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Investigation on the Use of Colistin in Critically Ill Patients at A Teaching Hospital in Ho Chi Minh City

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ABSTRACT

Colistin is reintroduced into therapeutic protocols as a last resort antibiotic against multidrug-resistant pathogens. In February 2019, the International Consensus Guidelines on optimizing the use of colistin stipulated an official recommendation on a higher colistin dosing regimen based on pharmacokinetic/pharmacodynamic (PK/PD) data. This study aimed to assess the current colistin dosing at a teaching hospital and to identify rates and risk factors of colistin-induced nephrotoxicity. This retrospective cross-sectional study was conducted on patients admitted to the Intensive Care Unit, treated for severe infection with at least five days of intravenous colistin from April 2018 to April 2019. KDIGO criteria were used to identify acute kidney injury (AKI) during treatment. Most patients (n=104, 87.4%) were diagnosed with pneumonia mainly due to *Acinetobacter baumannii*. Colistin resistance was detected in four cases during the study period. Rational dosing following the PK/PD approach, the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) was observed in 33 (27.7%), 39 (32.8%), and 44 cases (38.2%), respectively. Eighty-five cases (71.4%) were evaluated as rational dosing following at least one of the three dosing guidelines. Clinical efficacy was recorded in 59 patients (49.6%). A lower maintenance dose and a longer delay from the onset of infection to colistin initiation were observed in the group with treatment failure (p=0.002 and p=0.025, respectively). KDIGO-defined AKI occurred in 70 patients (58,8%). Multivariate analysis showed that concomitant vasopressors (OR=16.52; 95% CI 5.37-50.83; p=0.001), furosemide (OR=5.24; 95% CI 1.89-14.55; p=0.001), and hypoalbuminemia (<25 g/L) (OR=6.24; 95% CI 2.17-17.93; p=0.001) were significantly associated with nephrotoxicity. To conclude, our study showed dosing inconsistencies among clinicians and high colistin-induced nephrotoxicity incidence despite the low PK/PD-based dosage rate. Concomitant vasopressors, furosemide, and hypoalbuminemia were independent predictors for colistin-induced AKI.

Keywords: colistin, critically ill patients, nephrotoxicity, dosage, multidrug-resistant

INTRODUCTION

Colistin is reintroduced into therapeutic protocols as salvage therapy for gram-negative bacteria (GNB) infections, notably multidrug-resistant (MDR) and extensively drug-resistant strains. Given the global prevalence of antimicrobial resistance and the lack of commercialization of new therapeutic molecules, colistin is increasingly used, contributing to the rapid emergence of colistin resistance (Wangchinda *et al.,* 2018). Since 2015, numerous studies have reported the spread of plasmid-mediated colistin resistance encoded by mcr-like genes after its first occurrence in China, raising constant fear of clinical therapeutic impasse.

Optimizing colistin dosing is one of the recommended strategies to cope with this possible situation. Accordingly, the 2019 International Consensus Guidelines (ICG 2019) on optimizing the colistin administration officially recommended a higher colistin dosing based on PK/PD data over FDA- and EMA-approved recommendations (Tsuji *et al.,* 2019, Nation *et al.,* 201, Nation *et al.,* 2017). The PK/PD-based approach was established to achieve a target concentration at steady state ($C_{ss\ target}$) of 2 mg/L. This concentration has been proven to be effective against infecting organisms with minimum inhibitory concentration (MIC) ≤2 mg/L (for bloodstream infection) or <1 mg/L (for respiratory infection) (Tsuji *et al.,* 2019, Nation *et al.,* 2017). Notably, although the $C_{ss\ target}$ of 2 mg/L might be suboptimal for lower respiratory tract infections due to its low lung tissue penetration after intravenous administration, it should also be considered as maximum tolerable exposure. Nephrotoxicity is the most significant adverse effect of colistin therapy and is associated with increased mortality. This would impose a limitation on dose escalation and increase the need for therapeutic drug monitoring (Nation *et al.,* 2016). Our center documented some first colistin-resistant cases and the variation in the choice of colistin dosing guidelines among the treating physicians. This study was conducted to assess the current colistin dosing at the center and to identify rates and risk factors of colistin-induced nephrotoxicity - its most common treatment-limiting adverse reaction.

MATERIAL AND METHODS

Study design and population

This retrospective cross-sectional study was conducted between April 2018 and April 2019 using data collected from electronic medical records of critically ill patients at the Intensive Care Unit (ICU) of the University Medical Center of Ho Chi Minh City (UMC HCMC), a teaching hospital with 1,000 inpatient beds. The required sample size was estimated using the formula as follows:

$$\text{Sample size} \geq \frac{Z_{1-\alpha/2}{}^2 \times p \times (1-p)}{d^2} = \frac{1.96^2 \times 0.362 \times (1-0.362)}{0.1^2} = 89$$

with p=0.362 based on the study (Eljaaly *et al.,* 2021).

However, this study included all eligible cases aged at least 18 years old, diagnosed with severe infections due to minimally susceptible GNB, and receiving at least five days of intravenous colistin during the study period. For patients who took several courses of antibiotic treatment with colistin due to recurrent GNB infections during their hospital stay, the first was included in the study. Patients were excluded if they were pregnant or breastfeeding, had an increase in serum creatinine (SCr) >50% within 72 hours before colistin initiation, or had been diagnosed with end-stage kidney disease requiring renal replacement therapy (RRT). Patients receiving inhaled colistin as monotherapy (without intravenous colistin) or with missing data regarding renal function testing during colistin therapy were also excluded.

The decision to initiate colistin and initial colistin dose was at the discretion of the treating physicians based on susceptibility testing results of isolated pathogens and estimated Cockroft-Gault creatinine clearance (CrCl), respectively. Patients were followed up until hospital discharge or death.

Study variables, definitions and measurements

Data variables included age, sex, weight, Charlson comorbidity score, invasive procedures, types of infection, sepsis or septic shock, causative organisms and their susceptibility, loading dose (LD), daily maintenance dose (MD) of IV colistin, MD per ideal body weight (IBW), adjunctive inhaled colistin dose, duration of therapy (DOT), cumulative dose, combined antibiotic agents, concomitant use of other nephrotoxic agents, daily SCr, clinical responses to treatment (symptoms and signs of infection), pro-calcitonin (PCT), C-reactive protein (CRP), total leukocyte count (TLC). Infection severity (sepsis and septic shock) was diagnosed following the SEPSIS-3 (Singer *et al.,* 2016).

Colistin MICs were determined using broth microdilution only when ordered by the treating physician after the pathogens were isolated. The isolates were considered colistin-susceptible during the study period if MIC colistin was ≤2 mg/L as per the European Committee on Antimicrobial Susceptibility Testing (2019). Therapeutic indication of colistin is defined as rational when isolates were fully susceptible to colistin +/- minimally susceptible to other antibiotics on antibiogram (must be carbapenem-resistant).

Evaluation of colistin dosage was based on three official recommendations, i.e., FDA, EMA, and ICG 2019. Colistin dose was defined as rational when following at least one of the three recommendations.

Table I. KDIGO criteria for acute kidney injury

	Serum creatinine	Urine output
Diagnostic criteria	≥0.3 mg/dL increase within 48 hours OR ≥1.5 times baseline within 7 days	<0.5 mL/kg/h for >6 h
Staging criteria		
Stage 1	1.5 -1.9 times baseline OR ≥0.3 mg/dL increase	<0.5 mL/kg/h for 6-12 h
Stage 2	2.0-2.9 times baseline	<0.5 mL/kg/h for 12-24 h
Stage 3	≥3.0 times baseline OR Increase in SCr to ≥4.0 mg/dL OR Decrease in eGFR to <35 mL/min/1.73 m^2 OR Initiation of kidney replacement therapy	<0.3 mL/kg/h for ≥24 h OR Anuria for ≥12 h

eGFR=estimated glomerular filtration rate; SCr=serum creatinine

Clinical cure was defined as the resolution of symptoms and signs of infections along with normalization of TLC, neutrophil percentage, and CRP (<5 mg/L), especially with confirmation of PCT <0.5 ng/mL (Rhee, 2017). Microbiological follow-up was done at least weekly after the initiation of colistin therapy. Microbiological response to treatment was defined as eradicating MDR bacteria in all follow-up cultures. AKI was determined based on the increase in the SCr level as per KDIGO criteria (Table I), urine criterion was not used for staging (Acute Kidney Injury Work Group 2012).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 (IBM Corp, Somers, NY, USA). Continuous normally distributed data, expressed as mean ± standard deviation (SD), were compared using an independent sample t-test. Non-normally distributed data, expressed as median (interquartile range), were compared using the Mann-Whitney U-test. Categorical data are expressed as frequency (n) and percentage (%) of events and compared by the chi-square test if ≤20% of expected cell counts <5 or the Fisher exact test if >20% of expected cell counts <5. Logistic regression was used to identify risk factors statistically associated with AKI. All variables with a P-value <0.05 in the bivariate analyses were examined for the presence of multi-collinearity between covariates with variance inflation factor (VIF) via doing a correlation test between independent variables using Collinearity diagnostics tool of IBM SPSS. All variables with a VIF <2 were included in the final multivariate analysis, with forward stepwise (Forward-LR) entry method. The data were analyzed at a confidence level of 95%. In all comparisons, all P-values were 2-sided and a P-value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Patients' characteristics

Of 173 critically ill patients in the ICU receiving colistin therapy over the study period, 119 patients meeting all the inclusion/exclusion criteria were included in the final analysis (Figure 1). The patient characteristics, including demographics, clinical conditions, and characteristics of infectious episodes (Table II).

Patients were treated mainly for pneumonia (87.4%) and catheter-related bloodstream infection (22.7%). Among them, 23 patients (19.3%) had two foci of infection: pneumonia and bloodstream infection. Fifty patients (42%) experienced septic shock, and 23 (19.3%) sepsis.

Three patients (2.5%) carried strains defined as multisensitive and one patient received empirical colistin therapy without microbiological evidence for MDR infection. Accordingly, 115 patients (96.6%) carried ≥1 MDR strain. Of these patients, 18 (15.1%) were infected by two germs. Of 140 MDR isolated strains, 84 strains were *Acinetobacter baumannii* (60.0%), 46 *Klebsiella pneumoniae* (32.9%), 7 *Pseudomonas aeruginosa* (5.0%), 2 *Escherichia coli* (1.4%). All GNB strains were carbapenem-resistant; 30 were susceptible only to colistin. Only 32 strains had available colistin MIC (22.2%), which was obtained only when being ordered by the treating physicians, often 1-2 weeks after colistin initiation.

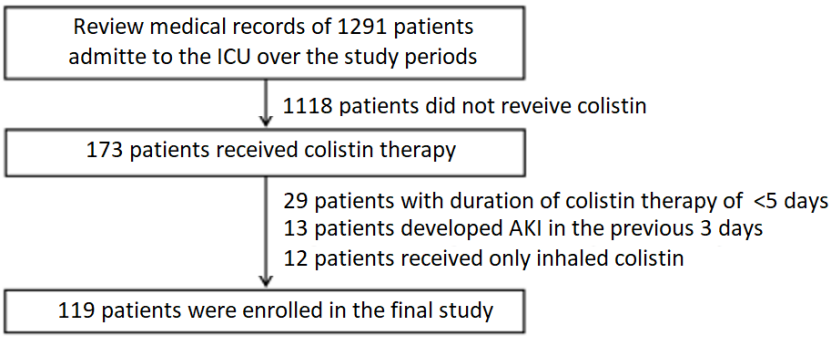

Figure 1. Patient recruiting process

Table II. Patient characteristics including demographics, clinical conditions, and characteristics of infectious episodes

Variable	Result
Demographics and clinical conditions	
Male, n (%)	73 (61.3%)
Age (years), median (IQR)	77 (66-86)
Ideal body weight (kg), mean ± SD	55.6 ± 8.5
Baseline serum creatinine (mg/dL), mean ± SD	1.3 ± 0.6
Baseline creatinine clearance (mL/min), median (IQR)	40.6 (29.6-72.6)
Prior hospitalization within 90 days, n (%)	45 (37,8%)
Length of ICU stay (days), median (IQR)	30 (21-42)
Acute respiratory distress syndrome, n (%)	81 (68,1%)
Circulatory failure requiring vasopressor agents, n (%)	54 (45,4%)
Severe anemia requiring blood transfusion, n (%)	49 (41.2%)
Hyperbilirubinemia, n (%)	30 (25,2%)
Hypoalbuminemia (serum albumin <25 g/L), n (%)	52 (43,7%)
Charlson score, median (IQR)	5 (4-7)
Hypertension, n (%)	64.7%
Diabetes mellitus, n (%)	37.0%
Chronic kidney disease, n (%)	31.9%
Characteristics of infectious episodes	
Sepsis	23 (19.3%)
Septic shock	50 (42%)
Pneumonia	104 (87.4%)
Bloodstream infection	33 (27.7%)

These available MICs ranged from 0.75 to 16 mg/L (Figure 2). All four patients with colistin-resistant strains experienced therapeutic failure with colistin IV and were then treated with tigecycline-based therapy but all experienced treatment failure.

The previous study by Bang (2017) at the same center did not declare any colistin-resistant strains but a high proportion of irrational colistin indication (Bang and Trang 2018). In this study, the emergence of colistin-resistant strains was documented. This situation would end up in a therapeutic impasse soon and accentuate the importance of increasing the rational use of colistin. UMC HCMC later issued a decree restricting the empirical use of this critical antibiotic. This empirical prescription must be implemented in the setting of treatment failure with all other therapeutic options. For this reason, the rate of rational colistin indication in this study was higher than that of the previous study by Bang (2017) (96.6% vs. 32.8%).

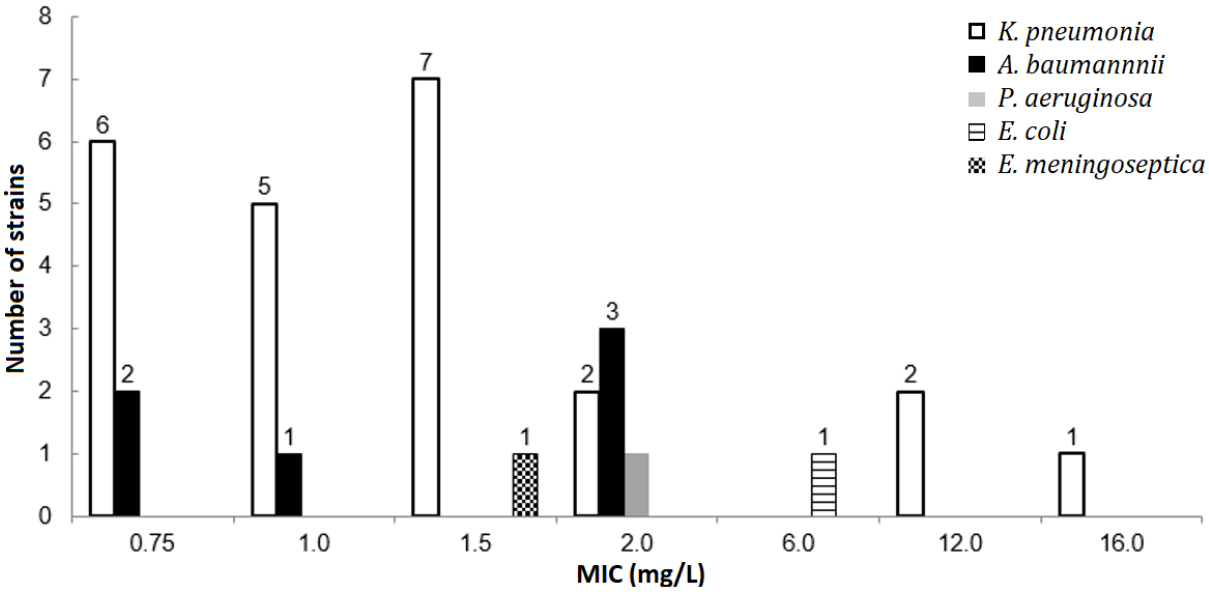

Figure 2. Available MIC values.

Characteristics of colistin therapy

Colistin was initiated after the onset of the infectious episode 15 days (7-22), with a mean daily dose of 6 ± 2 MIU (ranging from 2 to 12 MIU/day). An LD of 9 MIU was used in 15 patients (12.6%). The median duration of colistin therapy was 13 days (10-18), and the mean cumulative dose was 88.9 ± 38.6 MIU. One hundred and four patients (87.4%) received adjunctive inhaled colistin due to pneumonia. In all cases, colistin was used in combination therapy with carbapenems in 73 patients (61.3%) and sulbactam-based therapy in 62 (52.0%).

Rationality of therapeutic indication

One hundred and fifteen cases (96.6%) had rational colistin indication. Among four cases with irrational colistin indication, three carried multisensitive strains (sensitive to ≥3 groups of antibiotics on antibiogram) and one patient received empirical colistin therapy before obtaining a culture test result positive for MDR GNB, whereas this patient had previously been treated with only meropenem in eight days in monotherapy.

Rationality of colistin dosage

Generally, overdosing was significantly more common in patients with CrCl <30 mL/min following PK/PD dosing approach, FDA- and EMA-approved dosage. The overall rate of rational dosage following g at least one of the three dosing guidelines were found to be modest (85/119 patients, 71.4%), but each individual rate was low (27.7%, 38.2%, and 32.8%, according to PK/PD dosing approach, FDA, and EMA, respectively) (Table III). This statistical dispersion reflected inconsistent choice of dosing regimen among the physicians. We suggest establishing a uniform modality of colistin administration at the UMC HCMC to systematically optimize the current dosage and avoid the excessive risk of AKI without compromising antibacterial activity.

Colistin efficacy

Clinical cure with confirmation of PCT level of less than 0.5 ng/mL and relief of infection signs and symptoms was recorded in 59 out of 119 infected patients (49.6%), mainly after 5-14 days of treatment. Among these patients, microbiological eradication was found in 33 cases (55.9%).

In the successfully treated group, colistin therapy was initiated after a shorter delay from the onset of infection than in the failed group, with a statistically significant difference (13 vs. 17.5, p=0.025). DOT in general or a DOT ≥14 days in particular did not show a statistically significant difference between the two groups (p=0.934 and p=0.361, respectively). The successfully treated group received a higher average MD and a higher average MD per IBW, with a statistically significant difference (6.5 vs. 5.4 MIU, p=0.002).

Table III. Colistin dosage stratified by dosing guidelines and renal clearance

Dosage regimen	Stratification	Overall n (%)	Creatinine clearance (mL/min)				
			<10 (n=4)	10-<30 (n=19)	30-<50 (n=37)	50-<80 (n=18)	≥80 (n= 41)
ICG 2019 (n=119)	Underdosing	80 (67.2%)	0	16 (84.2%)	13 (35.1%)	14 (77,8%)	37 (90,2%)
	Rational dosing	33 (27.7%)	2 (50.0%)	0	23 (62.2%)	4 (22,2%)	4 (9.8%)
	Overdosing	6 (5.4%)	2 (50.0%)	3 (15.8%)	1 (2.7%)	0	0
FDA-approved dose (n=115)*	Underdosing	1 (0.9%)	-	0	0	1 (5.6%)	0
	Rational dosing	44 (38.2%)	-	0	6 (16.2%)	9 (50.0%)	29 (70.7%)
	Overdosing	70 (60.9%)	-	19 (100%)	31 (83.8%)	8 (44.4%)	12 (29.3%)
EMA-approved dose (n=119)	Underdosing	68 (57.1%)	0	16 (84.2%)	13 (35.1%)	39 (66.1%)	
	Rational dosing	39 (32.8%)	0	0	23 (62.2%)	16 (27.1%)	
	Overdosing	12 (10.1%)	4 (100%)	3 (15.8%)	1 (2.7%)	4 (6.8%)	

FDA guideline does not recommend MD for the CrCl <10 mL/min group (n=4)

On the whole, the clinical cure rate was quite similar to that reported in the previous study of Bang (2017) (49.6% vs. 47.5%) or Trifi et al. (2016) in the low-dose group receiving 6 MIU/day (49.6% vs. 41.3%), but significantly lower than that in Sorlí et al. (2017) (79%) or Binh (2015) (67.9%) even with a similar mean MD (6 MIU/day) (Trifi *et al.,* 2016, Binh *et al.,* 2015, Sorli *et al.,* 2017). It might be because our study involved critically ill patients in ICU who had many physiological changes and more severe infections. Notably, it should also be aware that a significant temporal delay in receiving an effective targeted treatment is associated with therapeutic failure, leading to sepsis or septic shock, which are associated with kidney injury and increased mortality (Nation *et al.,* 2019, Zarjou and Agarwal 2011). Indeed, the proportion of septic shock in the failed group was significantly higher than that in the successfully treated group (36/60 (60.0%) vs. 14/59 (23.7%), p=0.001).

Besides, previous studies based on clinical and PK/PD data demonstrated minimal clinical efficacy of colistin even if colistin MIC was ≤2. For this reason, the Clinical and Laboratory Standards Institute (CLSI) guideline from the 30th edition published in 2020 just renders a colistin-intermediate result for GNB with MIC ≤2 instead of a susceptible result as per previous CLSI guideline editions (Clinical and Laboratory Standards Institute CLSI 2020). Accordingly, Infectious Diseases Society of America Guidance strongly prefers new FDA-approved beta-lactam/beta-lactamase inhibitor combinations instead of colistin for treating carbapenem-resistant GNB infection and only limits colistin to uncomplicated MDR cystitis (Tamma *et al.,* 2021).

Colistin nephrotoxicity

Characteristics of colistin-related AKI

Generally, patients in the study had a wide range of CrCl, varying from 5.42 to 180.6 mL/min with a median of 40.6 mL/min. KDIGO-defined AKI occurred in 70 patients (58.8%), with 29, 32, and 9 cases in stages 1, 2, and 3, respectively. The spared group presented a better baseline CrCl (p=0.033, respectively). AKI appeared mainly in the first week after the start of colistin therapy, on average 6.5 (4-9.25) days.

Colistin-induced AKI rates range from 12% to 69% in the literature (Eljaaly *et al.,* 2021, Trifi *et al.,* 2016, Binh *et al.,* 2015, Sorli *et al.,* 2017). Our finding of a 58.8% nephrotoxicity risk was consistent with the studies that characterized colistin-induced AKI throughout colistin therapy, e.g., the study by Sorlí (58.8% vs. 53.8%) with approximate mean MD (6 MIU vs. 5.5 MIU). Yet, this rate was higher than that of most series, namely, that of Trifi (29.3%) or Binh (21%). Notably, the KDIGO criteria used in our study were not applied as frequently as the RIFLE criteria to patients receiving colistin. However, recent studies on colistin-induced nephrotoxicity have increasingly benefited from the KDIGO criteria because it is found to be more sensitive and more predictive of the occurrence of AKI than RIFLE and gives higher nephrotoxicity rates (Luo *et al.,* 2014).

Factors associated with nephrotoxicity

In bivariate analysis, age >80 years, presence of previous AKI, baseline CrCl, Charlson comorbidity score >5 points, hypoalbuminemia, the state of septic shock or hypotension requiring vasopressor agents, DOT ≥14 days, number of concomitant nephrotoxic agents, and concomitant

intake of furosemide or vancomycin were significantly associated with AKI (Table IV). When examining the presence of multi-collinearity between the covariates, there was slight collinearity between the two variables "Number of concomitant nephrotoxic agents" and "Furosemide" (VIF=2.215 and VIF=2.004, respectively). The variable "Number of concomitant nephrotoxic drugs" was excluded from the final multivariate analysis because of its overlap with "Furosemide" and "Vancomycin", and other nephrotoxic agents were only administered in very few cases. Multivariate analysis showed that concomitant vasopressors (OR=16.52; 95% CI 5.37-50.83), furosemide (OR=5.24; 95% CI: 1.89-14.55), and hypoalbuminemia (OR=6.24; 95% CI 2.17-17.93) were significantly associated with colistin-induced AKI. Our finding is consistent with colistin nephrotoxicity risk factors described in the literature (Tsuji *et al.,* 2019).

Among the three independent risk factors of colistin-induced AKI, the use of vasopressors is the most important determinant (OR=16.52). For vasopressor agents, particularly norepinephrine (the most commonly prescribed vasopressor), despite its agonist action on alpha-1 receptors that induces general and renal vasoconstriction, there is no data yet to define the effects of norepinephrine on the kidney. However, it might be the clinical condition requiring its administration that counts states of shock with hypovolemia and systemic hypotension. These are possible mechanisms of AKI regardless of colistin use.

As for hypoalbuminemia, this predictive factor has also been confirmed in numerous studies, namely, that of Giacobbe (2018) or Omrani (2015). Currently, it is considered inappropriate to modify colistin dose in patients with hypoalbuminemia (Tsuji *et al.,* 2019). However, these results suggest that severe hypoalbuminemia (albuminemia <25 g/L) is a real risk factor for AKI under colistin therapy or not, and some authors have suggested some possible mechanisms. First, about 26-41% of serum colistin binds to albumin with a high affinity under normal conditions. A decrease in albuminemia will reduce the binding rate of colistin to proteins and thus lead to an increase in its free form, leading to increased toxicity (Giacobbe *et al.,* 2018, Fiaccadori *et al.,* 2016). Additionally, severe hypoalbuminemia is responsible for altering the distribution of fluids and drugs due to a decrease in oncotic pressure, causing relative hypovolemia and compromising kidney infusion. Hypoalbuminemia would also reduce the trapping of reactive oxygen species by albumin and DNA synthesis of renal tubular cells, thus reducing its antioxidant activity and kidney protection (Wiedermann *et al.,* 2010).

For furosemide, the study by Bang (2017) also demonstrated a significant association between concomitant furosemide and AKI (Bang and Trang 2018). Concomitant use of diuretics has a high potential to cause AKI in patients with true or relative hypovolemia in ICU (dérique Schortgen, 2011). Nevertheless, using diuretics in critically ill patients is inevitable, and furosemide has a relatively modest risk profile. After all, these three factors seem to be non-modifiable. Treating physicians can rely on modifiable risk factors as shown in bivariate analysis (DOT, daily MD, concomitant use of nephrotoxic agents) to take the necessary therapeutic measures in patients at higher risk of AKI.

Regarding colistin dosage, the successfully treated group received higher average MD (p=0.002), but daily MD does not significantly associate with renal toxicity (p=0.551), even with daily MD per kg IBW ≥150,000 IU/kg/day (or 5 mg/kg/day, maximum MD according to the FDA). These data show that higher doses of colistin could be used safely. Similarly, Trifi et al. (2016) verified that the high-dose regimen (9 MIU/day) was more effective, with no significant renal toxicity (Trifi *et al.,* 2016). Yet, this result was contrary to the study by Shields (2017), in which an MD of ≥5 mg/kg/day is an independent predictor of AKI (Shields *et al.,* 2017). Though the PK/PD approach with a higher colistin dose regimen was established to produce a $C_{ss\ target}$ of 2 mg/L (proven to be effective against strains with MIC ≤1 mg/L), PK/PD characteristics of colistin are subject to significant variability, and this dosage was based on data focusing mainly on bloodstream infection. Besides, this $C_{ss\ target}$, also the maximum tolerability threshold, is still suboptimal for the systemic treatment of pneumonia (Cheah *et al.,* 2015). Due to a very modest clinical efficacy and a high frequency of colistin-induced AKI, colistin should be regarded as a last-line agent, and safer alternatives with minimal nephrotoxicity such as new beta-lactam/beta-lactamase inhibitor combinations should be considered, when possible, for treating carbapenem-resistant infection as recommended by Infectious Diseases Society of America Guidance (Tamma *et al.,* 2021).

Table IV. Factors associated with colistin-induced nephrotoxicity.

Variable	Bivariate analysis		Exam of collinearity	Multivariate analysis	
	OR (95% CI)	P	VIF	OR (95% CI)	p
Female	1.43 (0.35-1.60)	0.056	-		
Age	1.03 (0.99-1.06)	0.067	-		
Age >80 years	2.44 (1.07-5.60)	**0.033**	1.431	-	-
Baseline SCr	0.96 (0.67-1.39)	0.844	-		
Baseline CrCl	0.99 (0.98-1.00)	**0.011**	1.676	-	-
Pre-existing CKD	2.17 (0.95-4.95)	0.066	-		
Previous AKI	5.05 (2.29-11.13)	**<0.001**	1.625	-	-
Charlson score ≥5	2.99 (1.37-6.54)	**0.006**	1.426	-	-
Obesity	1.16 (4.47-2.82)	0.750	-		
Diabetes mellitus	1.02 (0.48-2.17)	0.964	-		
Hypertension	1.75 (0.82-3.75)	0.150	-		
Hypoalbuminemia	4.11 (1.84-9.20)	**0.001**	1.131	6.24 (2.17-17.93)	**0.001**
Hyperbilirubinemia	1.90 (0.78-4.62)	0.154	-		
Septic shock	3.661 (1.64-8.18)	**0.002**	1.564	-	-
Vasopressor agents	14.64 (5.45-39.38)	**<0.001**	1.628	16.52 (5.37-50.83)	**<0.001**
Time interval between the onset of infection and colistin therapy	1.03 (1.00-1.06)	0.096	-		
DOT >14 days	2.10 (1.00-4.43)	**0.049**	1.127	-	-
Daily MD (MIU)	0.98 (0.81-1.18)	0.801	-		
MD per kg IBW >100,000IU/kg/day	1.179 (0.49-2.18)	0.659	-		
MD per kg IBW >150,000IU/kg/day	0.741 (0.28-1.98)	0.551	-		
Number of concomitant nephrotoxic agents	2.36 (1.44-3.90)	**0.001**	**2.215**	-	-
Furosemide	4.71 (2.15-10.30)	**<0.001**	**2.004**	5.24 (1.89-14.55)	**0.001**
Aminoglycoside	2.15 (0.22-21.30)	0.513	-		
Vancomycin	3.07 (1.14-8.31)	**0.027**	1.409	-	-
Teicoplanin	5.33 (0.64-44.82)	0.123	-		
Amphotericin B	1.05 (0.17-6.54)	0.956	-		

Results of multivariate analysis: Omnibus: p <0.05; Hosmer & Lemeshow Test: p=0.49 (>0.05); -2 Log likelihood=98.72; Predictive power of the model: 84%. AKI=acute kidney injury; CKD=chronic kidney disease; CrCl=creatinine clearance; DOT=duration of therapy; IDW=ideal body weight; MD=maintenance dose; SCr=serum creatinine; VIF=variance inflation factor

This study has some limitations worthy of consideration: small sample size, dosing inconsistencies, the lack of treatment randomization in most studies, and the presence of confounders (concomitant nephrotoxic medications). Additionally, the information on clinical responses might be misinterpreted and incomplete through electronic medical records. We could not assess the role of adjunctive inhaled colistin in pneumonia treatment or monitor colistin plasma levels, given that ICG 2019 recommends targeting a 24-hour area under the curve and $C_{ss\ target}$ of 50 mg.hour/L and 2 mg/L.

The critically ill population in this study could represent other likely candidates for colistin therapy in the real world. However, the low PK/PD-based dosage rate in this study (27.7%) suggests that our finding of a 58.8 % nephrotoxicity incidence is not representative of the true risk associated with optimal dosing recommended to

produce target concentrations of maximal tolerability threshold. Our results are preliminary and require further confirmation by extensive studies.

CONCLUSION

To conclude, our study showed dosing inconsistencies among clinicians and high colistin-induced nephrotoxicity incidence despite the low rate of PK/PD-based dosage that was established to produce adequate drug exposure. Clinicians should consider colistin as a last-line agent and cautiously weigh the risks versus benefits of colistin therapy. Concomitant vasopressors, furosemide, and hypoalbuminemia were independent predictors for colistin-induced nephrotoxicity. Notably, the emergence of colistin-resistant strains, which was documented in this study, raises the importance of increasing the rational use of colistin.

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