Association Between Colistin Dose and Microbiologic Outcomes in Patients With Multidrug-Resistant Gram-Negative Bacteremia

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Background. Colistin is increasingly used for the treatment of multidrug-resistant gram-negative infections. However, colistin dosing varies greatly and the optimal regimen is unknown. The purpose of this study was to determine if colistin dosing correlates with patient outcomes.

Methods. This retrospective study included patients with gram-negative bacteremia treated with intravenous colistin for at least 72 hours. The primary objective was to determine if colistin dose (mg of colistin base activity/kg/day) independently predicts day-7 microbiological success. Secondary objectives included evaluation for an association between colistin dose and 7-day mortality, 28-day mortality, and the development of acute kidney injury (AKI).

Results. Seventy-six patients were included in the analysis, with 52 patients (68%) achieving 7-day microbiological success. The median colistin dose was significantly higher in patients who achieved microbiological success (2.9 vs 1.5 mg/kg/day; P = .011). After adjusting for baseline severity of illness and concomitant tigecycline use, higher colistin dose independently correlated with microbiological success (adjusted odds ratio per 1 mg/kg/day = 1.74; 95% confidence interval, 1.11–2.71; P = .015). The median colistin dose was also significantly higher among survivors at day 7 (2.7 vs 1.5 mg/kg/day; P = .007). However, no difference was observed in colistin dose when comparing survivors and nonsurvivors at day 28. A significantly higher colistin dose was given to patients who developed AKI during therapy (3.8 vs 1.6 mg/kg/day; P < .001).

Conclusions. Higher colistin dose independently predicted microbiological success, which may partially explain the similar association with 7-day mortality. However, higher colistin doses may also precipitate worsening renal function.

Keywords. colistin; gram-negative; hepatitis C; bacteremia.

INTRODUCTION

Gram-negative bacteria (GNB) are the most common cause of nosocomial bloodstream infections [1–3]. Sepsis associated with GNB is associated with significant morbidity and mortality [4, 5]. The timely administration of appropriate antibiotics is paramount in the treatment of sepsis [6, 7]. However, the increasing rates of resistance among GNB presents significant therapeutic challenges for clinicians. In particular, the proliferation of carbapenem-resistant Enterobacteriaceae [8] has prompted a revival in the use of systemic colistin.

Colistin is a bactericidal antibiotic first discovered and used approximately 60 years ago. However, concerns of adverse effects, including nephrotoxicity and neurotoxicity, limited its use [9]. Due to colistin’s early approval and minimal clinical experience with the drug, little is known about the best way to utilize this medication [9]. Given the crucial role of colistin in current practice, it is imperative to optimize its dosing to maximize effect and decrease emergence of resistance, while minimizing toxicities.
Clinically, there is not a universally accepted dosing recommendation for colistin. However, the renewed interest in the use of colistin has led to some further understanding of its pharmacokinetics (PK) and dosing. A recent small study of 18 critically ill patients demonstrated that the maximum steady-state plasma concentration of colistin, dosed according to package insert recommendations, was 2.3 mg/L [10], which is only slightly above the susceptibility breakpoint of 2 mg/L for *Pseudomonas aeruginosa* and *Acinetobacter baumannii* set by the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing [11, 12]. In light of a pharmacodynamic (PD) target that relies on maximizing peak plasma concentrations, the current dosing scheme for colistin may be inadequate [10]. Furthermore, the current package insert for colistin suggests drastic dose reductions for renal insufficiency [13], which may be beyond what is necessary based on recent data [14].

In light of colistin’s crucial role as one of the last-line options for the treatment of multidrug-resistant organisms, and suggestions from recent literature that the current dosing recommendations may be inadequate to provide optimal activity, further investigations on colistin dosing are warranted. As such, this study sought to determine whether an association exists between colistin dose and microbiological eradication rate in patients with carbapenem-resistant gram-negative bacteremia.

**METHODS**

A retrospective cohort study was performed on all patients at a large, academic, tertiary care medical center who received intravenous colistin for at least 72 hours for the treatment of a carbapenem-resistant gram-negative bloodstream infection from 2005–2010. A searchable database was queried for patients with a blood culture positive for a carbapenem-resistant GNB who had received colistin as an inpatient. Patients were excluded if they were less than 18 years of age, received colistin for <72 hours, or had polymicrobial bacteremia. Furthermore, only the first bacteremic episode that met all the inclusion and exclusion criteria was included. This study was approved by a local institutional review board.

The primary objective was to determine if colistin dose (mg/kg/day) independently predicts microbiological outcome at day 7 of therapy. The colistin dose reported in this manuscript is mg of colistin-base activity (CBA). In the United States, colistin is available as colistimethate for injection (Coly-Mycin M), which is a prodrug that is hydrolyzed in vivo to the active form, colistin (1 vial of colistimethate for injection contains 150 mg CBA). Internationally, 150 mg CBA is equivalent to 4.5 million international units (IU). Colistin dosing was based on institutional standards that corresponded with package insert recommendations for both dosing and renal function adjustments; however, the dosing regimen was ultimately decided by the treating clinician. The weight used throughout the analyses of results was dosing body weight (DBW) in kilograms (kg). DBW was defined as the patient’s ideal body weight (IBW), or if the patient’s actual body weight (ABW) was 130% or more of their IBW, the following formula was used to calculate dosing body weight: DBW = IBW + 0.4(ABW – IBW) [15].

Microbiologic success was defined as eradication of the original causative organism from subsequent blood cultures by day 7 of therapy, whereas microbiologic failure was defined as persistence of the original causative organism in subsequent blood cultures by day 7 or death by day 7. In the absence of follow-up blood cultures, eradication of causative organism was presumed based on documented clinical improvement. Clinical improvement was defined as a white blood cell count less than 12,000 cells/mm³ without a documented fever for at least 48 hours. The secondary objectives included evaluating the effects of colistin dose on day-7 mortality, day-28 mortality, and the incidence of acute kidney insufficiency (AKI). AKI was defined in terms of the Risk, Injury, and Failure categories as per the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria and assessed on day 7 after the initiation of colistin [16]. Patients with baseline end-stage renal disease were excluded from the AKI analysis.

Data collected from each patient’s medical record included demographics (age, gender), height, weight, components of the Pitt bacteremia score (PBS) [17], components of the Charlson comorbidity index [18], culture data, source of infection (as documented in the medical record by the treating physicians), daily colistin dose, length of stay until start of colistin, concomitant antibiotic therapy dose and duration, timing of antibiotic therapy, daily temperature and white blood cell count, and mortality. Renal function was assessed at baseline and day 7 of colistin therapy by documenting serum creatinine and the use of renal replacement therapy. Patients were divided into 2 groups based on whether they achieved microbiologic success at day 7 of colistin therapy.

**Microbiological Methods**

Blood culture bottles were sent for routine cultures as part of clinical care. Automated systems were utilized to process the blood cultures (BacTAlert, bioMerieux, Durham, NC). Identification and routine antimicrobial susceptibility testing were performed with Vitek 2 instruments (bioMerieux). When applicable, special antimicrobial susceptibility testing for colistin was performed using the E-test method. Interpretive criteria for colistin were extrapolated from data on its in vitro activity against *A. baumannii* and *P. aeruginosa*, as described by the CLSI [11].
Statistics
Categorical data were analyzed using either Fisher exact test or χ² test, and continuous data were analyzed using Mann–Whitney U test. The Mann–Whitney U test was chosen for continuous data as a conservative measure due to the challenges of determining true normality with a small data set. All tests of significance were 2-tailed, and P < .05 was considered statistically significant. The primary objective of the study was assessed using multivariate logistic regression to assess for independent predictors of microbiological success. Baseline characteristic differences that met statistical criteria (P < .10) on univariate analysis with biologic plausibility for affecting microbiologic success were analyzed using a multivariate logistic regression model. The Hosmer–Lemeshow goodness-of-fit test was used to test the power of the model. A receiver operating characteristic (ROC) curve was constructed to assess the predictive accuracy of colistin dose for day-7 microbiologic success. The optimal dose threshold was determined by the point on the ROC curve with the best sensitivity and specificity for predicting microbiologic success. All statistical analyses were performed using SPSS version 14.0 for Windows (Chicago, IL). Results are expressed as n (%) or median (interquartile range [IQR]) when in tabular format unless otherwise specified.

RESULTS
One hundred thirty-seven adult patients met our initial electronic screening criteria of having monomicrobial carbapenem-resistant gram-negative bacteremia and received colistin during their stay. Of these 137 patients, a total of 76 patients met inclusion criteria for the study, and 61 patients were excluded because they did not receive intravenous colistin for ≥72 hours. Of the 76 patients, 60 (79%) were critically ill and receiving care in an intensive care unit. Overall, 52 patients (68%) achieved microbiological success at day 7 of colistin therapy. Success was adjudicated based on follow-up blood cultures for 71 (93.4%) patients; the remaining 5 (6.6%) patients did not have repeat cultures drawn and were adjudicated based on clinical criteria. Patient characteristics on the first day of colistin therapy were assessed by comparing patients who had achieved microbiological success (n = 52) and those with microbiologic failure at day 7 (n = 24; Table 1). Overall, there were no significant differences between groups in terms of gender, age, DBW, and CCI. On univariate analysis, the median PBS was significantly higher in the microbiological failure group (6.0 vs 4.0; P = .002).

The distribution among infecting pathogens and source of infection were not significantly different between groups (Table 1). The most common source of infection was catheter-related, with catheter removal rates approaching or achieving 100% in each group. Colistin sensitivity was performed on isolates from 58 patients (76.3%) with 56 (97%) GNB demonstrating a colistin minimum inhibitory concentration (MIC) ≤2.0 mg/L. The median colistin MIC in both groups was 2.0 mg/L.

Median colistin dose in mg/kg/day was significantly higher in the day-7 microbiological success group than in the microbiological failure group (2.90 mg/kg/day vs 1.50 mg/kg/day, respectively; P = .011; Table 1). The area under the ROC curve was 0.68 (95% confidence interval [CI], 0.54–0.82; P = .011), suggesting colistin dose is a good predictor of day-7 microbiologic success (Figure 1). The optimal dose threshold based on the ROC plot was 2.1 mg/kg/day of colistin, with a sensitivity of 67% and a specificity of 63%. Concomitant antibiotic use was common in both the microbiological success and failure groups (71% vs 75%; P = .79). Tigecycline, aminoglycoside, and carbapenem were used in 31%, 44%, and 31%, respectively, among patients who achieved microbiologic success. This was similar among patients who did not achieve microbiologic success. Tigecycline concomitantly with colistin in the microbiological failure group compared to the microbiological success group, although this difference did not reach statistical significance (P = .051).

A multivariate logistic regression model of 7-day microbiological success, which incorporated colistin dose in mg/kg/day, PBS, and concomitant tigecycline therapy, was performed to adjust for baseline differences between group (Table 2). Increased colistin dose was independently associated with microbiologic success, whereas increased PBS and tigecycline use was associated with microbiologic failure.

Regarding secondary outcome measures, univariate analyses revealed a significantly higher colistin dose among patients that survived at 7 days (2.7 mg/kg/day vs 1.5 mg/kg/day; P = .007), but no significant difference in colistin dose among patients that survived at 28 days (2.0 mg/kg/day vs 2.3 mg/kg/day; P = .996). In our study, 27 patients (36%) experienced some degree of AKI; 10 patients (37%) met criteria for risk, 7 patients (26%) for injury, and 10 patients (37%) for failure, according to the RIFLE criteria. In terms of safety endpoints, the development of risk, injury, or failure was associated with a higher colistin dose (3.6 mg/kg/day vs 1.7 mg/kg/day; P < .001). Colistin dose was not significantly different among the 3 categories of AKI.

DISCUSSION
The results of this retrospective study indicate that an increased weight-based daily dose of colistin independently
predicts day-7 microbiologic success and correlates with day-7 mortality. On multivariate analysis, a higher colistin dose was associated with microbiologic success, whereas a higher baseline PBS and coadministration with tigecycline were each associated with microbiologic failure. The analysis did not find a significant difference in colistin dose between day-28 survivors or nonsurvivors. The safety analysis revealed that patients who developed AKI received significantly higher colistin doses.

The association between an increased colistin dose and improved outcomes is in agreement with other investigations. Falagas and colleagues [19] conducted a retrospective study of 258 patients with microbiologically documented infections treated with colistin. The investigators found a stepwise decrease in mortality associated with increasing daily colistin dose, with the percent mortality associated with 3 million IU (100 mg CBA), 6 million IU (200 mg CBA), and 9 million IU (300 mg CBA) being 38.6%, 27.8%, and 21.7%, respectively [19]. On multivariate analysis, a higher colistin dose independently predicted survival [19]. Similarly, in a recent prospective observational study by Dalﬁno and colleagues [20], colistin administered at a higher-than-recommended dose of 9 million IU (300 mg CBA) loading dose, followed by 4.5 million IU (150 mg CBA) intravenously every 12 hours (with adjustments for renal dysfunction) achieved a higher cure rate (82%) than any previous studies. The median (IQR) daily dose used in the current study was 160 mg (100–250 mg) CBA, which is considerably less than the doses used in the study by Dalﬁno and colleagues.

Our study is unique to the studies mentioned above in several ways. The retrospective study by Falagas and colleagues [19] was for all patients who received colistin and had microbiologically documented pathogens. However, the authors acknowledge that the differentiation between colonization and infection was challenging. Furthermore, the study documented

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Microbiological Success at Day 7 (n = 52)</th>
<th>Microbiological Failure at Day 7 (n = 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td>22 (42.3)</td>
<td>13 (54.2)</td>
<td>.335</td>
</tr>
<tr>
<td>Age, years</td>
<td>61.0 (49.3–67.0)</td>
<td>60.0 (52.3–72.3)</td>
<td>.461</td>
</tr>
<tr>
<td>DBW, kg</td>
<td>70.7 (60.4–78.0)</td>
<td>76.5 (67.9–95.7)</td>
<td>.080</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.6 (23.2–33.2)</td>
<td>33.2 (24.8–39.2)</td>
<td>.154</td>
</tr>
<tr>
<td>Pitt bacteremia score</td>
<td>4.0 (2.0–5.0)</td>
<td>6.0 (3.3–7.0)</td>
<td>.002</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.1 (0.8–2.0)</td>
<td>1.8 (0.9–2.6)</td>
<td>.263</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>3.0 (2.0–5.0)</td>
<td>3.0 (2.3–5.0)</td>
<td>.302</td>
</tr>
<tr>
<td>Duration of hospitalization prior to positive blood culture, days</td>
<td>17.7 (4.68–32.9)</td>
<td>14.6 (9.59–26.5)</td>
<td>.754</td>
</tr>
<tr>
<td>Days from index blood culture to first dose of colistin</td>
<td>2.87 (1.10–4.10)</td>
<td>2.80 (1.42–3.72)</td>
<td>.849</td>
</tr>
<tr>
<td>Responsible pathogen</td>
<td></td>
<td></td>
<td>.286</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>19 (37.3)</td>
<td>13 (54.2)</td>
<td>.211</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>14 (26.9)</td>
<td>4 (16.7)</td>
<td>.328</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>19 (37.3)</td>
<td>7 (29.2)</td>
<td>.609</td>
</tr>
<tr>
<td>Source of infectiona</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter-related</td>
<td>22 (42.3)</td>
<td>12 (50.0)</td>
<td>.531</td>
</tr>
<tr>
<td>Catheter removal</td>
<td>22/22</td>
<td>11/12</td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>14 (26.9)</td>
<td>5 (20.8)</td>
<td>.569</td>
</tr>
<tr>
<td>Respiratory</td>
<td>9 (17.3)</td>
<td>6 (25.0)</td>
<td>.434</td>
</tr>
<tr>
<td>Skin/soft tissue</td>
<td>1 (1.9)</td>
<td>1 (4.2)</td>
<td>.535</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>6 (11.5)</td>
<td>1 (4.2)</td>
<td>.421</td>
</tr>
<tr>
<td>Endovascular</td>
<td>1 (1.9)</td>
<td>1 (4.2)</td>
<td>.535</td>
</tr>
<tr>
<td>Isolates with colistin MIC ≤2 mg/dL</td>
<td>41/43</td>
<td>15/15</td>
<td>1.0</td>
</tr>
<tr>
<td>Colistin dose (in CBA) in mg/kg/day (DBW)</td>
<td>2.90 (1.70–3.68)</td>
<td>1.50 (1.10–2.0)</td>
<td>.011</td>
</tr>
</tbody>
</table>

Continuous data presented as median (interquartile range) and nominal data as n (%).

Comparison of P values for continuous data using Mann–Whitney U test and either Fisher exact test or χ² test for categorical variables.

Abbreviations: BMI, body mass index; CBA, colistin base activity; DBW, dosing body weight; MIC, minimum inhibitory concentration.

a One patient in microbiologic success group with 2 possible sources for the bloodstream infection; 2 patients in microbiologic failure group with 2 possible sources for the bloodstream infection.
the use of colistin over a 7-year period, where a higher colistin dosing scheme was systematically implemented in the latter 2 years. Hence, the difference in outcomes associated with higher colistin doses could partially be explained by advancements in care. The current study only included patients with gram-negative bacteremia, which minimizes the challenges in the differentiation between colonization and infection. Furthermore, during the course of the study, no systematic change in the colistin dosing scheme was implemented. The pilot study by Dalfino and colleagues [20] provides valuable information regarding the potential increase in response rate with higher doses of colistin; however, the study did not have a comparator arm and therefore contrasts in response rates must be made with historical studies.

The association between higher doses of colistin and improved clinical outcomes corresponds with the PK and PD data garnered by recent investigations. Garonzik et al [14] conducted a PK study of colistin in 105 critically ill patients. Results indicated that approximately 85% of only approximately 12% of patients achieved steady-state colistin concentrations >4 mg/L. Based on pharmacokinetic modeling, the authors concluded that a loading dose based on steady-state colistin target concentration, and a maintenance dose based on renal function and target concentration, should be utilized. Of note, utilizing the equations provided would consistently result in higher colistin doses than those currently recommended in the product package insert. Similarly, Plachouras and colleagues [10], using a population PK analysis, recommended for a loading dose of 300 to 400 mg CBA followed by a maintenance dose of 150 mg twice daily to reach serum concentration targets. Taken together, these recent PK and PD studies revealed a need for higher doses of colistin to maximize efficacy. The current study provides further clinical evidence that higher colistin doses may be associated with better outcomes.

However, the preliminary findings of possible better outcomes with optimized colistin dosing should be tempered with the equal possibility of worsening renal function associated with increased colistin doses. Univariate analyses of our data revealed that patients who developed nephrotoxicity had higher daily colistin doses. The results of this study echo the findings from other recent investigations [21, 22]. Pogue and colleagues [21], in a retrospective study, found that 43% of patients who received colistin developed either AKI risk (13%), injury (17%), or failure (13%) as defined by the RIFLE criteria. In multivariate analysis, they found that colistin dose of >5.0 mg/kg/day of IBW was independently predictive of the development of renal insufficiency. Similarly, DeRyke et al [22]
evaluated nephrotoxicity associated with colistin dosing in terms of actual and ideal body weight among 30 patients. Patients experiencing nephrotoxicity received a significantly higher daily dose in terms of IBW (5.5 mg/kg vs 4.4 mg/kg; P = .011).

This study has several limitations. Due to the retrospective nature of the study, there are inherent shortcomings, including confounding by indication and baseline discrepancies between groups that might not have been accounted for in analyses. During the study period, colistin was routinely adjusted for renal dysfunction as described by the package insert. Hence, it is conceivable that patients who received a lower dose of colistin had worse renal function, and therefore were more likely to have worse outcomes due to underlying severity of illness. However, baseline renal function was not significantly different between the groups, and therefore not included in the multivariate analysis. Furthermore, the primary outcome of microbiologic success should be less easily confounded by other baseline factors. Microbiological success was utilized as the primary outcome due to the retrospective design of this study and the fact that microbiological data were consistently available for most patients in the study. Furthermore, patients who develop carbapenem-resistant gram-negative bacteremia are usually severely ill or immunocompromised [8]; therefore, other outcomes such as mortality and length of stay may be severely confounded by the patient’s baseline illness. The design of the study excluded patients who received colistin for <72 hours, which may have excluded patients that died shortly after the receipt of colistin. However, it would be difficult to ascertain the effects of colistin on microbiologic outcome if therapy for a shorter time period was utilized and similar inclusion criteria were used in other studies [19]. In addition, the average time to colistin therapy from the time the index culture was drawn was approximately 3 days. It is unclear whether these findings would be applicable if adequate empiric therapy was provided at an earlier time. Lastly, our analysis of nephrotoxicity was not complete because it was not adjusted for other factors such as the receipt of other nephrotoxins or fluid status. In addition, the design of the study did not allow an accurate assessment in the progression or recovery from the renal injury.

In conclusion, results of the study indicate that a higher colistin dose in mg/kg/day independently predicts microbiologic success at day 7 of colistin therapy. Patients that survived at day 7 were given significantly higher colistin doses, but doses were not significantly different among patients who were alive at 28 days compared to those who had died by 28 days. Patients meeting criteria for AKI received significantly higher colistin doses in our study. Further study is warranted to more accurately describe the ideal colistin dosing regimen to optimize efficacy and minimize toxicity.

Note

Potential conflicts of interest. All authors: No reported conflicts.
All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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