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MAJOR ARTICLE

Weighing the Odds: Novel β-Lactam/β-Lactamase Inhibitor Use in Hospital-Acquired and Ventilator-Associated *Pseudomonas aeruginosa* Pneumonia for Patients Who Are Morbidly Obese

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Background. *Pseudomonas aeruginosa* is a leading cause of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP). Novel β-lactam/β-lactamase inhibitor (BL/BLI) combinations are often used for these infections; however, limited data exist to guide the dosing of BL/BLI in patients who are morbidly obese. Thus, we sought to evaluate the clinical and safety endpoints of patients who are morbidly obese (body mass index ≥35 kg/m^2) and non–morbidly obese (<35 kg/m^2) and receiving BL/BLI for *P aeruginosa* HABP/VABP.

Methods. This retrospective study was based on a cohort of patients hospitalized at 2 urban academic medical centers in Detroit, Michigan, from August 2014 through February 2021 with *P aeruginosa* HABP/VABP who were receiving BL/BLI (ceftazidime/avibactam, ceftolozane/tazobactam, or meropenem/vaborbactam) for ≥72 continuous hours. The primary endpoint was presumed treatment failure, defined as the presence of all-cause in-hospital mortality or the continuation of infectious symptoms. Analyses were adjusted for possible confounding with inverse probability of treatment weighting. Multivariable regression was used to identify predictors of treatment failure.

Results. In total, 285 patients with HABP (61.4%) and/or VABP (56.1%) were enrolled (morbidly obese, n = 95; non–morbidly obese, n = 190). The median Acute Physiology and Chronic Health Evaluation II score was 23 (IQR, 13–26), and 60% of patients were admitted to the intensive care unit at index culture collection. Patients who were morbidly obese demonstrated significantly greater odds of presumed treatment failure vs those who were non–morbidly obese (58.9% vs 37.9%, respectively; adjusted odds ratio, 1.675 [95% CI, 1.465–1.979]). In multivariable analysis, morbid obesity (1.06; 95% CI, 1.02–1.79), prolonged time to BL/BLI initiation (1.47; 95% CI, 1.28–2.66), renal dose–adjusted BL/BLI in the first 48 hours of therapy (1.12; 95% CI, 1.09–1.75), and continuous renal replacement therapy during BL/BLI therapy (1.35; 95% CI, 1.06–1.68) were independently associated with increased odds of presumed treatment failure.

Conclusions. Among hospitalized patients receiving BL/BLI for *P aeruginosa* HABP/VABP, those who were morbidly obese had significantly greater odds of presumed treatment failure when compared with those who were non–morbidly obese.

Keywords. ceftazidime/avibactam; ceftolozane/tazobactam; meropenem/vaborbactam; obesity; *Pseudomonas aeruginosa*.

Obesity is a global health crisis. Data from the Centers for Diseases Control and Prevention reveal that over one-third of adults in the United States aged ≥20 years experience obesity [1]. Globally, more than half a billion adults are obese, and experts estimate that by 2030, obesity will affect 75% of the US population [2]. Researchers have linked obesity to detrimental health outcomes and have found that it significantly increases health care costs [3–5]. Patients with obesity experience a higher prevalence of infections as compared with those without obesity, and research has connected obesity to inferior overall clinical outcomes related to infections [6, 7]. Additionally, patients with obesity have a higher likelihood of developing infections during their stay in the intensive care unit (ICU) and

Received 22 June 2023; editorial decision 21 August 2023; accepted 24 August 2023; published online 28 August 2023

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https://doi.org/10.1093/ofid/ofad454

necessitate more intricate antimicrobial treatments than those without obesity [8, 9].

Selecting appropriate antimicrobial dose regimens for patients who are critically ill and obese is challenging due to the various pathophysiologic alterations associated with obesity, including differences in cardiac output, lean fat masses, and renal blood flow [10, 11]. Such alterations can affect drug pharmacokinetics (PK), resulting in altered drug exposure and therapeutic failure [11]. Different PK studies of conventional β-lactams have confirmed altered PK in patients who are obese/morbidly obese as compared with those who are not [12]. However, whether these alterations are clinically significant to warrant dose adjustments remains debatable.

Pseudomonas aeruginosa infection can be challenging to treat due in part to its multiple resistance mechanisms, and it remains the leading cause of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) with high mortality rates [13]. Clinicians frequently employ novel β-lactam/β-lactamase inhibitor (BL/BLI) combinations to treat challenging cases of HABP/VABP caused by *P aeruginosa* [14]. Limited data exist to guide the dosing of novel BL/BLI in patients who are morbidly obese [10, 15, 16]. This study aimed to compare clinical and safety outcomes in patients with and without morbid obesity with *P aeruginosa* HABP/VABP who were receiving ceftazidime/avibactam, ceftolozane/tazobactam, or meropenem/vaborbactam as definitive therapy.

METHODS

Study Design and Population

This retrospective cohort study examined adult patients admitted to 2 urban academic medical centers in Detroit, Michigan, between August 2014 and February 2021. The study focused on patients with diagnosed HABP/VABP caused by *P aeruginosa* and treated with ceftazidime/avibactam, ceftolozane/tazobactam, or meropenem/vaborbactam as definitive therapy. The participants were categorized into 2 groups based on their body mass index (BMI): morbidly obese (≥35 kg/m^2) and non–morbidly obese (<35 kg/m^2), aligning with previous BL/BLI analyses [15]. Inclusion criteria required patients to have *P aeruginosa* isolated from a respiratory sample; meet the definitions of lower respiratory tract infection per the Centers for Diseases Control and Prevention/National Healthcare Safety Network [17]; receive antimicrobial therapy with demonstrated in vitro activity within 72 hours of positive respiratory culture; and receive ≥72 continuous hours of a novel BL/BLI at package insert doses current as of 2022 [18–20]. Exclusion criteria included patients who died before obtaining culture results, those transferred from an outside hospital with a known *P aeruginosa* culture, and patients with cystic fibrosis. The primary outcome of the study was a composite of presumed treatment failure, defined as all-cause in-hospital mortality or the continuation of infectious symptoms attributable to *P aeruginosa* HABP/VABP. Infectious symptoms attributed to *P aeruginosa* HABP/VABP were defined as an elevated ratio of partial pressure of arterial oxygen to fraction of inspired oxygen and/or increased supplemental oxygen requirements after the first 72 hours through the end of BL/BLI therapy as compared with baseline [21]. Secondary outcomes included individual components of the primary outcome and presumed treatment-emergent adverse effects, such as nephrotoxicity and/or hepatotoxicity during therapy or *Clostridioides difficile*–associated diarrhea within 30 days of the end of BL/BLI therapy.

Patient characteristics, including demographics and baseline attributes, were analyzed in addition to comorbidity burden as determined by the Charlson Comorbidity Index. Furthermore, the evaluation encompassed measurements of organ function and severity of illness by utilizing the most elevated scores from the Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment (SOFA), and Pitt bacteremia assessment taken within 48 hours prior to or on the same day as the primary culture collection [22]. Data were collected from the electronic health records and recorded in REDCap (Research Electronic Data Capture) [23].

Only the first course of inpatient BL/BLI therapy lasting ≥72 hours was considered for patients who received multiple courses. A new BL/BLI course was defined by a gap ≥72 hours between doses. The term "index event" or "index episode" was used to describe the infection episode that initiated the administration of a new BL/BLI medication. Yet, the term "index culture" indicated the initial respiratory culture sample collected during the index episode.

Microbiological Investigation

All isolates were identified by clinical microbiology laboratories within the 2 study centers. Susceptibility testing was performed with testing methods either automated (Phoenix [BD] or Vitek-2) or manual (gradient diffusion strips [ETEST; Biomerieux] or Kirby-Bauer disks).

Statistical Analysis

A power analysis was conducted to determine the sample size. Based on previous studies evaluating novel BL/BLI use in patients who were obese, a conservative estimate of 17% clinical treatment failure for the obese group was anticipated. Therefore, a sample size of 285 patients, with a matching rate of approximately 1:2 (obese:nonobese, 95:190), was established to achieve 85% power at the 95% confidence level. Cohort attributes were documented by presenting categorical data as frequency and percentage, while continuous data were represented by median and IQR. Categorical variables were analyzed with χ^2 analysis, whereas continuous variables were assessed via a 2-sample *t* test assuming equal variances. All tests were conducted with

a 2-tailed approach, and a significance level ≤.05 was applied to determine statistical significance.

To ensure comparability between groups at index culture collection and enable unbiased comparisons, propensity scores were generated through multivariable logistic regression [24]. The calculation of propensity scores included the following covariates: sex, baseline serum creatinine, colonization with resistant organisms (defined as 2 positive cultures at least 3 months apart within a 12-month period), SOFA score, mechanical ventilation for ≥48 hours prior to the positive *P aeruginosa* culture, ICU admission, and definitive BL/BLI treatment. Covariates were chosen by their statistical difference between groups with a *P* value ≤.1 and/or clinical significance. Inverse probability of treatment weighting (IPTW) was applied via the propensity scores to create a pseudo-population that balanced potential covariate biases, simulating a randomized treatment scenario. The balance of covariates was assessed through the Kolmogorov-Smirnov goodness-of-fit statistic and standardized mean difference, with >0.1 and >0.2 indicating an imbalance, respectively. The predictive ability of the propensity score model was evaluated by the area under the receiver operating characteristic curve.

Bivariate regression analyses were subsequently conducted to compare primary and secondary outcomes between the morbidly obese and non–morbidly obese pseudo-study cohorts. Odds ratio (OR) and adjusted OR with 95% CI were calculated. In the IPTW pseudo-study population, a univariate analysis was performed to identify factors associated with presumed treatment failure. Prespecified variables of interest included morbid obesity, Charlson Comorbidity Index score, immunosuppression, SOFA score, BL/BLI minimum inhibitory concentration (MIC), time to BL/BLI therapy, receipt of renal dose–adjusted BL/BLI within the first 48 hours of therapy (excluding patients who had a creatinine clearance <30 mL/min and/or were undergoing hemodialysis), continuous renal replacement therapy (CRRT), and concomitant systemic antipseudomonal therapy. Time to BL/BLI therapy was defined as the time elapsed from index culture collection to receipt (administration) of the first dose of BL/BLI. Receipt of renal dose–adjusted BL/BLI therapy was defined as receipt of the following at any time during the first 48 hours of BL/BLI therapy: ceftolozane/tazobactam <3 g, ceftazidime/avibactam <2.5 g, or meropenem/vaborbactam <4 g administered per dose. Covariates with $P < .2$ in the univariate analysis were included in the final model. Data analysis was performed with IBM SPSS Statistics for Windows version 29. The study received approval from the institutional review boards of Wayne State University, Henry Ford Health System, and the Detroit Medical Center's research committee.

RESULTS

Patient Characteristics

This study evaluated 285 patients (morbidly obese, n = 95; non–morbidly obese, n = 190) who had HABP/VABP and a respiratory culture positive for *P aeruginosa* and fulfilled the inclusion criteria. Baseline demographic and clinical characteristic data between groups are listed in Table 1. The median age was 62 years (IQR, 51.5–72), 66.7% were male, and 60% were admitted to the ICU at the time of index culture collection. Other than baseline differences in body habitus between groups, the morbidly obese cohort had fewer males (54.7% vs 72.6%, $P < .003$), more patients admitted to the ICU while hospitalized (91.6% vs 80.5%, $P < .016$), and more VABP diagnoses (70.5% vs 48.9%, $P < .001$) as compared with the non–morbidly obese cohort. Antimicrobial susceptibility data for each BL/BLI are displayed in Figure 1. In total, 30.2% of the cohort had a polymicrobial respiratory culture with Enterobacterales being the most common concomitant isolate (present in 24.2% of polymicrobial cultures). The receipt of active therapy and the time to active therapy prior to the initiation of novel BL/BLI were similar between groups (46.2%; median, 1.7 days [IQR, 0.6–2.4]).

Infection Management and Clinical Course

Regarding infection management (Table 2), the receipt of each BL/BLI was similar between groups with most patients receiving ceftolozane/tazobactam (59.6%), followed by ceftazidime/avibactam (25.6%) and meropenem/vaborbactam (14.7%). Time to BL/BLI initiation was also similar between groups at a median 3.4 hours (IQR, 2.1–4.8). In total, 25.6% of patients received concomitant systemic antipseudomonal therapy with the BL/BLI, with amikacin being the most common (6%). The overall duration of BL/BLI therapy was similar between the morbidly obese and non–morbidly obese groups at median days of 8.6 (IQR, 5.6–13.2) and 7.6 (IQR, 5.3–13.3; $P = .532$), respectively. Hospital and ICU length of stay was also similar between groups at median days of 30 (IQR, 16–52) and 14 (IQR, 8–30).

Outcomes

The propensity score distribution between patients with and without morbid obesity was adequately balanced after IPT weighting, as demonstrated by the Kolmogorov-Smirnov test with pre- and post-IPT weighting *P* values of .039 and .458, respectively. The prediction ability of the propensity score model with an area under the receiver operating characteristic curve was 84.7%. Unadjusted and IPTW-adjusted primary and secondary endpoints are presented in Table 3. In the IPTW analysis, the morbidly obese cohort had significantly greater odds of clinical treatment failure as compared with the non–morbidly obese cohort (adjusted OR, 1.675; 95% CI, 1.465–1.979). No difference in BL/BLI-associated adverse events were identified between the morbidly obese and non–morbidly obese groups.

In univariate analysis, the primary composite outcome of presumed treatment failure was significantly associated ($P < .05$) with morbid obesity, longer time to BL/BLI therapy, renal dose–adjusted BL/BLI in the first 48 hours of BL/BLI therapy, CRRT, and concomitant antipseudomonal therapy.

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Patients, Median (IQR) or No. (%)			*P* Value
	Total (N = 285)	≥35 mg/kg^2 (n = 95)	<35 mg/kg^2 (n = 190)	
Age, y	62 (51.5–72)	64 (58–72)	61 (48–72)	.138
Male sex	190 (66.7)	52 (54.7)	138 (72.6)	.003
Race				
African American	131 (46)	44 (46.3)	87 (45.8)	.995
Caucasian	116 (40.7)	38 (40)	78 (41.1)	.887
Other	37 (13)	13 (13.7)	13 (6.8)	.261
Body mass index, kg/m^2	26.6 (21.5–36.7)	38.4 (36.2–40.7)	25.2 (19.4–27.3)	<.001
Body surface area	1.9 (1.7–2.2)	2.2 (2.1–2.3)	1.8 (1.6–1.9)	<.001
Ideal body weight	67.7 (57–75.3)	64.1 (54.2–73)	68.7 (59.4–77.7)	.012
Baseline creatinine				
Serum, mg/dL	0.89 (0.69–1.2)	1 (1–1.4)	0.82 (0.6–1.09)	0.072
Clearance, mL/min	84 (55.4–114)	85 (56–113.2)	80.8 (53.4–117.8)	.239
Admitted from				
Home	117 (41.1)	36 (37.9)	81 (42.6)	.452
Long-term acute care	6 (2.1)	2 (2.1)	4 (2.1)	.677
Nursing home/long-term care facility	95 (33.3)	35 (36.8)	60 (31.6)	.407
Inpatient rehabilitation	7 (2.5)	1 (1.1)	6 (3.2)	.256
Referral from clinic	5 (1.8)	1 (1.1)	4 (2.1)	.455
Hospital transfer[a]	53 (18.6)	20 (21.1)	33 (17.4)	.476
Charlson Comorbidity Index score	5 (2–7)	4 (2–6)	5 (3–7)	.189
Comorbid conditions				
Heart failure	58 (20.4)	24 (25.3)	34 (17.9)	.151
COPD/asthma	90 (31.6)	33 (34.7)	57 (30)	.904
Chronic kidney disease	66 (23.2)	26 (27.4)	40 (21.1)	.243
Hemodialysis dependent	32 (11.2)	10 (10.5)	22 (11.6)	.779
Immunosuppressed[b]	35 (12.3)	14 (14.7)	21 (11.1)	.372
MDR risk factors				
≥24 h antibiotics within ≤90 d	219 (76.8)	76 (80)	143 (75.3)	.412
≥48 h hospitalization ≤90 d	199 (69.8)	69 (72.6)	130 (68.4)	.504
Surgery ≤30 d before index culture	41 (14.4)	16 (16.8)	25 (13.2)	.414
Colonization with resistant GN organism[c]	128 (44.9)	42 (44.2)	86 (45.3)	.836
ICU admission	240 (84.2)	87 (91.6)	153 (80.5)	.016
Medical	138 (48.4)	51 (53.7)	87 (45.8)	.209
Surgical/trauma	64 (22.5)	23 (24.2)	41 (21.6)	.616
Other	38 (13.3)	12 (12.6)	26 (13.7)	.805
In ICU at index culture collection	171 (60)	63 (66.3)	108 (56.8)	.124
Score				
SOFA	7 (4–9)	8 (5–10)	7 (4–9)	.059
APACHE II	23 (13–26)	24 (15–28)	22 (11–24)	.113
Prior to index positive *P aeruginosa* culture				
Hospitalized for ≥48 h	175 (61.4)	56 (58.9)	119 (62.6)	.547
Mechanical ventilation for ≥48 h	160 (56.1)	67 (70.5)	93 (48.9)	<.001
Respiratory culture specimen				
Aspirate	65 (22.8)	26 (27.4)	39 (20.5)	.194
Bronchoalveolar lavage	55 (19.3)	18 (18.9)	38 (0.2)	.769
Sputum	165 (57.9)	53 (55.8)	112 (58.9)	.611
Polymicrobial index culture	86 (30.2)	27 (28.4)	59 (31.1)	.648
Other isolates in culture[d]				
Acinetobacter spp	19 (6.7)	7 (7.4)	12 (6.3)	.737
Enterobacterales spp	69 (24.2)	25 (26.3)	44 (23.2)	.557
Stenotrophomonas maltophilia	15 (5.3)	5 (5.3)	10 (5.3)	>.999
Gram-positive pathogen	50 (17.5)	14 (14.7)	36 (18.9)	.187
Fungal pathogen	6 (2.1)	2 (2.1)	4 (2.1)	>.999
Concomitant GN bacteremia[e]	10 (3.5)	4 (4.2)	6 (3.2)	.427

Table 1. Continued

Characteristic	Patients, Median (IQR) or No. (%)			*P* Value
	Total (N = 285)	≥35 mg/kg^2 (n = 95)	<35 mg/kg^2 (n = 190)	
Active antibiotic therapy prior to BL/BLI[f]				
Amikacin	18 (6.3)	8 (8.4)	10 (5.3)	.302
Aztreonam	4 (1.4)	0 (0)	4 (2.1)	.381
Cefepime	39 (13.7)	14 (14.7)	25 (13.2)	.715
Ciprofloxacin	5 (1.8)	1 (1.1)	4 (2.1)	.523
Colistin	6 (2.1)	0 (0)	6 (3.2)	.205
Levofloxacin	3 (1.1)	0 (0)	3 (1.6)	.523
Meropenem	29 (10.2)	10 (10.5)	19 (10)	.889
Polymyxin B	13 (4.6)	2 (2.1)	11 (5.8)	.159
Tobramycin	17 (6)	3 (3.2)	14 (7.4)	.157
Time to active therapy, d[g]	1.7 (0.6–2.4)	1.5 (1.3–2.4)	1.8 (0.5–2.4)	.344

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BL/BLI, β-lactam/β-lactamase inhibitor; COPD, chronic obstructive pulmonary disease; GN, gram-negative; ICU, intensive care unit; MDR, multidrug resistant; *P aeruginosa, Pseudomonas aeruginosa*; SOFA, sequential organ failure assessment.

[a]Hospital transfer: inclusive of transfers from an outside hospital as well as those within the same hospital system.

[b]Immunosuppression factors: neutropenia (absolute neutrophil count < 500), splenectomy (functional or surgical), high-dose corticosteroids (prednisone ≥20 mg/d or equivalent).

[c]Colonization with resistant organism defined as 2 positive cultures at least 3 months apart over the course of 12 months.

[d]Totals for each group may exceed the cohort total due to some polymicrobial cultures having ≥2 isolated pathogens.

[e]*P aeruginosa* isolated from the blood at any time during BL/BLI therapy for positive respiratory culture.

[f]Receipt of at least 1 dose of antipseudomonal therapy demonstrating susceptibility in vitro as defined per M100 (31st ed; Clinical and Laboratory Standards Institute).

[g]Time elapsed from index culture collection to the administration of active therapy.

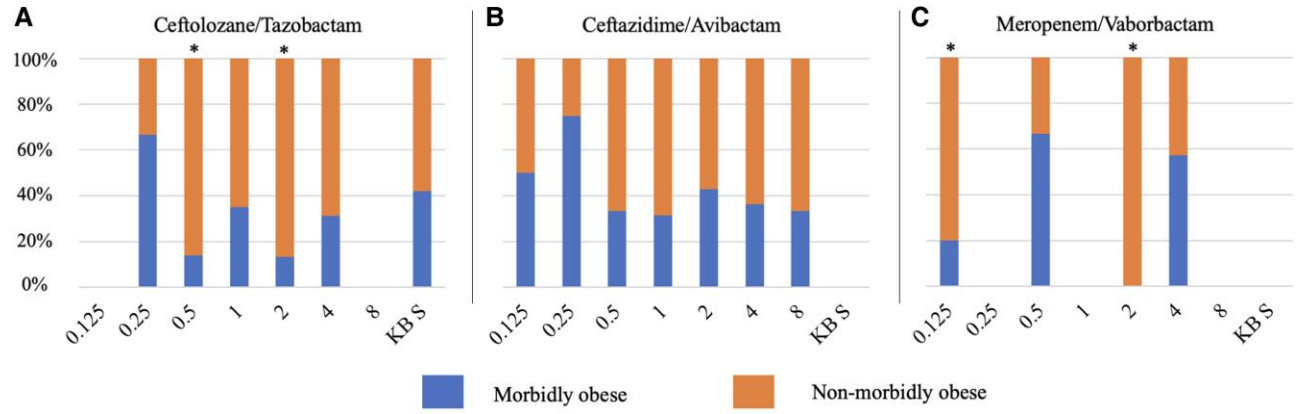
Charlson Comorbidity Index score, immunosuppression, and SOFA score were not significantly associated with presumed treatment failure ($P > .05$). In the multivariable logistic regression model (Table 4), morbid obesity (adjusted OR, 1.06; 95% CI, 1.02–1.79), prolonged time to BL/BLI initiation (1.47; 1.28–2.66), renal dose–adjusted BL/BLI in the first 48 hours of therapy (1.12; 1.09–1.75), and CRRT (1.35; 1.06–1.68) remained significant predictors of presumed treatment failure.

DISCUSSION

This study aimed to compare the clinical and safety outcomes in morbidly obese vs non–morbidly obese cases of *P aeruginosa* HABP/VABP among patients receiving ceftazidime/avibactam, ceftolozane/tazobactam, or meropenem/vaborbactam as definitive antibiotic therapy. Dose optimization of these novel agents has become necessary given the increased prevalence of multidrug-resistant *P aeruginosa* infections and limited therapeutic alternatives, especially in patients who are obese given their altered PK, which complicates PK/pharmacodynamic (PD) target attainment [10]. However, limited PK investigations and clinical outcome data exist to guide dosing of these agents in those who are morbidly obese with difficult-to-treat infections, and of the available literature, reported PK and clinical outcome data specific to individual BL/BLIs vary in terms of impact of morbid obesity.

In the current study, the primary composite outcome of presumed treatment failure occurred in 44.9% of the total cohort, which aligns with novel BL/BLI treatment failure in clinical trial and real-world retrospective studies [25–34]. However, clinical registry trial data for each novel BL/BLI are poorly generalizable to patients with morbid obesity due to the sparse number of patients with a BMI ≥35 kg/m^2 enrolled in each study. In ASPECT-NP and REPROVE—which respectively evaluated ceftolozane/tazobactam and ceftazidime/avibactam vs meropenem for the treatment of nosocomial pneumonia—the median BMI for the ceftolozane/tazobactam group was 27 (95% CI, 24–30) while the mean BMI for ceftazidime/avibactam was 23.7 (SD, 5.6) [35, 36]. Clinical trial data for meropenem/vaborbactam used to treat *P aeruginosa* HABP/VABP is lacking. Yet, in TANGO II—which evaluated meropenem/vaborbactam vs best-available therapy in patients with carbapenem-resistant Enterobacterales infection—the mean BMI for the meropenem/vaborbactam group was 27.2 (SD, 8.5), once again highlighting the sparse representation of patients with morbid obesity in novel BL/BLI clinical trials [37].

Only one outcome analysis has been conducted of novel BL/BLI among patients with morbid obesity enrolled in clinical trials [15]. Patients in that analysis participated in ASPECT-cIAI [38] or ASPECT-cUTI [39]: the phase 3 trials that evaluated ceftolozane/tazobactam for the treatment of complicated intra-abdominal infection (cIAI) or complicated urinary tract infection (cUTI), respectively. In the outcome analysis, clinical cure rates for cIAI and cUTI for patients with a BMI ≥35 kg/m^2 (17.2% and 9.1%) were similar to those for patients with a BMI <35 kg/m^2 (16.9% and 17%). This contrasts with the current study, which identified a significantly higher rate of presumed treatment failure in the morbidly obese group.



	Ceftolozane/tazobactam	Ceftazidime/avibactam	Meropenem/vaborbactam
Whole cohort	1 (0.2, 2)	1 (1, 2)	0.5 (0.125, 2)
Morbidly obese	1 (1, 1)	1 (0.25, 2)	0.5 (0.125, 4)
Non-morbidly obese	1 (0.5, 2)	1 (1, 2)	0.125 (0.125, 2)

Figure 1. Clinically reported antimicrobial susceptibility data of index culture isolates: *A*, ceftolozane/tazobactam; *B*, ceftazidime/avibactam; and *C*, meropenem/vaborbactam. MIC interpretive criteria established by M100 (31st ed; Clinical and Laboratory Standards Institute). Manual antimicrobial susceptibility tests included ETEST or Kirby-Bauer disk diffusion. MIC data are reported as median (IQR). $^*P < .05$: MIC differences between morbidly obese and non–morbidly obese groups. KB S, susceptible isolate per Kirby-Bauer test; MIC, minimum inhibitory concentration.

Variations between studies may be due to differences in the infectious sources evaluated (cIAI and cUTI vs HABP/VABP). Additionally, the definition of what constituted clinical cure or presumed treatment failure varied between studies. In the previous study [15], clinical cure was defined as "complete resolution or significant improvement in signs and symptoms of the index infection, such that no additional antimicrobials or interventions were required," whereas the current study focused on fraction of inspired oxygen readings and supplemental oxygen requirements, owing to the underlying infectious disease state of HABP/VABP.

To our knowledge, only 1 study has evaluated the target attainment of a novel BL/BLI used to treat *P aeruginosa* HABP/VABP in a patient with morbid obesity (BMI, 54.5 kg/m^2). In that single case report, ceftolozane/tazobactam was initially administered as recommended in the package insert (3 g intravenously every 8 hours via 1-hour infusion) but then switched to 9 g as a total daily dose administered via continuous infusion. Both regimens obtained adequate exposure (100% $fT > MIC$); however, a higher target (100% $fT > 4 \times MIC$) was achieved when 9 g was administered via continuous infusion. Notably, the patient was undergoing continuous venovenous hemodiafiltration during ceftolozane/tazobactam therapy and demonstrated higher total ceftolozane clearance and lower AUC as compared with patients who were nonobese [40–42]. In the current study, CRRT during BL/BLI therapy was an identified predictor of presumed treatment failure, highlighting the necessity for more data in this space. Additional PK simulations of ceftolozane in patients who were obese, based on a PK model developed in patients with a mean BMI of 27.3 kg/m^2 (range, 17–56), identified increased systemic ceftolozane clearance and a larger volume of distribution; yet, adequate target attainment was achieved at ceftolozane MICs up to 8 mg/L [15].

For ceftazidime/avibactam, 2 small PK studies conducted in patients with obesity demonstrated high variability and suboptimal serum concentrations of ceftazidime, with inadequate target attainment at MIC ≤8 mg/L, even with a dosing regimen of 2.5 g every 8 hours [43, 44]. In one of the studies, higher urinary creatinine clearance was identified as a risk factor for PK target failure in patients who were obese [43]. Another PK study comparing patients who were obese and non–morbidly obese with cUTI revealed that although the maximum concentration of ceftazidime/avibactam was slightly lower in the obese group, the total drug exposure was comparable between the groups. Additionally, early renal dose adjustments of ceftazidime/avibactam may add a level of complexity for dosing considerations in the obese cohort, given that a systematic review and meta-analysis of 11 observational studies identified that in patients with carbapenem-resistant gram-negative infections who were receiving ceftazidime-avibactam, early renal dose adjustments were associated with increased odds of mortality [45]. In the current study, renally adjusted BL/BLI in the first 48 hours of therapy was associated with increased odds of presumed treatment failure, highlighting another important consideration for individualized dosing of novel BL/BLI.

PK data for meropenem/vaborbactam use in patients with obesity are lacking, being limited to meropenem-specific PK. A population PK study demonstrated that meropenem PK

Table 2. Infection Management and Clinical Course

Characteristic	Patients, Median (IQR) or No. (%)			*P* Value
	Total (n = 285)	≥35 mg/kg^2 (n = 95)	<35 mg/kg^2 (n = 190)	
BL/BLI				
Ceftazidime/avibactam	73 (25.6)	29 (30.5)	44 (23.2)	.179
Ceftolozane/tazobactam	170 (59.6)	54 (56.8)	116 (61.1)	.495
Meropenem/vaborbactam	42 (14.7)	12 (12.6)	30 (15.8)	.478
Time to BL/BLI, d[a]	3.4 (2.1–4.8)	3.9 (2.5–5.1)	3.3 (2.1–4.7)	.594
During BL/BLI therapy				
RRT: hemodialysis or continuous	41 (14.4)	15 (15.8)	26 (13.7)	.293
Augmented renal clearance	60 (21.1)	18 (18.9)	42 (22.1)	.538
Concomitant systemic antipseudomonal therapy[b]				
Amikacin	17 (6)	5 (5.3)	12 (6.3)	.724
Ciprofloxacin	10 (3.5)	4 (4.2)	6 (3.2)	.649
Colistin IV	14 (4.9)	8 (8.4)	6 (3.2)	.052
Gentamicin	6 (2.1)	4 (4.2)	2 (1.1)	.081
Polymyxin B	14 (4.9)	5 (5.3)	9 (4.7)	.846
Tobramycin IV	12 (4.2)	4 (4.2)	8 (4.2)	.986
Infectious disease consult	275 (96.5)	93 (97.9)	182 (95.8)	.082
Duration of BL/BLI therapy	7.9 (5.5–13.3)	8.6 (5.6–13.2)	7.6 (5.3–13.3)	.532
Repeat negative culture	55 (19.3)	20 (21.1)	35 (18.4)	.444
Treatment-emergent BL/BLI resistance	2 (2.3)	1 (1.1)	1 (0.5)	.558
Length of stay, d				
Hospital	30 (16–52)	32.5 (18.75–53)	28 (15–52)	.165
Intensive care unit	14 (8–30)	15 (11–39.3)	13.5 (6.25–26.8)	.831
Discharge disposition				
Home	50 (17.5)	6 (6.3)	44 (23.2)	<.001
Nursing home/long-term care facility	122 (42.8)	45 (47.4)	77 (40.5)	.271
Rehabilitation center	23 (8.1)	8 (8.4)	15 (7.9)	.878
Hospice	20 (7)	6 (6.3)	14 (7.4)	.743
Morgue	64 (22.5)	27 (28.4)	37 (19.5)	.086
Infection-related 30-d readmission (to index)	17 (6)	5 (5.3)	12 (6.3)	.724
Microbiological recurrence within 30 d	82 (28.8)	15 (15.8)	67 (35.3)	.458
Symptomatic	30 (10.5)	11 (11.6)	19 (10)	.174
Treated	30 (10.5)	10 (10.5)	20 (10.5)	.404

Abbreviations: BL/BLI, β-lactam/β-lactamase inhibitor; IV, intravenous; RRT, renal replacement therapy.

[a]Time elapsed from index culture collection to the administration of BL/BLI therapy.

[b]Concomitant therapy: anti-*Pseudomonas* antibiotic administered for ≥48 hours while the patient was receiving definitive BL/BLI therapy.

parameters did not differ between patients with and without obesity and that administration via extended infusion achieved higher target attainment across all body weight groups [46]. However, as with ceftolozane, receiving CRRT during meropenem therapy was associated with a lower likelihood of reaching therapeutic targets in patients who were critically ill and morbidly obese [44]. Use of extended- or continuous-infusion meropenem with therapeutic drug monitoring did improve target attainment in those who were obese [47].

Notable limitations of this study include its retrospective study design, which limits the ability to establish causal relationship between treatment and outcomes. In addition, although the study was multicenter, enrolled patients were admitted to 2 large health care systems in a single metropolitan area, which may reduce generalizability. Furthermore, while propensity score analysis was used to address potential confounding factors and minimize bias, there may still be unmeasured confounding factors that could affect the outcomes. Unmeasured confounding may be evident in the current study wherein patients with and without morbid obesity demonstrated similar hospital and ICU lengths of stay, as well as similar durations of BL/BLI therapy, even though patients in the morbid obesity group had a significantly higher rate of presumed treatment failure, which differs from previous data [3, 48, 49]. Another possible limitation is our use of a composite endpoint to improve the ability to detect differences in the primary outcome between groups; however, we did report individual endpoints in the primary outcome for clarity and conducted a power analysis based on available data. Additionally, while the definition for morbid obesity used in the current study (BMI ≥35 mg/kg^2) aligns with that in a similar study [15], obesity quantification definitions in the literature vary widely; thus,

Table 3. Unadjusted and Adjusted Clinical Outcomes

Outcome	Full Cohort, No. (%)				Propensity Score IPTW Cohort	
	≥35 mg/kg^2 (n = 95)	<35 mg/kg^2 (n = 190)	*P* Value	OR (95% CI)	*P* Value	aOR (95% CI)
Presumed treatment failure	56 (58.9)	72 (37.9)	.021	1.545 (1.326–1.913)	.038	1.675 (1.465–1.979)
All-cause in-hospital mortality[a]	27 (28.4)	37 (19.5)	.076	1.187 (.707–1.501)	.194	0.762 (.506–1.148)
Continuation of infectious symptoms[b]	29 (30.5)	35 (18.4)	.025	1.521 (1.293–1.925)	.003	1.550 (1.369–1.821)
Treatment-emergent adverse event[c]						
Nephrotoxicity	7 (7.4)	6 (3.2)	.111	0.412 (.135–1.263)	.128	1.363 (.747–1.894)
Clostridioides difficile	5 (5.3)	7 (3.7)	.370	1.444 (.446–4.678)	.567	0.773 (.319–1.870)
Hepatotoxicity	2 (2.1)	5 (2.6)	.568	1.264 (.241–6.637)	.653	1.332 (.381–4.650)

Abbreviations: aOR, adjusted odds ratio; BL/BLI, β-lactam/β-lactamase inhibitor; IPTW, inverse probability of treatment weighting; OR, odds ratio.

[a]Starting from the end of the first 72 hours of BL/BLI therapy.

[b]Elevated ratio of partial pressure of arterial oxygen to fraction of inspired oxygen and/or increased supplemental oxygen requirements after the first 72 hours through the end of BL/BLI therapy as compared with baseline.

[c]Treatment-emergent adverse effects included nephrotoxicity and/or hepatotoxicity during therapy or *Clostridioides difficile*–associated diarrhea within 30 days of the end of BL/BLI therapy.

Table 4. Multivariable Logistic Regression Model of Predictors for Presumed Treatment Failure

Predictor[a]	aOR	95% CI
Morbid obesity (BMI ≥35 mg/kg^2)	**1.06**	**1.02–1.79**
Time to BL/BLI therapy	**1.47**	**1.28–2.66**
Renal dose-adjusted BL/BLI in the first 48 h of therapy [b]	**1.12**	**1.09–1.75**
CRRT during BL/BLI therapy	**1.35**	**1.06–1.49**
Concomitant antipseudomonal therapy [c]	0.78	.22–1.68

Bold indicates $P < .05$.

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; BL/BLI, β-lactam/β-lactamase inhibitor combination; CRRT, continuous renal replacement therapy.

[a]Univariate analysis predictors with $P \geq .2$ were excluded from the multivariable logistic regression model (Charlson Comorbidity Index score, immunosuppression, Sequential Organ Failure Assessment score, and BL/BLI minimum inhibitory concentration).

[b]Renal dose adjustment according to the packet insert. Patients who had a creatinine clearance <30 mL/min and/or were undergoing hemodialysis were excluded from the analysis.

[c]Concomitant therapy: anti-*Pseudomonas* antibiotic administered for ≥48 hours while the patient was receiving definitive BL/BLI therapy.

the findings of this study may not be generalizable in populations were other obesity classifications are used. Finally, this study lacked BL/BLI PK data in the form of serum BL/BLI concentrations, so we are unable to eliminate subtherapeutic dosing as a possible factor in presumed treatment failure cases.

In summary, limited data exist to guide BL/BLI dosing in patients who are morbidly obese and have *P aeruginosa* HABP/VABP. Furthermore, interpretation of BL/BLI exposure, especially at the site of infection, is difficult given the PK variabilities in such populations. Therapeutic drug monitoring–based dosing coupled with modified dosing administrations may be warranted for select scenarios to achieve PD targets, especially in patients who are critically ill and obese.

Notes

Patient consent statement. This study does not include factors necessitating patient consent.

Financial support. This work was supported by the National Institute of Allergy and Infectious Diseases (R21 AI163726 to M. J. R.).

Potential conflicts of interest. M. J. R. has received funds for research and consulting or participated in speaking bureaus for Abbvie, Entasis, Ferring, Melinta, Merck, Paratek Pharmaceuticals, Shionogi, Tetraphase, and T2 Bioscience. All other authors report no potential conflicts.

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