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CLINICAL THERAPEUTICS

Clinical and Microbiological Outcomes in Obese Patients Receiving Colistin for Carbapenem-Resistant Gram-Negative Bloodstream Infection

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ABSTRACT Carbapenem-resistant infections are associated with poor outcomes, and treatment options are limited. Colistin is one of few antibiotics which retain *in vitro* activity against carbapenem-resistant pathogens. However, despite the availability of international consensus guidelines for the dosing of polymyxins, there are limited data on the effects of dosing on clinical outcomes among obese patients with carbapenem-resistant Gram-negative bacteremia. This retrospective study evaluated whether obesity was associated with day 7 global cure rates among patients with carbapenem-resistant Gram-negative bacteremia who were treated with an ideal body weight (IBW)-based colistin dosing regimen. Secondary outcomes included microbiological cure, clinical cure, length of hospital stay, in-hospital mortality, and day 7 acute kidney injury. After screening to identify 167 patients, 77 (46.1%) and 90 (53.9%) were classified as obese and nonobese, respectively. Patient characteristics were well balanced at baseline, except that obese patients were more often female and received a higher daily dose per IBW (3.7 versus 2.9 mg/kg/day, $P = 0.03$). Global cure rates were similar between groups (44.2% for obese versus 55.6% for nonobese, $P = 0.14$). After adjusting for baseline differences, obesity was not a significant predictor of global cure (adjusted odds ratio [AOR], 0.59; 95% confidence interval [CI], 0.31 to 1.11; $P = 0.10$). Obesity was associated with a lower likelihood of microbiological clearance (72.7% versus 91.1%, $P = 0.02$). No other secondary outcome differences were observed, though each outcome was numerically worse among obese patients. Obesity was not associated with differences in global cure rates. However, the difference in microbiological clearance warrants further investigation.

KEYWORDS bacteremia, carbapenem resistant, colistin, polymyxins

The incidence of severe Gram-negative multidrug-resistant (MDR) nosocomial infections is increasing (1). MDR pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* account for high mortality, especially in critically ill patients (1–4). Colistin is among the few remaining therapies that can be used to treat MDR Gram-negative bloodstream infection. However, until recently, colistin pharmacokinetics (PK) were poorly understood.

Recent advances in the understanding of colistin PK (5) have led to changes in the package insert dosing recommendations in both the United States and the European Union (6). Current United States colistin labeling recommends dosing based on ideal body weight (IBW) with subsequent adjustments based on renal function, whereas the European labeling suggests standard (non-weight-based) doses adjusted based on renal function. Furthermore, recent PK studies suggest that colistin should be administered initially as a one-time loading dose based on IBW, with the maintenance dose

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dependent on target steady-state concentration and estimated creatinine clearance (1, 7, 8). Recent international consensus guidelines on the optimal use of polymyxins suggest using a standard loading dose of 300 mg colistin base activity (CBA), followed by a non-weight-based maintenance dose that is adjusted for renal function (9). However, the guideline dosing recommendations were largely derived from PK analyses, with minimal clinical investigations in obese patients.

Changes in antimicrobial PK have been well documented in obese patients, which can impact clinical success and risk of toxicity (10). As the prevalence of adult obesity exceeds 30% in the United States (11), these considerations are now more relevant than ever. With the discrepancy between current consensus guidelines and package insert dosing recommendations (weight-based versus non-weight-based), investigations in obese patients are warranted, since this population is potentially susceptible to underdosing. To date, three studies have evaluated adverse outcomes associated with colistin dosing in obese patients (12–14). Gauthier and colleagues evaluated risk factors associated with acute kidney injury (AKI) in overweight and obese patients and found that a body mass index (BMI) of $\geq$31.5 kg/m^2 was an independent risk factor associated with AKI (13). DeRyke and colleagues evaluated 30 patients who received colistin and determined that overdosing obese patients using actual body weight (ABW) corresponded with increased incidence of nephrotoxicity (12). Both of these studies were performed at a time when colistin PK was less well understood and weight-based dosing regimens were more heterogeneous. Colistin dosing guidelines at our institution correspond to recommendations in the updated FDA product label (8), utilizing a renally adjusted maintenance dose that is based upon IBW. This study evaluated whether obese patients, dosed according to IBW, have similar clinical and adverse outcomes as nonobese patients.

RESULTS

Three hundred thirty patients were screened for inclusion, with 163 excluded due to receipt of colistin for $<$72 h ($n = 87$), lack of documented bloodstream infection ($n = 70$), and polymicrobial infection ($n = 6$). The remaining 167 patients were included, with 90 (53.9%) classified as nonobese and 77 (46.1%) classified as obese. Baseline, microbiological, and treatment characteristics are summarized in Table 1. Overall, patients were well balanced between groups, except that obese patients were numerically less likely to be male (42.9% versus 56.7%, $P = 0.075$) and received a higher median milligram/kilogram IBW/day dose (3.7 versus 2.9 mg/kg/day, $P = 0.03$). As expected, the milligram/kilogram ABW/day dose had the opposite trend (2.0 versus 2.6 mg/kg/day, $P < 0.001$). The majority of patients (94.6%) were in the intensive care unit (ICU) when bacteremia was diagnosed, with no difference between groups. Baseline severity of illness scores and use of organ-supportive therapy (vasopressor, mechanical ventilation, and dialysis) were similar between groups. The use of combination therapy during the first 7 days of therapy, times to receipt of colistin, pathogenic species distributions, and MIC distributions were also similar between groups. Among those with central venous catheters at the time of bacteremia identification, the frequencies of documented catheter removal within 48 h were similar between groups (63% versus 73%, $P = 0.20$).

Overall, 50 nonobese patients (55.6%) and 34 obese patients (44.2%) experienced global cure ($P = 0.14$) (Fig. 1). A multivariable logistic regression model, which included sex and dose (per mg/kg IBW/day) did not find obesity to be a significant independent predictor of day 7 global cure (adjusted odds ratio, 0.59; 95% confidence interval [CI], 0.31 to 1.11; $P = 0.10$) (Table 2). Since such a large proportion of patients required renal replacement therapy at baseline, a stratified analysis was performed, which also did not reveal any differences in global cure rates between obese and nonobese patients (dialysis patient cure rates, 31.6% versus 35.9%, $P = 0.69$; nondialysis patient cure rates, 56.4% versus 70.6%, $P = 0.16$).

Secondary outcomes are shown in Fig. 1 and Table 3. When evaluating the individual components of global cure, obesity was associated with a significantly lower

TABLE 1 Baseline patient, pathogen, and treatment characteristics

Characteristic[a]	Value for: Nonobese ($n = 90$)	Obese ($n = 77$)	P value
Male (n [%])	51 (56.7)	33 (42.9)	0.075
Age (yrs) (median [IQR])	61.7 (51.1–70.2)	59.6 (49.1–67.9)	0.47
BMI (kg/m^2) (median [IQR])	24.7 (20.6–27.4)	35.6 (32.9–42.7)	<0.001
IBW (kg) (median [IQR])	65.0 (52.4–73.0)	59.3 (54.7–73.0)	0.43
ABW (kg) (median [IQR])	69.7 (59.6–80.9)	103.0 (89.8–124.5)	<0.001
LOS, prior (days) (median [IQR])	24.4 (9.6–38.8)	15.8 (4.6–35.9)	0.17
ICU (n [%])	83 (92.2)	75 (97.4)	0.18
SCr (mg/dl) (median [IQR])	1.5 (0.8–2.3)	1.3 (0.8–2.2)	0.16
Dialysis (n [%])	39 (43.3)	38 (49.8)	0.44
IHD	20 (22.2)	13 (16.9)	
CRRT	19 (21.1)	25 (32.5)	
Vasopressors (n [%])	33 (36.7)	36 (46.8)	0.19
Mechanical ventilation (n [%])	60 (66.7)	53 (68.8)	0.77
CCI (median [IQR])	3 (2–5)	3 (1–4)	0.64
PBS (median [IQR])	4 (2–6)	4 (3–6)	0.29
SOFA (median [IQR])	8 (5–11)	9 (6–12)	0.17
Bacteremia source (n [%])			0.19
High risk	49 (54.4)	34 (44.2)	
Low risk	41 (45.6)	43 (55.8)	
Pathogen (n [%])			0.59
P. aeruginosa	28 (31.1)	22 (28.6)	
K. pneumoniae	36 (40)	28 (36.4)	
A. baumannii	23 (25.6)	26 (33.8)	
Other	3 (3.3)	1 (1.3)	
Colistin MIC (μg/ml) (median [IQR])	2.0 (0.5–2.0)	1.0 (0.5–2.0)	0.31
Time to receipt of colistin (h) (median [IQR])	66.2 (28.1–101.5)	53.4 (24.2–82.1)	0.32
Loading dose (n [%])	37 (41.1)	36 (46.8)	0.46
Dose (mg/kg IBW/day) (median [IQR])	2.9 (2.1–4.1)	3.7 (2.1–5.0)	0.03
Dose (mg/kg ABW/day) (median [IQR])	2.6 (1.6–3.7)	2 (1.3–2.8)	<0.001
Average daily dose (mg) (median [IQR])	194.0 (125–250)	212.5 (150–279.3)	0.049
Monotherapy (n [%])	14 (15.6)	9 (11.7)	0.47
Concomitant therapy (n [%])			
Aminoglycoside	30 (33.3)	29 (37.7)	0.56
Carbapenem	31 (34.4)	13 (16.9)	0.66
Tigecycline	35 (38.9)	33 (42.9)	0.60
Ceftazidime-avibactam	10 (11.1)	6 (7.8)	0.47
Ceftolozane-tazobactam	5 (5.6)	6 (7.8)	0.56
Duration of treatment (days) (median [IQR])	9.1 (5.5–12.0)	8.6 (4.8–12.8)	0.95

[a]ABW, actual body weight; BMI, body mass index; CCI, Charlson comorbidity index; CRRT, continuous renal replacement therapy; IBW, ideal body weight; ICU, intensive care unit; IHD, intermittent hemodialysis; IQR, interquartile range; LOS, length of stay; PBS, Pitt bacteremia score; SCr, serum creatinine; SOFA, sequential organ failure assessment.

likelihood of microbiological clearance (72.7% versus 91.1%, $P = 0.02$). Two patients did not have follow-up culture data (both in the nonobese group) who were deemed to have microbiological clearance based on clinical improvement. No other differences in secondary efficacy outcomes (clinical improvement at day 7, in-hospital mortality, and length of stay [LOS] after bacteremia) were observed between obese and nonobese patients. The incidences of AKI were also similar between groups, with no differences in the distributions of the different stages of AKI.

DISCUSSION

Dosing of colistin remains a challenge, despite advances in the understanding of its PK. Enhanced understanding of colistin PK has led to changes in product labeling internationally. However, a recent PK evaluation of the different novel dosing recom-

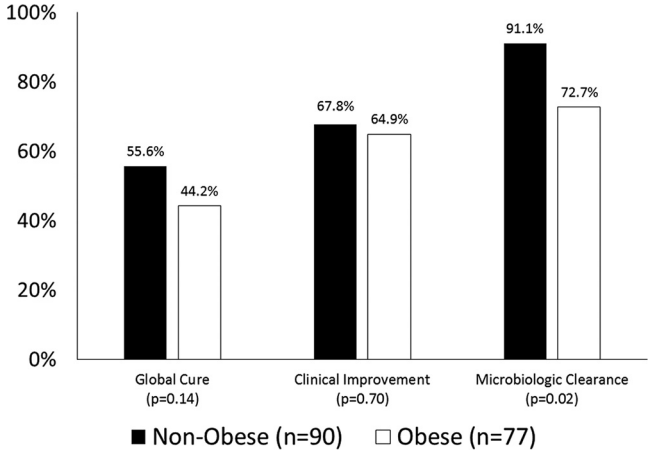

FIG 1 Primary and secondary outcome comparisons of obese and nonobese patients receiving colistin for the treatment of carbapenem-resistant Gram-negative bacteremia.

mendations demonstrated that pharmacodynamic target attainment was still extremely variable, particularly when patients had good renal function or the dosing regimen was attempting to target a higher average steady-state concentration (6). Current dosing recommendations suggest either IBW-based or non-weight-based dosing; however, few clinical studies have evaluated these dosing recommendations among obese patients. This retrospective study evaluated whether obesity affects patient outcomes in those with carbapenem-resistant bacteremia treated with intravenous colistin. While no significant difference in the primary outcome of day 7 global cure was observed, all efficacy outcomes were numerically worse in obese patients, with microbiological clearance being significantly lower.

These findings in obese patients warrant further discussion. Existing colistin PK models were derived from a limited number of patients, with few in the extremes of patient weight. Indeed, the highest patient body weight evaluated in the most recent PK model evaluations was 122 kg (1, 7). Furthermore, while the volume of distribution of colistimethate (prodrug of active colistin) is consistently found to be low (5.3 to 13.5 liters), the volume of distribution of formed colistin varies drastically (7.2 to 189.0 liters) (5). Although the low volume of distribution of colistimethate potentially supports the use of IBW-based dosing, the potentially high volume of distribution of formed colistin may give one pause when dosing obese patients by IBW. Given the complexity and interpatient variability of colistin PK, more clinical evaluations are required to assess patient outcomes based on contemporary dosing recommendations.

In the present study, obese patients received a higher dose based on IBW than nonobese patients. Since the use of renal replacement therapy and baseline renal function were similar between groups, this difference in dosing is likely due to clinician biases to dose obese patients more aggressively. However, despite receipt of a higher median daily dose, obese patients had numerically poorer efficacy outcomes. Previous studies have consistently demonstrated that a higher dose of colistin corresponds with improved infectious outcomes, albeit with increased nephrotoxicity. In a retrospective, single-center cohort study by Falagas and colleagues, it was concluded that mortality among patients who received an average daily colistin dose of 100 mg CBA (38.6%) was

TABLE 2 Multivariable regression: global cure

Factor	Adjusted odds ratio (95% CI[a])	*P* value
Male	0.85 (0.46–1.58)	0.60
Dose (per mg/kg IBW[b]/day)	1.07 (0.89–1.29)	0.46
Obese	0.59 (0.31–1.11)	0.10

[a]CI, confidence interval.
[b]IBW, ideal body weight.

TABLE 3 Secondary efficacy and safety outcomes

Outcome[a]	Value for: Nonobese ($n = 90$)	Obese ($n = 77$)	*P* value
Day 7 mortality (*n* [%])	19 (21.1)	19 (24.7)	0.58
In-hospital mortality (*n* [%])	41 (45.6)	43 (55.8)	0.18
LOS, postbacteremia (days) (median [IQR])	14.0 (7.2–26.5)	12.8 (7.5–27.1)	0.50
AKI (*n* [%])	22 (43.1), $n = 51$	21 (53.8), $n = 39$	0.31
Stage 1	8 (36.4)	6 (28.6)	
Stage 2	6 (27.3)	6 (28.6)	
Stage 3	8 (36.4)	9 (42.9)	

[a]AKI, acute kidney injury; IQR, interquartile range; LOS, length of stay.

higher than the mortality among patients who received 200 mg CBA (27.8%) and 300 mg CBA (21.7%) (15). Furthermore, Gibson and colleagues, using a classification and regression tree analysis-derived cutoff, determined that patients who received >4.4 mg CBA/kg/day based on IBW were more likely to achieve global cure, microbiological clearance, and day 7 survival (16). As such, the findings of the present study appear to be contrary to those of previous studies, since obese patients were being dosed more aggressively but had similar or worse outcomes. It is possible that if obese patients were not dosed more aggressively, further differences in outcome may have been observed.

The majority of the patients from this study were admitted to an ICU, with the use of vasopressors, mechanical ventilation, and renal replacement therapy similar between obese and nonobese patients. Numerous studies have evaluated outcomes associated with obese patients in the critical care setting, with discrepant results. However, several meta-analyses have found improvements among obese critically ill patients (17–19), a phenomenon that has been called the "obesity paradox." Our study found no significant differences in mortality, with obese patients experiencing a numerically higher (10.2%) in-hospital mortality. Existing studies on obesity and outcomes in critically ill patients do not take into account the potential effects of antimicrobial PK. It is possible that the discrepant results observed in these studies may be associated with underlying patient selection.

This study has several limitations. Due to the retrospective nature of the study, there may be unaccounted baseline differences between groups. The design of the study excluded patients who received colistin for <72 h, which may have excluded patients who died shortly after the receipt of colistin. This exclusion criterion was incorporated because it would be difficult to ascertain the effects of colistin on global cure if therapy for a shorter time period was included, and previous studies utilized similar inclusion criteria (15). A second limitation, common to many single-center studies, is the external validity of the findings. Due to differences in local pathogen epidemiology and MIC distribution, the present study findings may not be applicable to other centers. In our study, the range of colistin MICs was 0.5 to 2 μg/ml, which is similar to other centers (20). However, the present findings may not be applicable to institutions with dramatically different colistin MIC distributions. It should also be noted that commercially available colistin susceptibility testing frequently produces disparate results, which may further complicate susceptibility interpretation across different institutions (21). Furthermore, colistin dosing protocols vary widely; therefore, these results may also differ from those of an institution where renal dose adjustments are performed differently. The time to first *in vitro*-active therapy was not evaluated in the present study. However, in our local practice, it is rare to provide empirical coverage against carbapenem-resistant pathogens unless there has been a history. Hence, it is likely that colistin was the first active agent prescribed to these patients. As such, the findings from this study may also not apply to centers that routinely provide empirical therapy with activity against carbapenem-resistant pathogens. Lastly, this study may have been underpowered to detect a smaller difference in global cure rates. This study was powered to detect a 20% absolute difference in the primary outcome. Numerically, this study observed a lower

TABLE 4 Colistin dosing regimen during the study period

Colistin dose (mg/kg IBW)	Renal function[a]
3, optional dose load	All
1.5 (q8h)	CrCl of ≥30 ml/min or CRRT
1.5 (q12h)	CrCl of 10–30 ml/min
1.5 (q24h)	CrCl of <10 ml/min or IHD

[a]CrCl, creatinine clearance calculated using Cockcroft-Gault equation (using adjusted body weight for obese patients and ideal body weight for nonobese patients); CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis.

global cure rate among obese patients (44.2% versus 55.6%); however, this 11.4% absolute difference was not enough of a treatment effect for statistical significance. It is possible that a smaller, but still clinically significant, difference exists, which was not detected by this study. Hence, the conclusions from the present findings should be that there is no more than a 20% difference in global cure rates between obese and nonobese patients.

In this study, obesity was not associated with differences in global cure rates in patients treated with colistin for carbapenem resistant Gram-negative bloodstream infection. However, all efficacy outcomes, including global cure, clinical improvement, microbiological clearance, and day 7 and in-hospital mortality, were numerically worse among obese patients. The significant difference observed in microbiological clearance warrants further investigation.

MATERIALS AND METHODS

A retrospective cohort study was performed on all patients at a large, academic, tertiary-care medical center who received intravenous colistin (as colistimethate sodium) for at least 72 h for the treatment of a carbapenem-resistant Gram-negative bacterium bloodstream infection (CR-GNB BSI) from January 2010 to October 2017. Carbapenem resistance was defined as a MIC of ≥1 μg/ml of ertapenem or ≥2 μg/ml of doripenem, imipenem, or meropenem. Patients were excluded if they were less than 18 years of age, received colistin for less than 72 h, or had polymicrobial bacteremia. Furthermore, only the first CR-GNB BSI episode that met all inclusion criteria was included. This study was approved by the local institutional review board.

After inclusion, patients were divided into two cohorts based on BMI: obese patients (≥30 kg/m^2) and nonobese patients (<30 kg/m^2). Daily colistin dose, reported as milligram/kilogram of CBA was collected for the first 7 days of therapy from a review of the medication administration record (30 mg of CBA = 1 million IU). Receipt of ≥3 mg/kg IBW on day 1 of therapy was recorded to determine the use of a loading dose. The dosing protocol and renal dose adjustments used during the study period can be found in Table 4. Patients' ABW and BMI were collected, and IBW was calculated as follows: male IBW = 50 kg (+ 2.3 kg for every inch over 5 feet), female IBW = 45.5 kg (+ 2.3 kg for every inch over 5 feet) (22).

The primary objective was to determine if rates of global cure at day 7 of therapy are similar between obese and nonobese patients. Global cure was a composite endpoint defined as clinical improvement and microbiological clearance by day 7. Clinical improvement was defined as having a white blood cell count (WBC) of less than 12,000 cells/mm^3 or a ≥25% reduction in WBC, being afebrile for ≥48 h, and being hemodynamically stable without the need for vasopressors. Microbiological clearance was defined as eradication of the original causative organism from subsequent blood cultures by day 7 of therapy, whereas microbiological failure was defined as persistence of the original causative organism in the subsequent blood cultures by day 7. In the absence of follow-up culture data, patients with clinical improvement were deemed to have microbiological clearance. Secondary objectives included evaluating the individual components of the composite global cure outcome, hospital length of stay (LOS), day 7 mortality and AKI, and overall in-hospital mortality. Nephrotoxicity was defined using the criteria provided by the Kidney Disease Improving Global Guidelines (KDIGO), where AKI was defined as an increase in serum creatinine (SCr) of ≥0.3 mg/dl within 48 h or ≥1.5 times baseline within 7 days (23). AKI was further staged into 3 categories: stage 1, increased SCr 1.5 to 1.9 times baseline; stage 2, increased SCr 2.0 to 2.9 times baseline; and stage 3, increased SCr ≥3.0 times baseline, absolute value ≥4.0 mg/dl, or requirement of renal replacement therapy. Patients with baseline end-stage renal disease or requiring renal replacement therapy on day 1 of therapy were excluded from the nephrotoxicity analysis.

Data collected from each patient's medical record included demographics (age and sex), height, weight, components of the Pitt bacteremia score (PBS) used to predict mortality risk in the setting of BSI (24), components of the Charlson comorbidity index (CCI) (25), components of the sequential organ failure assessment score (SOFA) (26), culture data, source of bacteremia (as documented in the medical record by the treating physicians), daily colistin dose, concomitant antibiotic therapy (defined as any aminoglycoside, carbapenem, tigecycline, or other agent that was added to colistin therapy within 24 h of colistin initiation), timing of antibiotic therapy, daily temperature and white blood cell count, and mortality. Source of bacteremia was further categorized based on associated risks for mortality as previously described: low risk (catheter, genitourinary, pancreaticobiliary) and high risk (lung, peritoneum, unknown) (27).

Assuming a global cure rate of 50% in the nonobese group (16, 28), 166 patients would be needed to achieve an 80% power with an alpha of 0.05 in a one-tail test to detect a 20% absolute difference between groups. Categorical data were analyzed using either the χ^2 test or Fisher's exact test, as appropriate. Continuous data were analyzed using the Mann-Whitney U test. The Mann-Whitney U test was chosen for continuous data as a conservative measure because of the challenge of determining normality with a small data set. The primary objective was assessed using multivariable logistic regression to assess for independent predictors of global cure. Factors entered into the multivariable logistic model included obesity and any baseline differences between groups that had a P value of <0.1 on bivariate analysis. Correlation matrix was utilized, and factors which were colinear were systematically eliminated from the final multivariable logistic regression to preserve the overall predictive ability of the model. All statistical analyses were performed using STATA version 14.0 for Windows (StataCorp, College Station, TX).

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