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ORIGINAL RESEARCH

Colistin Loading Dose in Septic Patients with Gram Negative Infections

Abdulrahman I Alshaya[1–3], Khalid Bin Saleh[1–3], Mohammed Aldhaeefi[1–3], Hisham A Baderldin[1–3], Farris O Alamody[1], Qusai A Alhamdan[1], Mohammed A Almusallam[1], Omar Alshaya[1–3], Khalid Al Sulaiman[1–3], Shaima Alshareef[3], Shuroug A Alowais[1–3], Shmeylan A Al Harbi[1–3], Ghassan Alghamdi[2,4]

[1]College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [2]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia; [3]Department of Pharmaceutical Care Services, King Abdulaziz Medical City, Riyadh, Saudi Arabia; [4]College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

Correspondence: Abdulrahman I Alshaya, College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, Email alshayaab@gmail.com

Purpose: Intravenous (IV) colistin is commonly used to treat multidrug-resistant gram-negative infections. It is primarily eliminated renally and may induce acute kidney injury (AKI) at a rate of up to 53%. Consequently, septic patients who require colistin administration have an additional risk of developing AKI. The aim of this study is to investigate clinical failure and AKI predictors for septic patients treated with IV colistin.

Methods: This retrospective cohort study was conducted at a tertiary teaching hospital in Saudi Arabia. Adult septic patients with suspected or confirmed gram-negative infections who received colistin admitted to the hospital between May 2016 and December 2020 were screened after obtaining IRB approval. AKI was defined based on the AKI Network criteria. We investigated the incidence of clinical failure based on colistin dosing and AKI risk factors, such as the development of septic shock, severity of illness, and medication co-administration using a multiple logistic regression model.

Results: After screening 163 patients, 103 patients were included in the analysis. No difference was observed between the colistin dosing strategies for clinical failure. Of the included predictors, development of septic shock (OR: 3.75; 95% CI 1.18–13.15), carbapenem co-administration (OR, 3.96; 95% CI, 1.134–15.57) were associated with an increased risk of AKI. The other factors were not significant predictors.

Conclusion: Clinical failure was not affected by colistin dosing strategies in our cohort of patients with sepsis. Moreover, the co-administration of carbapenems and the development of septic shock may increase the risk of inducing AKI in adult septic patients treated with IV colistin. Further studies are required to confirm these findings.

Keywords: sepsis, infection, colistin, loading dose, gram-negative, renal failure

Introduction

Sepsis and septic shock caused by multidrug-resistant (MDR) gram-negative bacteria (GNB) are emerging epidemics responsible for increased morbidity and mortality worldwide.[1] The lack of effective antimicrobial agents against certain resistant GNB, such as *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Klebsiella pneumoniae*, requires the use of colistin as a last-line resort.[2] Colistin is a bactericidal antibiotic that disrupts the membrane integrity of GNB and shows activity against MDR-GNB, but with an increased risk of dose-dependent side effects, such as nephrotoxicity and neurotoxicity.[3] Colistin is a prodrug that requires further metabolism to be converted into its active metabolite and requires a loading dose (LD) to reach the required therapeutic plasma concentration. Urgent administration of an effective antibiotic regimen is an essential first step in managing sepsis and septic shock, preferably within the first hour of diagnosis.[4] According to the recent consensus guidelines, an appropriate LD of colistin base activity (CBA) infused at 0.5–1 h is recommended, with the administration of the first maintenance dose (MD) based on the patient's renal function after 12–24 h.[5]

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Pharmacokinetic studies of colistin showed a slow conversion rate of the inactive drug colistimethate sodium to the active drug colistin, which may take up to 3 days without an LD to achieve therapeutic drug concentration given its long half-life.[6] The administration of an LD in intensive care units (ICUs) is challenging considering the comorbidities and concomitant medications that could increase the risk of developing serious side effects due to colistin administration.[5,6]

The impact of using colistin LD for clinical cure in ICU patients was evaluated in four observational studies with a relatively small sample size. In the first study (25 patients with sepsis), clinical cure and bacteriological clearance were achieved in 82.1% and 73.9% of the patients, respectively, with a reported incidence of acute kidney injury (AKI) of 17.8%.[7] The second study (70 patients with severe sepsis and septic shock) reported clinical resolution in 77% of the patients, with an AKI incidence of 44%.[8] Neither of these two studies involved a comparator group. The third study (46 patients with an initial LD and 46 patients without an LD) had various infection sites and reported clinical cure in 63% of the patients in the LD group and in 41.3% of the patients without an LD (p=0.04).[9] AKI occurred in 32.2% and 26% of the patients in the LD and comparator groups, respectively (p=0.64). The fourth study evaluated MDR-GNB pneumonia (30 patients with an initial LD and 42 patients without a LD) and reported a clinical cure in 55% of the patients belonging to the LD group and in 67% of the patients in the comparator group (p=0.31).[10] The LD group experienced more AKI than the comparator group (58% vs 50%, p=0.59). The latter two studies indicate contradictory results regarding the use of colistin LD for clinical cure, with an agreement on the higher incidence of AKI in the LD group. However, these results were not statistically significant.

In this study, we aimed to investigate the rate of clinical failure along with the incidence of AKI following the administration of colistin LD vs no LD in critically ill patients with sepsis or septic shock.

Methods

Study Design and Participants

This was a single-center retrospective cohort study. Adult ICU patients with suspected or confirmed gram-negative infections admitted between May 1, 2016, and December 31, 2020, were included in the study. All patients were administered at least two doses of intravenous colistin during their ICU admission to any of the 10 ICUs in the National Guard Health Affairs (NGHA) central region institutions. The institutional review board (IRB) approval for this study was granted by the King Abdullah International Medical Research Center (KAIMRC) (study number NRC21R/071/03). Patient consent form was waived by the ethics committee as part of the IRB approval, based on the retrospective nature of the study to abides by the Declaration of Helsinki Law. Patients were included in the study if they were critically ill, aged ≥18 years, and diagnosed with sepsis based on the International Classification of Diseases, Tenth Revision (ICD-10) codes. Patients who used colistin empirically for suspected or confirmed gram-negative infections were included. After screening, patient should have received a loading dose per the discretion of clinician in the loading dose group. Maintenance dosing of colistin was counted from the first dose if the treating clinician did not document the purpose of this dosing. Pregnant patients were excluded from the study. Events were documented if they happened during the ICU stay until ICU discharge after improvement or in-hospital mortality, whichever occurred first.

Setting

This study was conducted in the adult medical, surgical, trauma, and burn ICUs at KAMC, a tertiary-care academic referral NGHA hospital in Riyadh, Saudi Arabia. The ICU admits critically ill patients and operates as closed units with a 71-ICU bed capacity with 24/7 onsite coverage by critical care board-certified intensivists.

Data Collection

In this study we included demographic and clinical data such as age, sex, weight, and obesity, based on a body mass index of >35 kg/m^2. Data collection for baseline characteristics included, but was not limited to, the source of infection, baseline temperature, lactic acid upon diagnosis, baseline serum creatinine, and cumulative fluid balance within 72 h of ICU admission. Additionally, the vasoactive-inotropic score, acute physiology and chronic health evaluation (APACHE II) score, and sequential organ failure assessment score were assessed. Comorbidities prior to ICU admission including

hypertension, heart failure, diabetes mellitus, chronic kidney disease, dialysis, and AKI prior to colistin administration, based on chart documentation were included. Additionally, mechanical ventilation, resistant patterns (if available), and co-administration of nephrotoxic medications, including aminoglycosides, vancomycin, beta-lactams, and loop diuretics, were taken into consideration. Inhaled colistin and intravenous colistin LD and MD in milligram per kilogram and duration of intravenous therapy (days) were reviewed and recorded from our electronic medical records. After screening, patient's who were stratified to the LD group should have received a documented loading dose per the discretion of clinician in the notes aside from the electronic order. Maintenance dosing of colistin was counted from the first dose if the treating clinician did not document the purpose of this dosing in the charts. Changes in MD was followed in case of adjustments in renal function and the research team decided to use first dosing after LD as an MD for consistency.

Objective

This study aimed to investigate the rate of clinical failure and AKI predictors in critically ill septic patients when comparing the intravenous LD of colistin with no LD administration.

Outcomes

The major outcome was the rate of clinical failure between the two groups. Minor outcomes included mechanical ventilation duration, hospital and ICU length of stay (LOS), in-hospital mortality, and discharge functional status. The days until which the patients were afebrile, re-infection within 3 days, colistin-induced nephrotoxicity, and neurotoxicity were reported.

Definition(s)

- Sepsis was defined using the ICD-10 Clinical Modification code.[11]
- Critically ill patient was defined as any patient who was admitted to the ICU.
- Septic shock: Any source of infection, lactic acid >2 mmol/L, requiring vasopressors to maintain a systolic blood pressure of >90 mmHg.
- Clinical failure was defined as persistence or worsening of the presenting signs and symptoms or death occurring within 4 days of treatment.
- AKI was defined using the AKI Network (AKIN) definition.[12]

Data Management and Statistical Analysis

Descriptive statistics were used to summarize the patient demographics and clinical outcomes, with data presented as medians (interquartile range (Q1-Q3)] and frequencies (percentages), as appropriate. The Mann–Whitney *U*-test was used to compare continuous variables. Pearson's chi-square test was used to compare the categorical variables. We estimated the unadjusted odds ratio (OR) of failure between the two groups and the associated 95% confidence intervals (CIs) using the Baptista–Pike method. Thereafter, we used a multiple logistic regression model to calculate the OR of clinical failure (major outcome) after adjusting for heart failure, chronic kidney disease, hypertension, diabetes mellitus, septic shock, dialysis, mechanical ventilation, pneumonia, intra-abdominal infections, urinary tract infection, and bacteremia. Statistical significance was defined as a two-sided p value <0.05. Statistical analyses and data graphing were performed using Prism 9 version 9.2.0.

Results

Of the 163 patients screened, 103 were included in this study. The baseline demographics are shown in Table 1. In our study, 83 (80.58%) patients had a documented diagnosis of septic shock upon colistin administration. Hypertension and diabetes mellitus were the most common comorbidities among 65 (63.11%) and 63 (61.17%) patients, respectively. Fifty-six patients (54.37%) received colistin LD. Nighty-one (88.35%) patients in our study had at least one additional nephrotoxic medication co-administered with colistin. Of those nephrotoxic medications, carbapenems and vancomycin were the most administered among 80 (87.91%) and 71 (78.02%) patients, respectively. The median colistin LD administered to the patients in our study was 160 mg CBA (approximately 2 million IU colistimethate sodium

Table 1 Baseline Demographics

Characteristic	Loading Dose Patients (n=56)	No Loading Dose Patients (n=47)	p-value
Age, years*	69 [57.75–78]	69 [59–78]	0.573
Gender, male°	30 (53.57)	31 (65.96)	0.166
Weight, kg*	73.75 [62–90.63]	71.9 [56.9–89]	0.403
Other comorbidities:			
• CKD°	25 (44.64)	18 (38.3)	0.515
• Hypertension°	37 (66.07)	28 (59.57)	0.496
• Heart failure°	11 (19.64)	12 (25.53)	0.475
• DM°	35 (62.50)	28 (59.57)	0.767
• PNA°	30 (53.57)	23 (48.94)	0.639
• IAI°	4 (7.14)	3 (6.38)	0.879
• UTI°	13 (23.21)	13 (27.66)	0.605
• Bacteremia°	16 (28.57)	12 (25.53)	0.729
• HD°	37 (66.07)	25 (53.19)	0.183
Septic shock°	48 (85.71)	35 (74.47)	0.151
On Mechanical Ventilation Upon Diagnosis°	42 (75)	32 (68.09)	0.437
Lactic acid*	3.175 [1.68–10.22]	2.51 [1.58–5.04]	0.254
Steroid use°	40 (71.43)	36 (76.60)	0.553
Other nephrotoxic medications°	50 (89.29)	41 (87.23)	0.746
VIS*	55 [8–450]	14.5 [1.5–466]	0.115
APACHE II*	26 [17.5–30]	25 [21–31]	0.919
SOFA*	12 [9.25–16]	12 [9.5–15]	0.588
Days on mechanical ventilation, days*	5 [2.25–10.75]	5 [2–15]	0.833
Duration of intravenous colistin course, days*	3 [1–6]	7 [2.75–11]	0.0075

Notes: *Median [IQR1-IQR3], °n (%).
Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; PNA, pneumonia; IAI, intra-abdominal infection; UTI, urinary tract infection; HD, hemodialysis; VIS, vasoactive-inotropic score; APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

equivalent) and the median maintenance dose was 85 mg CBA (approximately 1 million IU colistimethate sodium equivalent) twice daily. Intravenous colistin median treatment duration in our population was 4 days.

Major Outcome

A summary of the major and minor outcomes of patients who underwent LD and no LD is shown in Table 2. Eighty (77.67%) patients in our study experienced clinical failure during their indexed hospitalization based on our definition of clinical failure. Among these patients, 47 (58.75%) received an LD (Table 2). However, clinical failure was not statistically significant (OR 2.21, 95% CI 0.89–5.4, p=0.09).

Based on our multiple logistic regression model, patients with septic shock (OR 5.851, 95% CI, 1.610–23.3; p=0.0086) and those receiving dialysis (OR 3.410, 95% CI, 1.085–11.6; p=0.0398) had a higher incidence of clinical failure, as shown in Figure 1. Co-administration of carbapenems and progression to septic shock were associated with

Table 2 Minor Outcomes

	Colistin Loading Dose Patients (n=56)	No Colistin Loading Dose Patients (n=47)	p-value
Hospital length of stay (LOS), days	30.5 [13–66.75]	25 [14.75–55]	0.560
ICU LOS, days	11.5 [6–31.75]	15.5 [6.5–29.5]	0.523
Days on mechanical ventilation, days	5 [2.25–10.75]	5 [2–15]	0.522

increased odds of inducing AKI, while vancomycin co-administration was associated with lower odds of inducing AKI, as shown in Figure 2.

Minor Outcomes

No difference was observed in any of the secondary outcomes between the two groups. Fourteen (13.59%) patients developed AKI during colistin therapy, of which eight (57.14%) received an LD. The administration of colistin LD did not affect the incidence of AKI (OR 1.08, 95% CI 0.42–2.74, p=0.86). The probability of admission to the ICU for ≤7 days was not significantly lower among patients who received an LD (OR 0.78, 95% CI 0.3–1.89, p=0.6). The median ICU LOS was 11.5 days and 15.5 days among patients who received an LD in comparison to those who did not. This difference was not statistically significant (p=0.56).

In our study, the mortality rate was 81.55% (84 patients). Of these patients, 46 (54.76%) underwent LD. Interestingly, LD administration had no impact on mortality (OR 1.09, 95% CI 0.42–2.74, p=0.87). Among the remaining 19 (18.44%) patients who were discharged after hospitalization, 17 (89.47%) died. Of these, nine (52.94%) received an LD. One (5.26%) patient from each group was discharged to a rehabilitation or dialysis center. The difference between the groups in terms of the destination of patients' discharge upon completion of their hospital course was not statistically significant (p=0.98).

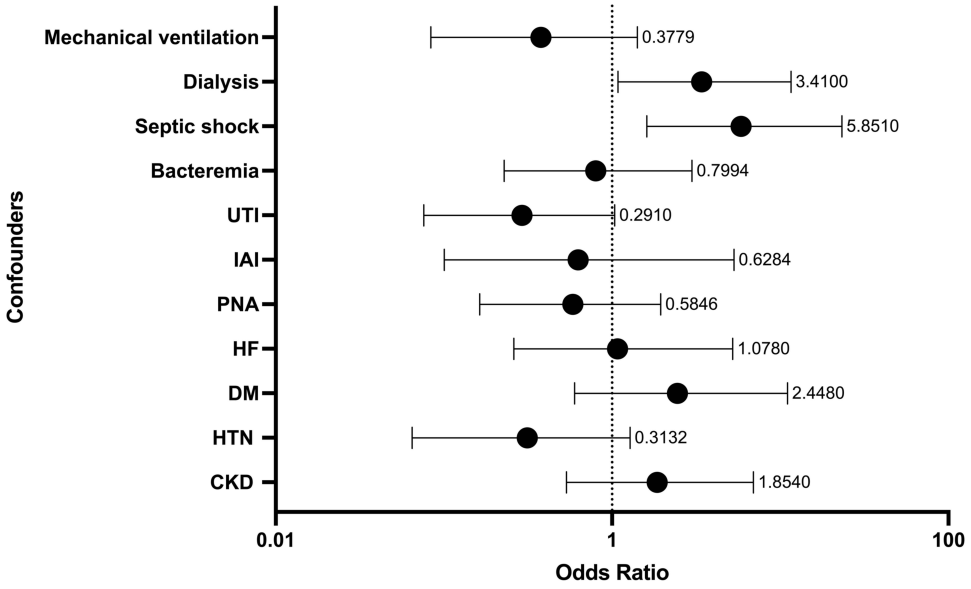

Figure 1 Forest plot for multiple logistic regression of clinical failure prediction.

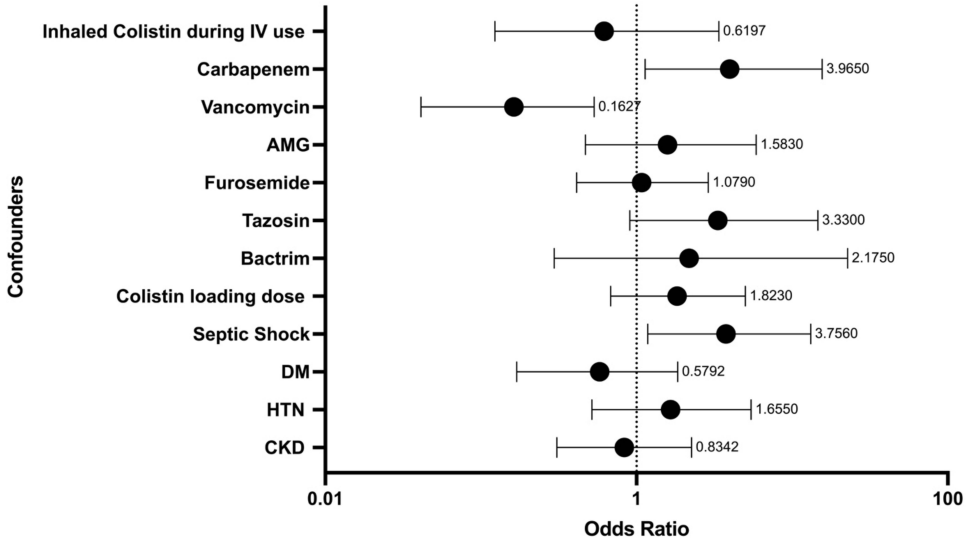

Figure 2 Predictor for acute kidney injury in septic patients using intravenous colistin.

Discussion

In our retrospective study, we compared the efficacy and safety of using colistin LD versus no LD in critically ill patients with sepsis or septic shock. Patients who underwent LD showed no differences in clinical and safety outcomes. This might be attributed to the low median LD used in our institution. The median colistin LD administered to the patients in our study was 160 mg CBA (4.8 million IU colistimethate sodium equivalent), which is lower than the recommended LD by the 2019 international consensus guidelines.[5]

Colistin therapy comprising an LD in critically ill patients was correlated with variable rates of clinical cure from 50% to 82%.[7–13] However, the loading dose used in the previously mentioned studies was higher (300 mg CBA) than that used in our study. Studies that have compared the clinical outcomes between an LD and a standard dosing regimen of colistin in critically ill patients have shown conflicting results. In a retrospective study of 92 patients with MDR-GNB who received colistin for >24 h, an LD of 9 MIU (equivalent to 300 mg CBA) was associated with a significantly higher cure rate, defined as both clinical and microbiological resolution, compared with a standard dose of 6 MIU (200 mg CBA), 63% vs 41.3% (p=0.04), with no significant increase in AKI (32.2% vs 26%; p=0.64) or mortality (23% vs 27.5%; p=0.6).[9] A previous study of 127 patients also demonstrated the achievement of both clinical and microbiological cure with a high dose of colistin (>4.4 mg/kg/day, approximately 300 mg CBA per day for an ideal body weight of 70 kg) compared with the standard dose on day 7 of therapy. However, only 15.7% of the patients received an LD. High-dose colistin was the only independent predictor of cure rate (OR 3.40, 95% CI 1.37–8.45, p=0.008).[14] It is worth mentioning that both studies reported colistin minimal inhibitory concentrations (MICs) of ≤2 mcg/mL.[9,14] However, the MIC was not reported in our study, which may limit our ability to have a proper comparison.

Two studies have shown significant improvement in microbiological but not clinical response with LD administration.[15,16] The first study was a prospective cohort comparing the effectiveness of 300 mg CBA LD (n=174) with no loading dose (n=81) in MDR *Acinetobacter baumannii* infection.[16] Only microbiological response was higher with LD administration (87.9% vs 70.4%; p=0.0006). Clinical response and mortality were similar between patients with and without LD (65.5% vs 70.4%; p=0.442) and (33.3% vs 3.1%; p=0.854). Although most of the included patients had comorbidities (80.3%), patients undergoing renal replacement therapy were excluded, and only 54% of patients were admitted to the ICU in the LD group, with a mean APACHE II score of 14.13. Unlike our study, in which the median APACHE II score was 26 and 85.7% of patients had septic shock, dialysis and septic shock were predictors of clinical failure (OR 3.410, 95% CI 1.085–11.6, p=0.0398) and (OR 5.851, 95% CI 1.610–23.3, p=0.0086), respectively. In addition, colistin MIC was very low (0.64–1 mcg/mL); however, this was not documented in our study. These factors could explain the high rate of clinical failure and mortality in our study (77.67% and 81.55%, respectively). The second

study evaluated the relationship between target colistin concentration and treatment outcomes in a retrospective cohort of 153 critically ill patients with MDR organisms and found no significant association.[16] There was no difference between the clinical cure (n=43) and clinical failure group (n=80) in terms of LD administration (clinical cure 60% vs clinical failure 42%; p=0.057); however, it was more likely to result in microbiological eradication in those who received an LD (OR 2.783, 95% CI 1.126–6.880, p=0.027).[16] These findings were further supported by a recent meta-analysis of eight observational studies that used high-dose colistin. Administration of an LD was associated with a higher rate of microbiological response (risk ratio [RR] 1.23, 95% CI 1.10–1.39), but not clinical response (RR 1.04, 95% CI 0.87–1.24).[9] The high rate of clinical failure and mortality in our study regardless of LD administration could be due to the inherent characteristics of our patient population and the severity of illness, as evidenced by the high proportion of patients with septic shock, high APACHE II score, vasopressor use, and comorbidities, including dialysis, which were excluded in many studies.[8,13,15–17]

Some patients in our study developed AKI (13.5%), which was not associated with LD administration. Although the incidence of nephrotoxicity reported in previous studies was higher, based on the AKIN criteria,[7–9,17] there was no significant difference between patients receiving a colistin LD and those receiving a standard regimen[9,16,18] (LD 58% vs standard dose 50%, p=0.59).[9]

A high mortality rate was observed in our study even in patients receiving an LD (OR 1.09, 95% CI 0.42–2.74, p=0.8). In a retrospective study of 258 patients, a higher colistin dose was associated with improved survival; mortality was 38.6% with doses of 3 MIU of colistin, 27.8% with 6 MIU of colistin, and 21.7% with 9 MIU of colistin (p=0.009).[11] However, it has not been shown to affect 28 days mortality in other studies.[9,10,14,15]

Although colistin is important as a salvage therapy for many MDR-GNBs, emerging agents are promising, safe, and effective. Treatment of carbapenem-resistant Enterobacteriaceae with ceftazidime-avibactam was associated with improved clinical outcomes and decreased 30 days mortality when used initially compared with colistin or alone.[18–20] Similarly, meropenem-vaborbactam was shown to be a safe and effective alternative in selected patients, and ceftolozane-tazobactam was shown to be safe and effective for MDR *P. aeruginosa*.[21–23]

Our study was limited by its retrospective design and the small number of patients. In addition, LD was relatively lower than the doses recommended by recent guidelines.[5] Clinical failure due to low exposure to colistin or higher MIC could not be excluded because plasma colistin concentration and MIC of isolated organisms were not available. The lack of institutional guidelines for colistin dosing may have affected the variability in dosing, which may be an added limitation. However, our sample size in this study was relatively larger than the recently published data for patients with sepsis and septic shock.[8–13]

In conclusion, in our retrospective study regarding the use of colistin in critically ill patients, LD administration was not associated with the clinical failure rate or mortality reduction. Predictors of colistin-induced AKI may include progression of septic shock and carbapenem co-administration. Optimization of colistin dose is required through the implementation of institutional guidelines to achieve a high rate of adequate LD and improve treatment outcomes. Further studies are needed to confirm these findings.

Ethics Approval

IRB approval for this study was granted by IRB of KAIMRC with study number NRC21R/071/03.

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Disclosure

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