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Comparative Efficacy of Twice and Thrice Daily Colistin Administration in Critically Ill Patients Battling Multi-Drug Resistant Gram-Negative Infections: An Observational Study

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ABSTRACT

Introduction: Colistin, a polymyxin antibiotic often reserved for treatment of multidrug-resistant Gram-negative infections, exhibits a narrow therapeutic index. Careful consideration of the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of colistin is essential to maximize its efficacy and minimize toxicity. Both thrice-daily and twice-daily administration regimens have been employed, with critically ill patients posing unique challenges regarding colistin's PK/PD. **Methods**: This retrospective observational study compared the mortality rates, cure rates, length of hospital stay, nephrotoxicity, and readmission rates associated with thrice-daily and twice-daily administration of a fixed total daily dose of 9 million international units (MIU) of colistin in 151 critically ill patients with multidrug-resistant Gram-negative infections. Propensity score matching with a 1:5 case-control ratio was performed using XLSTAT software (by Addinsoft), and outcomes were analysed using logistic regression analysis. **Results**: Thrice-daily dosing of colistin was recorded in 125 patients, and twice-daily dosing in 26 patients. A total of 73 patients were included in the final analysis after propensity score matching. The 28-day mortality rates, clinical cure rates, and microbiological failure rates were comparable between the two groups (Odds ratio (OR) [95% confidence-interval (CI)] = 0.48 [0.07-3.46], *P*=0.467; 1.67 [0.31-8.90], *P*=0.548; 0.13 [0.001-19.5], *P* = 0.428, respectively). Hospital readmission rates within 90 days (OR [95% CI] = 1.05 [0.12-9.10], *P*=0.964) and duration of hospital stay (Beta coefficient = 1.55, *P*=0.683) were also comparable between the two groups. The incidence of nephrotoxicity-related AKI events during Colistin therapy was significantly lower with the 4.5 MIU twice-daily regimen (OR [95% CI] = 0.04 [0.004-0.35], *P*=0.004). **Conclusion**: Twice-daily colistin administration significantly reduces the risk of nephrotoxicity-related AKI events compared to thrice-daily administration in critically ill patients with multidrug-resistant Gram-negative infections.

INTRODUCTION

The optimal dosing frequency for colistin has been a subject of ongoing research since the antibiotic re-emerged as a vital option in the treatment of multidrug-resistant Gram-negative infections. However, its use was significantly reduced in the 1980s due to concerns over its safety profile, including nephrotoxicity and neurotoxicity. As a last-line antibiotic in the World Health Organization's Access, Watch, and Reserve (AWaRe) classification, colistin is reserved as a last resort treatment for multidrug-resistant Gram-negative infections [1]. The prevalence of carbapenem resistance among Gram-negative pathogens has been increasing in India over the past decade, often leading to the consideration of colistin as a treatment option [2]. Optimizing colistin dosing is crucial to maximize antibacterial efficacy, minimize nephrotoxicity,

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and prevent the emergence of colistin-resistant strains. An essential pharmacokinetic (PK)/pharmacodynamic (PD) parameter to monitor during colistin therapy is the area under the plasma concentration-time curve across 24 h at steady state (AUCss, 24_h). Optimal efficacy, depending on the site of infection, requires a target AUCss, 24hr of at least 50 milligram-hours per liter. However, elevated colistin levels have been linked to an increased risk of acute kidney injury [3].

Therapeutic drug monitoring of colistin is often challenging due to limited availability of testing facilities. Dosing usually follows established guidelines. The 2016 'Colistin: Adult and Pediatric Guideline for South Africa' suggests a maintenance dose of 3 MIU every 8 h or 4.5 MIU every 12 h after the initial loading dose in critically ill adults with normal renal function, but this may vary depending on individual patient needs [4]. The 2019 international consensus guidelines published by the American College of Clinical Pharmacy (ACCP) for the optimum therapeutic use of polymyxins recommend a daily maintenance dose of 300mg – 360mg colistin base activity (CBA), which represents the active moiety of colistin, equivalent to 9 MIU – 10.8 MIU divided into two doses given at 12-h intervals for adults with normal renal function. In patients with creatinine clearance exceeding 90 mL/min, doses beyond 9 MIU per day may be considered [5]. Establishing an optimal regimen for treating multidrug-resistant Gram-negative infections in critically ill patients requires further research to address the inconsistencies in recommended dosing frequencies for colistin administration across guidelines [6-8].

While both the twice-daily (4.5 MIU) and thrice-daily dosing regimens of colistin can achieve comparable AUCss, 24h values within a similar range, the peak concentration is expected to be marginally higher with the twice-daily regimen. However, the comparative clinical outcomes and adverse effect profiles associated with these two dosing strategies in critically ill patients with multidrug-resistant Gram-negative infections remain unclear due to a scarcity of comparative studies. This retrospective observational study aimed to compare the efficacy and safety of thrice-daily and twice-daily dosing strategies of colistin, using the same total daily dose of 9 MIU, in critically ill patients at a tertiary care center. The primary outcomes were 28-day mortality, clinical response, and microbiological failure. Secondary outcomes included 90-day readmission rates, length of hospital stay, and the incidence of acute kidney injury associated with colistin administration.

MATERIAL AND METHODS

Study design and setting. This retrospective observational study was conducted on patients with severe multi-drug resistant Gram-negative infections admitted to the medical intensive care unit (MICU) who received intravenous colistin therapy.

Sampling. A purposive convenience sampling approach was used, as colistin was the standard treatment protocol for managing multi-drug resistant Gram-negative infections in the hospital during the study period. We included all patients who met the established eligibility criteria during the 15-month observational period from August 8, 2021, to November 8, 2022.

Group categorization and treatment. Patients were categorized into two groups based on the frequency of administration of the total daily dose of colistin: a 3 MIU thrice-a-day (TID) group or a 4.5 MIU twice-a-day (BD) group. Both groups received combination therapy with colistin and another antibiotic, which has been the institutional guidelines for treating multi-drug resistant Gram-negative infections. As no universally accepted guidelines existed to choose one regimen over the other, the divided dosing regimen of colistin was determined by the treating clinicians.

Ethical approval. The study protocol was approved by the institutional review board (IRB) of Aster Malabar Institute of Medical Sciences Ltd (MIMS), Calicut, Kerala, India (Reference No: 76/22). Patient data was managed in accordance with the committee's guidelines for human research.

Microbiological testing. Bacteria were identified from various clinical specimens, including blood, urine, respiratory tract specimens (sputum, endotracheal aspirate, or bronchoalveolar lavage), cerebrospinal fluid, pleural fluid, tissue, wound swab, or drain fluid. Antibiotic susceptibility testing was performed using the VITEK® 2 compact system and the Kirby-Bauer antibiotic susceptibility testing method.

Inclusion criteria. Age greater than 12 years, admission to the intensive care unit (ICU) and receipt of colistin as part of their treatment regimen for a multi-drug resistant Gram-negative infection. Patients in both group who developed acute kidney injury (AKI) after starting colistin therapy and subsequently received dosages adjusted for renal impairment were included in the analysis.

Exclusion criteria. Patients with established chronic kidney disease (CKD) were excluded as their colistin regimens differed from those being compared. Patients with AKI prior to the initiation of colistin therapy were excluded. Patients who received colistin therapy for less than 24 h were excluded due to the difficulty in attributing outcomes to colistin therapy. Patients on extracorporeal membrane oxygenation (ECMO) were excluded from the analysis due to altered pharmacokinetics in that setting.

Study setting. This study was conducted in the medical intensive care unit (MICU) at Aster Malabar Institute of Medical Sciences, a tertiary care hospital located in Calicut, Kerala, India. The MICU caters to medical and burn patients and has a capacity of 32 beds. It is staffed with intensivists and support personnel 24 h a day.

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Data collection and management. Data were collected from the hospital's electronic record system, including demographic information (age and gender), details of the type of infection, microbiological culture reports, reasons for initiating colistin treatment, initiation date of colistin, serum creatinine levels, co-administration of nephrotoxic medications, susceptibility patterns of identified pathogens, the date of discontinuing colistin therapy, development of AKI, duration of hospitalization, clinical outcomes at 28 days, and re-admissions within 90 days. When patients or their relatives were unavailable for in-person interviews, telephone interviews were conducted. All variables were recorded in an electronic data collection sheet. The definitions used in the study were as shown in Table 1. Bias was minimized by masking the data collector to statistical analyses, and the statistician was blinded to the specifics of the study data.

Study endpoints. The study assessed several endpoints, which included 28-day mortality from any cause, clinical response or microbiological treatment failure within 28 days, development of colistin-associated AKI, length of hospital stay, and re-admission within 90 days.

Table 1. Definitions of study variables

Term	Definition
Clinical Outcomes	
Critically Ill Patient	An individual necessitating intense monitoring and care due to a severe medical condition with organ failure and a potentially reversible illness.
Clinical Cure	Clinical response to the infection treated with colistin, as assessed by the treating clinician and extracted from the electronic medical record.
Microbiological Failure	Isolation of the same organism from a clinical sample after the standard treatment duration for that type of infection, together with persisting or worsening clinical signs or symptoms.
Mortality	All-cause mortality within 28 days of colistin treatment initiation, among patients who received colistin treatment for at least 24 hours.
Length of Hospital Stay	Total hospitalization duration from the date of admission to the date of discharge.
Re-admission within 90 days	Unplanned re-admission to the same hospital within 90 days of discharge.
Renal Function	
Acute Kidney Injury (AKI)	Defined according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) criteria.
Co-Administration of Nephrotoxic Drugs	Concurrent administration of at least one nephrotoxic drug for a minimum of 24 h during the same hospitalization period as colistin treatment.
Microbiological Criteria	
Susceptibility of Gram-negative bacteria	Determined based on the Clinical and Laboratory Standards Institute (CLSI) criteria for zone diameters (Kirby-Bauer) and interpretive minimum inhibitory concentration (MIC) breakpoints.
Extended-Spectrum Beta-Lactamase (ESBL)-producing organism	Organisms demonstrating resistance to at least one third-generation cephalosporin but retaining susceptibility to all carbapenem agents.
Carbapenem-Resistant Organism	Bacteria resistant to one or more carbapenem antibiotics (meropenem, imipenem, ertapenem, or doripenem), as per CLSI criteria.
Pseudomonas with Difficult-to-Treat Resistance	Pseudomonas with non-susceptibility to all beta-lactam agents commonly used to treat Pseudomonas infections, including piperacillin-tazobactam, ceftazidime, and cefepime, as well as fluoroquinolones.

Data Extraction and propensity score matching. Data were extracted from electronic health records (EHRs) using Akhil Hospital's EHR system. Baseline characteristics were compared between the 3 MIU three times a day (TID) group and 4.5 MIU twice a day (BD) group. Propensity score matching (PSM) analysis (XLstat software, Lumivero, version 2023.2.1414 (1414)) was used to match patients (at a 1:5 matching ratio to increase the precision of the matching process) who received 4.5 MIU twice daily colistin to those who received 3 MIU thrice daily colistin, based on the patient's age, gender, infectious clinical syndrome, resistance mechanism of the bacterial pathogen, co-administration of other nephrotoxic drugs, empirical versus definite indication for colistin therapy, and the administration of a loading dose, thus minimizing the effect of selection bias. A robust matching algorithm, the Mahalanobis distance matching method, was used for matching, wherein one patient in the 4. MIU twice daily (BD) group was matched with 5 patients in the 3 MIU three times daily (TID) group. This method yielded the smallest within-pair Mahalanobis distance among all possible matches. Patients were matched only if the difference in the logit of the propensity score for the patient pairs was not more than 0.10 standard deviations.

Statistical analysis. The matched retrospective cohort was then subjected to further analyses. Categorical variables were presented as counts and percentages, while

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continuous variables were expressed as medians with quartiles. Categorical variables were compared using the Chi-square test or Fisher's exact test (when the expected count in any cell was less than 5), and continuous variables were compared using the Wilcoxon rank sum/Mann-Whitney U test. Multivariable logistic regression analyses were conducted to assess binary outcome variables (*e.g.*, mortality, clinical cure), while multivariable linear regression analyses were conducted to assess continuous outcome variables (*e.g.*, length of stay, creatinine levels), after adjusting for potential confounders.

Software and power analysis. All statistical analyses were performed using STATA/MP 16.1 software. A convenience sampling approach was employed to select patients for this study. A post-hoc power analysis was conducted to determine the statistical power for each outcome in the propensity-matched sample, using a type I error of 0.05 and type II error of 0.20 (power of 80%). Appropriate measures of the strength of association between variables, including odds ratios (OR) with their corresponding 95% confidence intervals (CIs), were reported. Statistical significance was defined as a *P*-value of less than 0.05.

RESULTS

A total of 506 patients admitted to the medical ICU received colistin therapy during the 15-month period from August 8, 2021, to November 8, 2022. Among them, 151 patients met the eligibility criteria for inclusion in the study (Figure 1). All 151 patients included in the study received a total daily dose of 9 MIU of colistin as long as their renal function remained normal. Among them, 149 patients received a loading dose of 9 MIU before transitioning to the maintenance dose. Before PS matching, 125 patients received a maintenance dose of 3 MIU of colistin thrice daily (TID), while 26 patients received 4.5 MIU of colistin twice daily (BD) as their maintenance colistin dosing regimen. A total of 73 matched patients were found using propensity score matching, with 16 patients in the 4.5 MIU twice daily (BD) group and 57 patients in the 3 MIU thrice daily (TID) group (1 patient in the BD group matched to 5 patients in the TID group). The most common infectious syndrome was hospital-acquired pneumonia (HAP), followed by bacteremia, among the study population. The median (quartiles Q1, Q3) length of colistin treatment was 8 (5, 10) days in the 3 MIU thrice daily (TID) group and 5.5 (3, 11) days in the 4.5 MIU twice daily (BD) group. None of the isolates were resistant to colistin. Co-administration of nephrotoxic drugs was not found in the medical records of 69.9% of the study population.

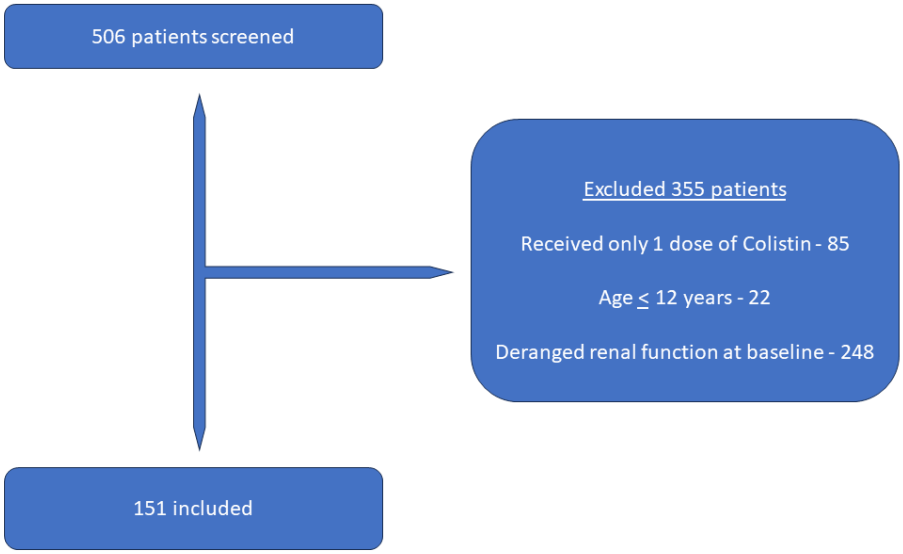

Fig. 1. Study flow diagram

Demographic and clinical characteristics. The demographic and clinical characteristics of the study population are summarized in Table 2. Before propensity score matching, the majority of patients in the 3 MIU TID group were men (68.8%), while the majority in the 4.5 MIU BD group were women (65.4%). However, this difference was not statistically significant after PS matching ($P = 0.452$). The median age of patients in both groups was between 18-65 years. The clinical presentations were categorized as shown in Table 2 to

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provide insight into the presumed pathogens before culture reports became available. After PS matching, urinary tract infections and bacteremia had a higher incidence in the 3 MIU TID group, while hospital-acquired pneumonia, skin and soft tissue infections, and complicated intra-abdominal infections were more frequent in the 4.5 MIU BD group. However, the differences in the distribution of infections between the two groups were not statistically significant (P>0.05). The antimicrobial resistance profiles of the isolated pathogens were classified according to the Infectious Diseases Society of America (IDSA) guidance document from 2022. Genetic analysis to identify carbapenemases and ESBLs was not conducted in all cases, and their production was estimated based on phenotypic markers (resistance to a carbapenem or a third-generation cephalosporin). Furthermore, no significant differences in the indication for colistin, use of a loading dose, number of days of colistin therapy, or co-administration of other nephrotoxic drugs were found between the two groups.

Table 2. Baseline characteristics of patients included in the study

Parameter	Before propensity score (PS) matching				After propensity score (PS) matching			
	Overall (151)	3 MIU TID (125)	4.5 MIU BD (26)	*P* value	Overall (73)	3 MIU TID (57)	4.5 MIU BD (16)	*P*-value
Gender								
Male, n (%)	95 (62.9%)	86 (68.8%)	9 (34.6%)	0.001^	38 (52.1%)	31 (54.4%)	7 (43.8%)	0.452^
Female, n (%)	56 (37.1%)	39(31.2%)	17 (65.4%)		35 (47.9%)	26 (45.6%)	9 (56.2%)	
Age (years)								
18 – 65, n (%)	108 (71.5%)	91 (72.8%)	17 (65.4%)	0.448^	45 (61.6%)	36 (63.2%)	9 (56.2%)	0.616^
>65, n (%)	43 (28.5%)	34 (27.2%)	9 (34.6%)		28 (38.4%)	21 (36.8%)	7 (43.8%)	
Infectious syndrome								
CAP, n (%)	2 (1.3%)	1 (0.8%)	1 (3.8%)	0.316*	2 (2.7%)	1 (1.8%)	1 (6.3%)	0.393*
HAP, n (%)	103 (68.2%)	83 (66.4%)	20 (76.9%)	0.297^	51 (69.9%)	39 (68.4%)	12 (75%)	0.612^
VAP, n (%)	2 (1.3%)	2 (1.6%)	0 (0%)	1*	1 (1.4%)	1 (1.8%)	0 (0%)	1*
Aspiration pneumonia, n (%)	9 (6.0%)	7 (5.6%)	2 (7.7%)	0.653*	6 (8.2%)	5 (8.8%)	1 (6.3%)	1*
Empyema, n (%)	1 (0.6%)	0 (0%)	1 (3.8%)	0.172*	0 (0%)	0 (0%)	0 (0%)	0*
BSI, n (%)	65 (43%)	57 (45.6%)	8 (30.8%)	0.170^	26 (35.6%)	21 (36.8%)	5 (31.3%)	0.680^
UTI, n (%)	15 (9.9%)	13 (10.4%)	2 (7.7%)	1*	8 (11%)	7 (12.3%)	1 (6.3%)	0.676*
SSTI, n (%)	16 (10.6%)	10 (8%)	6 (23.1%)	0.023^	8 (11%)	5 (8.8%)	3 (18.8%)	0.361*
CIAI, n (%)	8 (5.3%)	7 (5.6%)	1 (3.8%)	1*	4 (5.5%)	3 (5.3%)	1 (6.3%)	1*
CNS Infection, n (%)	1 (0.6%)	1 (0.8%)	0 (0%)	1*	1 (1.4%)	1 (1.8%)	0 (0%)	1*
Sepsis of unknown focus, n (%)	11 (7.3%)	10 (8%)	1 (3.8%)	0.691*	5 (6.8%)	4 (7%)	1 (6.3%)	1*
Type of organism identified on culture								
ESBL producing Enterobacteriaceae, n (%)	21 (13.9%)	20 (16%)	1 (3.8%)	0.128*	6 (8.2%)	5 (8.8%)	1 (6.3%)	1*
Carbapenem resistant Enterobacteriaceae, n (%)	78 (51.7%)	67 (53.6%)	11 (42.3%)	0.296^	41 (56.2%)	33 (57.9%)	8 (50%)	0.574^
Carbapenem resistant Acinetobacter baumanii, n (%)	73 (48.3%)	59 (47.2%)	14 (53.8%)	0.541^	33 (45.2%)	25 (43.9%)	8 (50%)	0.663^
Pseudomonas with difficult to treat resistance, n (%)	14 (9.3%)	12 (9.6%)	2 (7.7%)	1*	7 (9.6%)	6 (10.5%)	1 (6.3%)	1*
Co-administration of nephrotoxic drugs	38 (25.17%)	28 (22.4%)	10 (38.4%)	0.086^	22 (30.1%)	19 (33.3%)	3 (18.7%)	0.361*
Yes, n (%)	113 (74.83%)	97 (77.6%)	16 (61.5%)		51 (69.9%)	38 (66.7%)	13 (81.3%)	
No, n (%)								
Indication for Colistin therapy	48 (31.8%)	37 (29.6%)	11 (42.3%)	0.207^	26 (35.6%)	21 (36.8%)	5 (31.2%)	0.680^
Empirical, n (%)	103 (68.2%)	88 (70.4%)	15 (57.7%)		47 (64.4%)	36 (63.2%)	11 (68.8%)	
Definitive, n (%)								
Loading dose								
Received	149 (98.7%)	123 (98.4%)	26 (100%)	0.518^	71 (97.3%)	55 (96.5%)	16 (100%)	1*
Not received	2 (1.3%)	2 (1.6%)	0	1*	2 (2.7%)	2 (3.5%)	0 (0%)	
Days of Colistin therapy								
Median (Q1, Q3)	8 (5, 11)	8 (5, 11)	6 (4, 10.75)	0.086**	7 (5, 10)	8 (5, 10)	5.5 (3, 11)	0.384**

^The chi-squared test was performed to determine the significance of the differences between the groups, and the resulting *P*-values are reported. *Fisher's exact test was performed to calculate the exact *P*-value and determine the significance of the association between the variables. The resulting *P*-value is reported. **The Wilcoxon rank-sum test (also known as the Mann-Whitney U test) was performed to compare the distributions of continuous variables and determine the significance of the differences between the groups. The resulting *P*-value is reported. Abbreviations: MIU – Million International Units, TID – Thrice a day, BD – Twice a day, CAP-Community acquired pneumonia, HAP – Hospital acquired pneumonia, VAP – Ventilator associated pneumonia, BSI – Blood stream infection, UTI – Urinary tract infection, SSTI – Skin and soft tissue infection, CIAI – Complicated intra-abdominal infection, CNS – Central nervous system, ESBL – Extended-spectrum beta-lactamase

Primary outcome analysis and clinical results. In the primary outcome analysis, 8 patients (50%) in the 4.5 MIU BD group died within 28 days, compared to 32 patients (56.1%) in the 3 MIU TID group (P = 0.663). The 28-day all-cause mortality rates in both groups were not significantly different in the multivariable regression analysis (OR – 0.48; 95% CI [0.07 – 3.46]; P = 0.467) (Table 3).

Resolution of symptoms and signs of infection within 28 days was achieved by 7 patients (43.8%) in the 4.5 MIU BD group and 21 patients (36.8%) in the 3 MIU TID group (OR = 1.67; 95% CI [0.31 – 8.90]; P = 0.548)

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(Table 3). Persistence of bacteria in cultures or detection of bacteria in sterile sites within 28 days was observed in 1 patient (6.3%) in the 4.5 MIU BD group and 4 patients (7%) in the 3 MIU TID group (OR = 0.13; 95% CI [0.001 – 19.5]; *P* = 0.428) (Table 2). However, the study was underpowered to detect a true difference in the clinical outcome variables, with a sample size that provided less than 10% power to detect a significant effect.

AKI events in each group. Among the 16 patients who received the 4.5 MIU BD dosing after propensity score matching, 2 (12.5%) experienced acute kidney injury events. In contrast, among the 57 patients who received 3 MIU TID dosing, 25 (43.9%) developed acute kidney injury. The difference was statistically significant in the multivariable regression analysis, adjusting for age, gender, specific infectious syndromes (*e.g*. pneumonia, urinary tract infections), resistance profile of organism, indication and duration of colistin therapy, use of a loading dose of colistin and co-administration of nephrotoxic drugs as covariates (Odds ratio [95% CI] = 0.04 [0.004 – 0.350], *P* = 0.004) (Table 3). A post-hoc power analysis was conducted with a type I error rate of 0.05 to determine if this was a statistically significant difference, considering the small sample size (small compared to the desired power of 80%). The analysis showed 67% power to detect a statistically significant difference in AKI events between the two groups.

Table 3. Multivariable logistic regression analysis for the outcomes after propensity score matching

Outcomes	3 MIU TID	4.5 MIU BD	*P*-value	Odds ratio (95% CI)	*P*-Value[$]
28-day mortality, n (%)	32 (56.1%)	8 (50%)	0.663^	0.48 (0.07-3.46)	0.467
Clinical cure, n (%)	21 (36.8%)	7 (43.8%)	0.616^	1.67 (0.31-8.90)	0.548
Microbiological failure, n (%)	4 (7%)	1 (6.3%)	1*	0.13 (0.001-19.5)	0.428
AKI events during Colistin therapy, n (%)	25 (43.9%)	2 (12.5%)	0.022^	0.04 (0.004-0.35)	**0.004**
Readmission within 90 days, n (%)	16 (28.1%)	4 (25%)	0.947^	1.05 (0.12-9.10)	0.964
				Beta coefficient (95% CI)	***P* value[$**]**
Length of hospital-stay (Days), Median (Q1, Q3)	16 (13,30)	12.5 (6.75,35.5)	0.439[#]	1.55 (-6.04 – 9.14)	0.683

^ Chi-squared test*Fisher's exact test [#]Mann-Whitney U test. [$]Multivariable logistic regression analysis was used to estimate Odds ratio (OR) and *P*-value. [$**]Multiple linear regression model was used to estimate beta coefficient and *P*-value. Abbreviation: MIU – Million International Units, TID – Thrice a day, BD – Twice a day, CI – Confidence Interval, AKI – Acute Kidney Injury

Re-admission within 90 days. During the 90-day period following hospital discharge, 4 patients (25%) in the 4.5 MIU BD group were readmitted to the hospital, while 16 patients (28.1%) from the 3 MIU TID group experienced hospital readmission (OR = 1.05; 95% CI [0.12 – 9.10]; *P* = 0.964).

Length of hospital stay. Patients in the 4.5 MIU BD group had a median (quartiles Q1, Q3) hospital stay duration of 12.5 (6.75, 35.5) days, whereas the 3 MIU TID group had a median of 16 (13, 30) days. The difference in the length of hospital stay between the two groups was not statistically significant in a multivariable linear regression analysis (regression coefficient = 1.55; 95% CI [-6.04 – 9.14]; *P* = 0.683) (Table 3).

DISCUSSION

In this observational study, the patient outcomes, including clinical cure, 28-day all-cause mortality, and microbiological failure, did not differ significantly in a statistical analysis between the 4.5 MIU BD and 3 MIU TID colistin dosing groups. Similarly, the length of hospital-stay and hospital readmission rates within 90 days of discharge did not differ significantly in a statistical analysis between the two groups. The most significant finding was that the incidence of acute kidney injury, which is the most common side effect associated with colistin use, was statistically significantly lower in the 4.5 MIU BD group compared to the 3 MIU TID group.

Nephrotoxicity has been reported to occur in 18% to 60% of patients in the intensive care unit (ICU) receiving colistin [9, 10]. Therefore, identifying dosing strategies that can reduce the incidence of nephrotoxicity is of paramount importance when using this antibiotic in the management of multidrug-resistant Gram-negative infections.

Based on our review of the literature, this is the first study to conduct a head-to-head comparison of patient outcomes and nephrotoxicity associated with twice-daily (BD) versus thrice-daily (TID) fractionated dosing of a total daily colistin dose of 9 MIU in critically ill patients with MDR Gram-negative infections. Our study did not find a difference at a *P*-value threshold of 0.05 in the 28-day mortality, clinical cure, or microbiological failure between the 4.5 MIU BD group and 3 MIU TID group. However, it is important to note that the study was underpowered based on a power analysis, and a larger sample size would have been required to detect actual differences in these outcome variables.

Previous studies have reported different outcomes regarding the effective dosing regimen of colistin. A prospective study by Dalfino *et al*. (2012) found an 82% patient cure rate with a 9 MIU loading dose followed by a 9 MIU twice-daily maintenance regimen [9]. In contrast, a study by Ghazaeian *et al*. (2017) reported no difference in ICU length of stay and mortality between critically ill patients receiving 3 MIU TID versus 9 MIU once-daily colistin [11].

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Pharmacokinetic studies have suggested that a fractionated regimen of 9 MIU Colistin given 3 times daily may result in delayed and suboptimal steady-state concentrations, whereas the same total daily dose divided into two 4.5 MIU doses achieves steady state more rapidly [12, 13]. This is relevant because rapid bacterial killing is observed when the colistin peak concentration (C_{max}) is at or above the minimum inhibitory concentration, and modest post-antibiotic effect is seen at higher colistin concentrations. These pharmacodynamic factors may favor the 4.5 MIU BD dosing regimen over the 3 MIU TID regimen [14, 15].

The re-admission rates within 90 days of hospital discharge and the length of hospital stay did not differ at a *P*-value threshold of 0.05 between the 4.5 MIU BD and 3 MIU TID colistin dosing regimen groups in our study. However, the post-hoc power analysis revealed that the study was underpowered based on a power analysis to detect actual differences in these secondary outcome measures.

One of the key findings of our study was the lower incidence of AKI at a *P*-value threshold of 0.05 in the 4.5 MIU BD group compared to the 3 MIU TID group. Nephrotoxicity associated with colistin use is typically due to acute tubular necrosis with vacuolar degeneration and tubular casts, while the glomeruli are often preserved [16]. This nephrotoxicity usually occurs within the first 3–7 days of colistin therapy [17].

A recent study by Samarkos *et al*. (2022) compared the incidence of AKI between once-daily versus twice or thrice-daily colistin dosing regimens, but did not specifically investigate the difference between the twice-daily and thrice-daily regimens [18]. The mechanism underlying the lower AKI incidence with the 4.5 MIU BD dosing regimen observed in our study may be related to the longer time period between doses, allowing for better clearance of colistin from the proximal renal tubules, where it tends to accumulate and cause mitochondrial dysfunction [19, 20].

While colistin-induced AKI is typically reversible, full recovery of renal function may not always occur [21, 22]. Therefore, optimizing the dosing regimen to reduce the incidence of nephrotoxicity is of paramount importance when using colistin to treat MDR Gram-negative infections in critically ill patients.

In India, where therapeutic drug monitoring of colistin is not widely available in many parts of the country, a standard daily dose of 9 MIU of colistimethate sodium, equivalent to 300 mg of colistin base activity (CBA), is commonly administered in two or three divided doses to adult patients [5]. This dosing strategy is employed to achieve target concentrations, as colistin's pharmacokinetics are not significantly affected by patient weight, making weight-based dosing unnecessary.

The half-life of colistin among critically ill patients not receiving renal replacement therapy is estimated to be around 14.4 hours, which is substantially longer than the 8-hour dosing interval typically used in a thrice-daily regimen [23]. Considering the available evidence in the literature and the findings of the current study, the optimal dosing regimen for critically ill adult patients with creatinine clearance ≥ 50 mL/min appears to be a loading dose of 9 MIU followed by a maintenance regimen of two fractionated doses of 4.5 MIU given twice daily (BD) [21].

The use of a colistin loading dose and its association with AKI has produced inconsistent findings in the published literature. However, the potential benefits of a loading dose may outweigh the potential nephrotoxicity, and this approach deserves further investigation [24, 25].

This study had several notable strengths. First, it addressed a pressing clinical dilemma by directly comparing two commonly used colistin dosing regimens. Second, the use of propensity score matching to create the study population helped reduce selection bias, which can be a significant concern in a retrospective design. Third, the study was sufficiently powered to detect a statistically significant difference in the incidence of AKI between the study groups, which was a key finding. Finally, the blinding of the statistician helped eliminate the risk of detection bias.

However, the study also had some limitations. Colistin MICs were not determined using CLSI-recommended broth microdilution method, which is considered the gold standard [7]. Instead, the VITEK® 2 system, which employs a continuous automated monitoring approach, was used. While this may have been less precise than the broth microdilution method, the even distribution of MICs in the two groups did not affect the comparison of the outcome measures.

Other limitations of this study include its single-center, retrospective design and insufficient sample size to detect statistically significant differences in the clinical outcomes, such as 28-day mortality, clinical cure, and microbiological failure. Therefore, the results of this study may lack external validity and may not be applicable to other settings or populations.

In this observational study, the twice-daily (BD) administration of a total daily colistin dose of 9 MIU was associated with a substantially reduced incidence of AKI compared to the thrice-daily (TID) administration of 3 MIU. However, no observable differences were found in the clinical outcomes between the two dosing regimens.

Given the importance of reducing the risk of nephrotoxicity associated with colistin use in critically ill patients, the 4.5 MIU BD dosing regimen may be the recommended approach in clinical practice. Nevertheless, the comparative effectiveness of these two dosing strategies on clinical outcomes warrants further investigation in larger, prospective studies.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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