.2)	101 (30.4)	.745
Enterobacter spp	30 (5.1)	14 (5.4)	16 (4.8)	.731
Citrobacter spp	12 (2)	10 (3.9)	2 (0.6)	.005
Klebsiella spp	81 (13.8)	36 (14)	45 (13.6)	.874
Proteus spp	50 (8.5)	22 (8.6)	28 (8.4)	.956
Pseudomonas aeruginosa	58 (9.8)	25 (9.7)	33 (9.9)	.932
Acinetobacter baumannii	12 (2)	6 (2.3)	6 (1.8)	.653
Other gram-negative aerobic organisms	62 (10.5)	30 (11.7)	32 (9.6)	.425
Anaerobic organisms	8 (1.4)	0 (0)	8 (2.4)	.011
Definitive infection location				
CNS	4 (0.7)	3 (1.2)	1 (0.3)	.323
Bloodstream	55 (9.3)	25 (9.7)	30 (9)	.775
Bone/joint	8 (1.4)	4 (1.6)	4 (1.2)	.734
Infective endocarditis	2 (0.3)	2 (0.8)	0 (0)	.190
Skin/wound	35 (5.9)	13 (5.1)	22 (6.6)	.425
Respiratory	185 (31.4)	81 (31.5)	104 (31.3)	.960
Intra-abdominal	10 (1.7)	6 (2.3)	4 (1.2)	.345
Urinary tract/gynecologic	300 (50.9)	136 (52.9)	164 (49.4)	.397
Multiple infection sites	39 (6.6)	22 (8.6)	17 (5.1)	.096
CNS + skin/wound	2 (5.1)	2 (9.2)	0 (0)	.495
Urinary tract/gynecologic + bloodstream	15 (38.4)	7 (31.8)	8 (47)	.508
Urinary tract/gynecologic + respiratory	8 (20.5)	5 (22.7)	3 (17.6)	1.000
CNS + bloodstream	1 (2.6)	1 (4.5)	0 (0)	1.000
Respiratory + bloodstream	4 (10.2)	3 (13.6)	1 (5.9)	.618
Respiratory + infective endocarditis	1 (2.6)	1 (4.5)	0 (0)	1.000
Skin/wound + bone/joint	1 (2.6)	0 (0)	1 (5.9)	.436
Intra-abdominal + skin/wound	1 (2.6)	0 (0)	1 (5.9)	.436
Skin/wound + respiratory	1 (2.6)	0 (0)	1 (5.9)	.436
Bloodstream + bone/joint	1 (2.6)	0 (0)	1 (5.9)	.436
Bloodstream + urinary tract/gynecologic + intra-abdominal	1 (2.6)	1 (4.5)	0 (0)	1.000
Bloodstream + urinary tract/gynecologic + respiratory	3 (7.6)	2 (9.2)	1 (5.9)	1.000

Data are presented as No. (%).

Abbreviations: CNS, central nervous system; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

(1.4%) discharged to another hospital, 3 (0.5%) still admitted, and 1 (0.2%) discharged back to prison. Fifty-nine (10.0%) patients died during hospitalization. No differences were seen between groups. There were no additional deaths at 30 days postdischarge, and 449 (84.7%) patients were not readmitted within 30 days. Fifty (9.4%) patients were readmitted for an infectious cause ($P = .095$), and 31 (5.8%) were readmitted for a noninfectious cause ($P = .563$).

DISCUSSION

In this multicenter retrospective study, obese patients were more likely to experience clinical treatment failure when compared to nonobese patients; however, there was no clear driver of why treatment failure occurred more often in this population. Conversely, while obese patients experienced greater length of hospitalization, they had comparable rates of inpatient mortality.

Obese patients are more likely to have multiple comorbid conditions and tend to be younger when diagnosed [11]. Likewise, these obese patients were younger and had a higher disease burden than their nonobese counterparts. We anticipated that a population with greater comorbidities, coupled with the potential for underdosing of antibiotics, would experience greater rates of treatment failure. The most common cause of treatment failure in both groups was unresolved leukocytosis. One study of patients with ventilator-associated pneumonia evaluated the resolution of markers of infection and

Table 3. Definitive β-Lactam Therapy Management

Variable	Total (N = 589)	Obese (n = 257)	Nonobese (n = 332)	*P* Value
Definitive antibiotic selection				
β-lactam/β-lactamase inhibitors	1 (0.2)	1 (0.4)	0 (0)	.436
First-generation cephalosporins	47 (8)	14 (5.4)	33 (9.9)	.046
Third-generation cephalosporins	276 (46.9)	128 (49.8)	148 (44.6)	.207
Cefepime	263 (44.7)	113 (44)	150 (45.2)	.769
Anti-pseudomonal carbapenems	2 (0.3)	2 (0.8)	0 (0)	.190
Definitive drug regimens				
Piperacillin-tazobactam 3.375 g q6h	1 (100)	1 (100)	0 (0)	
First-generation cephalosporins				
500 mg q8h	1 (2.1)	0 (0)	1 (3)	1.000
1 g q8h	27 (57.4)	9 (64.3)	18 (54.5)	.537
1 g q12h	3 (6.4)	0 (0)	3 (9.1)	.544
1 g q24h	1 (2.1)	1 (7.1)	0 (0)	.298
2 g q8h	14 (29.8)	4 (28.6)	10 (30.3)	1.000
2 g q12h	1 (2.1)	0 (0)	1 (3)	1.000
Third-generation cephalosporins				
0.5 g q24h	1 (0.4)	1 (0.8)	0 (0)	.464
1 g q8h	1 (0.4)	1 (0.8)	0 (0)	.464
1 g q12h	3 (1.1)	2 (1.6)	1 (0.7)	.598
1 g q24h	215 (77.9)	94 (73.4)	121 (81.8)	.097
2 g q12h	2 (0.7)	0 (0)	2 (1.4)	.501
2 g q24h	54 (19.6)	30 (23.4)	24 (16.2)	.132
Cefepime				
0.5 g q24h	2 (0.8)	0 (0)	2 (1.3)	.508
1 g q6h	72 (27.4)	27 (23.9)	45 (30)	.272
1 g q8h	85 (32.3)	37 (32.7)	48 (32)	.898
1 g q12h	37 (14.1)	14 (12.4)	23 (15.3)	.497
1 g q24h	25 (9.5)	14 (12.5)	11 (7.3)	.166
2 g q8h	22 (8.4)	14 (12.4)	8 (5.3)	.041
2 g q12h	12 (4.6)	2 (1.8)	10 (6.7)	.060
2 g q24h	8 (3)	5 (4.4)	3 (2)	.295
Anti-pseudomonal carbapenems 1 g q6h	2 (100)	2 (100)	0 (0)	
Duration of definitive therapy, days				
β-lactam/β-lactamase inhibitors	2 days	2 days	…	
First-generation cephalosporins, median (IQR)	5 (4–7)	5 (4–6)	6 (4–7.5)	.364
Third-generation cephalosporins, median (IQR)	4 (3–6)	4 (3–6)	4 (3–6)	.169
Cefepime, median (IQR)	5 (4–7)	5 (4–7)	5 (4–7)	.216
Anti-pseudomonal carbapenems	4 days, 8 days	4 days, 8 days	…	

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

Abbreviations: IQR, interquartile range; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours.

determined that leukocytes did not return to normal levels until 8 days later [12]. Height and weight were not captured on the patients in this study. However, early resolution of leukocytosis as an indicator of clinical failure may lead to overestimations of the endpoint. Obesity is associated with low-grade inflammation leading to higher baseline leukocyte counts [13]. Although not significant among those with treatment failure, there were significantly more obese patients with unresolved leukocytosis in the total population. This may have led to greater rates of second antibiotic prescriptions.

Obese patients stayed in the hospital on average 2 days longer than nonobese patients, but with no greater mortality. Obesity has been associated with greater length of hospital stay in general hospitalized patients and in sepsis [14, 15]. Mortality rates of obese patients with sepsis and pneumonia are reported to be lower than nonobese patients, which may explain why, despite experiencing higher rates of treatment failure and longer length of stay, there was no excess mortality in the obese group [15–18]. It is unclear whether those patients who experienced treatment failure contributed significantly to the excess length of hospitalization in the obese group. Likewise, since this study included all types of infections and a variety of β-lactam antibiotics, it is not statistically sound to draw conclusions based on specific infections or antibiotics that were associated with

Table 4. Clinical Outcomes

Variable	Total (N = 589)	Obese (n = 257)	Nonobese (n = 332)	*P* Value
Discharge disposition				
Died during hospitalization	59 (10)	27 (10.5)	32 (9.6)	.728
Home	287 (48.7)	130 (50.6)	157 (47.3)	.428
Skilled nursing/rehabilitation facility	206 (35)	85 (33.1)	121 (36.4)	.395
Hospice	25 (4.2)	9 (3.5)	16 (4.8)	.432
Another hospital	8 (1.4)	5 (1.9)	3 (0.9)	.305
Still admitted	3 (0.5)	1 (0.4)	2 (0.6)	1.000
Prison	1 (0.2)	0 (0)	1 (0.3)	1.000
Treatment failure	240 (40.7)	131 (51)	109 (32.8)	<.001
Readmission in 30 days due to reinfection	50/240 (20.8)	27/131 (20.6)	23/109 (21.1)	.926
Second antibiotic added	61/240 (25.4)	36/131 (27.5)	25/109 (22.9)	.421
Leukocytosis	181/240 (75.4)	101/131 (77.1)	80/109 (73.4)	.507
Fever	53/240 (22.1)	25/131 (19.1)	28/109 (25.7)	.219
30-day inpatient all-cause mortality	59/240 (24.6)	27/131 (20.6)	32/109 (29.4)	.117
30-day readmission				
No readmission	449 (84.7)	188 (81.7)	261 (87)	.095
Readmitted; infection-related	50 (9.4)	27 (11.7)	23 (7.7)	.112
Readmitted; non-infection-related	31 (5.8)	15 (6.5)	16 (5.3)	.563

Data are presented as No. (%).

increased length of hospitalization or excess treatment failure. Future studies directed at individual antibiotics for specific infections will be necessary to evaluate these uncertainties.

There is limited evidence regarding dosing strategies of antimicrobials in obese patients. Physiologic changes associated with obesity may alter pharmacokinetic parameters such as volume of distribution and clearance, but these changes are not well defined for most antimicrobials and are challenging to predict. Cephalosporins are hydrophilic, so increases in volume of distribution would be less likely, as most agents would not freely distribute into excess adipose tissue [19]. In fact, studies with cefazolin for surgical prophylaxis have demonstrated that despite adequate serum concentrations in obese patients, tissue concentrations were inadequate [20, 21]. Increased doses of cefazolin and cefepime have been suggested to overcome changes in pharmacokinetics associated with obesity [22, 23]. Additionally, to achieve longer time of target concentration attainment, select β-lactam agents have been studied using prolonged-infusion dosing strategies [24, 25]. Improved clinical outcomes may be seen in critically ill patients utilizing prolonged infusion, but it is unknown whether this technique is beneficial for all patients [26, 27]. Both institutions utilized prolonged infusion in select patients during this study, but this was not standard practice during the time of our investigation. In our study of patients with mixed infections, it is unclear whether clinical outcomes and higher rates of treatment failure would be affected by modified dosing strategies in our population.

Table 5. Risk Factors for Treatment Failure

Factor	Odds Ratio (95% CI)	*P* Value
Obesity	2.30 (1.57–3.35)	<.001
Age	1.00 (.98–1.01)	.431
Female sex	0.76 (.52–1.11)	.152
Dementia	0.96 (.52–1.79)	.908
Enterobacter isolated	2.06 (.88–4.82)	.096
Citrobacter isolated	2.97 (.59–14.94)	.187
Pseudomonas isolated	1.78 (.94–3.39)	.078
Other gram-negative organism isolated	1.61 (.88–2.95)	.121
Definitive third-generation cephalosporin	0.94 (.47–1.87)	.856
Definitive fourth-generation cephalosporin	1.12 (.55–2.29)	.747
Respiratory source	3.07 (1.87–5.04)	<.001
Urinary-gynecologic source	1.02 (.63–1.64)	.934

Abbreviation: CI, confidence interval.

While recommendations for TDM are established for antimicrobials such as vancomycin and aminoglycosides to ensure safety and efficacy [28, 29], β-lactams have traditionally not required monitoring, given a wide safety profile. However, due to increasing antimicrobial resistance and pharmacokinetic variability, experts advocate for TDM of β-lactams to increase chances of achieving adequate serum concentrations in critically ill patients [23, 30, 31]. Although studies report variation in serum concentrations, TDM of β-lactams has not demonstrated greater rates of clinical success, although trials are ongoing [32]. Given altered β-lactam pharmacokinetics in obese patients and higher rates of treatment failure in our study group, TDM may be a reasonable option for this population; however, further studies are needed to determine its utility in clinical practice.

Limitations of this study include the retrospective study design. Specifically, the determination of primary treatment

failure relied on documentation in electronic health records. It is possible patients had sources of leukocytosis and fever that were unrelated to the primary end point. Second, baseline characteristics, specifically comorbidities, were not similar among obese and nonobese patients. However, the Charlson comorbidity index was higher in obese patients; therefore, this population would be expected to have higher mortality compared to nonobese patients. We saw no significant difference in 30-day mortality between groups with similar dosing strategies. Finally, our study broadly looked at infections treated with β-lactam antibiotics, which limits the ability to draw conclusions regarding specific β-lactam dosing effectiveness.

CONCLUSIONS

This study demonstrates that obese patients admitted for infections and treated with β-lactam antibiotics have higher rates of treatment failure compared to patients who are not obese. Additionally, obese patients had greater length of hospital stay without greater mortality. Obese patients had greater disease burden, which hinders the ability to draw conclusions on the dosing of β-lactam antibiotics. Future studies are needed to determine specific dosing recommendations for targeted infection types, as well as using more accurate markers of treatment success, in order to adequately conclude that obesity contributes to infection-related treatment failure.

Notes

Author contributions. All authors were involved in data collection, data analysis, and manuscript composition.

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