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Original Article

Colistin nephrotoxicity in critically ill patients after implementation of a new dosing strategy

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Abstract

Introduction: Intravenous colistin is increasingly used to treat multidrug-resistant Gram-negative infections. Highly variable nephrotoxicity rates have been reported. Recent PK/PD studies propose a loading dose and a maintenance dose for better efficacy, but data on the renal toxicity of such regimens are rare. This study aimed to evaluate the incidence and risk factors for nephrotoxicity related to colistin after implementation of a new dosing regimen including a loading dose.

Methodology: This was a prospective observational study that was made between adult patients who received a minimum of 48 hours of intravenous colistin from December 2012 to January 2014 at the medical and surgical intensive care units (ICU) of a university hospital. The severity of acute kidney injury (AKI) was defined by the RIFLE criteria.

Results: Fifty-nine patients met the inclusion criteria, and 31 (52.5%) developed nephrotoxicity. The APACHE-II score was > 15 in 81% of patients. The median time to nephrotoxicity was 7 days. Patients with AKI were in risk (10.2%), injury (16.9%), failure (25.4%), and none of the patients developed permanent renal insufficiency. A logistic regression model identified three predictors of colistin-associated nephrotoxicity: age; the number of days that estimated target plasma concentrations of colistin were ≥ 3.5 mg/L in the first week of therapy; and baseline creatinine level.

Conclusion: In this cohort of severely ill ICU patients, colistin led to a relatively high rate of nephrotoxicity. Further studies are needed to identify the optimal dose for both efficacy and safety.

Key words: Colistin; dosing; loading dose; nephrotoxicity; intensive care unit.

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Introduction

There has been an increasing clinical emergence of multidrug-resistant (MDR) Gram-negative pathogens especially *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae;* this is especially problematic in critically ill patients. Colistin and polymyxins are increasingly used as the last-line therapeutic options to treat MDR Gram-negative infections because of the increasing resistance pattern of these pathogens worldwide.

CMS (colistin methanesulfonatesodium) is colistin prodrug which is used parenterally and is hydrolyzed to colistin in vivo and in vitro. Highly variable nephrotoxicity rates were reported in recent studies. Over the last decade, the pharmacokinetics/pharmacodynamics (PK/PD) of colistin has been examined using in in vitro infection models, and such pharmacological information can optimize its clinical use [1,2]. Recent PK/PD studies propose a loading dose and a maintenance dose equation for better efficacy [1], but data are scarce on the renal toxicity of such regimens. The purpose of this study is to evaluate the incidence and risk factors for nephrotoxicity related to colistin after implementation of a new dosing regimen including a loading dose.

Methodology

Adult patients (≥ 18 years) who received a minimum of 48 hours of intravenous CMS (colistin) from 1 December 2012 to 1 January 2014 at medical and surgical intensive care units (ICU) at Marmara University Hospital in Turkey were included in this prospective observational study.

The patients receiving intravenous CMS treatment for ≥ 48 hours as part of their standard care due to the presence of a probable or a documented infection (pneumonia, urinary system infection, bloodstream infection, intra abdominal infection, central nervous system infection, and wound infection) caused by multidrug resistant Gram-negative bacilli were enrolled.

Patients were excluded if they were < 18 years of age, received ≤ 48 hours of colistin, or had a need for hemodialysis or other form of renal replacement therapy at the start of colistin treatment; we also excluded patients who developed nephrotoxicity or died within the initial 48 hours of initiation of colistin treatment. If a patient received colistin more than once, then only the first one was considered in evaluation. All patients received CMS (Colimycin^{TM}, KoçakFarma – Turkey) administered intravenously over 30 min. each vial contained 150 mg of colistin base activity (CBA).

The following clinical data were collected: age, gender, body weight, Acute Physiology and Chronic Health Evaluation (APACHE) II score (in the first 48 hours), comorbidities (hypertension, diabetes mellitus, chronic renal failure, coronary heart disease, immunosuppression), type of infection, daily doses and duration of colistin therapy, co-administered antibiotics, concomitant nephrotoxic agents (aminoglycosides, vancomycin, nonsteroidal anti-inflammatory drugs, intravenous radiocontrast agent, diuretics, mannitol), serum creatinine levels, as well as clinical and microbiological responses to therapy. Renal function was assessed daily.

Creatinine clearance was calculated via the Cockcroft-Gault formula. We did not interfere with the colistin doses given to patients. All patients received a loading intravenous CMS dose of 300 mg followed by a maintenance dose every 8 to 12 h based on the creatinine clearance (CrCl) estimate determined by the attending physician. The maintenance dose was calculated by attending physicians using the formula below [1]:

$$\text{Daily dose of colistin (CBA)(mg)} = \text{colistin } C_{ss,avg}\text{target}^{a} \times (1.50 \times \text{CrCL}^{*} + 30)$$

where: [a]:$C_{ss,avg}$: average steady-state plasma concentration; * Cockcroft and Gault equation was used to estimate CrCL, and this was then normalized to a body surface area of 1.73 m^2 in this study.

Also C-target MIC value was proposed up to 5 mg/L in the original colistin dosing study [1], the desired target concentration of colistin is generally between 2.5 - 3.5 mg/dL. At our institution a C-target of 2.5 mg/L was used because colistin is usually administered in combination with other antimicrobial agents. Dosing adjustments were done by the attending physicians when the renal function declined.

Clinical and microbiological response rates at the end of the treatment as well as the 30-day survival rates were recorded. Clinical responses were defined as the disappearance of all signs and symptoms of infection or their return to pre-infection state; clinical improvement was defined as moderate or significant improvement in the severity and/or signs and symptoms of infection. Clinical failure was defined as the absence of improvement in the signs and symptoms of infection including death or the presence of an indeterminate status (inability to assess the patient due to any cause). Microbiological success was defined as the achievement of bacterial eradication on day 7 of the treatment. Microbiological failure was defined as the persistence of the causative microorganism in microbiological cultures obtained from the same infectious focus regardless of clinical success.

Creatinine was monitored up to 14 days after discontinuation of treatment in patients who developed nephrotoxicity during colistin treatment. Nephrotoxicity and severity of acute kidney injury (AKI) was defined by RIFLE (risk, injury, failure, loss, and end-stage kidney disease) criteria [3].

MDR was defined as resistance to ≥ 1 agent in ≥ 3 antimicrobial categories [4]. Health care-associated pneumonia, urinary tract infection, central nervous system infection, intra abdominal infection, bloodstream infection, and wound infection (surgical wound infection and the others) were defined according to standardized criteria of CDC 2008 [5]. The definition of sepsis, severe sepsis, and septic shock were defined according to the 2008 sepsis guideline [6].

The actual colistin dose was given in 24-hour periods and creatinine clearance was estimated on the same day; these data were put into a same formula to estimate daily target plasma concentrations of colistin, retrospectively:

$$\text{Estimated colistin } C_{ss,avg}\text{target} = \frac{\text{Daily dose of CBA (mg)}}{1.50 \times \text{CrCL} + 30}$$

The primary outcome was the cessation of CMS treatment because of nephrotoxicity or because the patient met the risk, injury or failure (R, I, or F) criteria

secondary to renal toxicity. Secondary outcomes were to determine potential risk factors for renal toxicity.

The definition of neurotoxicity and the other adverse events was defined as Common Terminology Criteria for Adverse Events (CTCAE) [7].

Our study was conducted according to the principles of the Declaration of Helsinki. The institutional Ethical Committee of Marmara University School of Medicine approved this study prior to its initiation (Approval number: 70737436-050.01.04-1300049070).

Statistical Analysis

This study used NCSS (Number Cruncher Statistical System, 2007, USA) and PASS (Power Analysis and Sample Size, 2008 Statistical Software, Utah, USA) for statistical analyses. Student's t test was used to compare normally distributed quantitative data between the two groups. Comparison of non-normally distributed parameters between the two groups was performed by Mann Whitney U test. Fisher's exact test and Yates' continuity corrected chi squared test was used to compare qualitative data. Logistic regression (Backward-Conditional) was performed for the multivariate analysis of risk factors associated with colistin nephrotoxicity.

To maximize the correct prediction percentage, cut-values for group memberships were determined by ROC analysis of predicted values created by logistic regression analysis. Clinically relevant variables with *P* values below 0.1 via bivariate analyses were included in the multivariate analysis. In addition, variables that trended toward association with toxicity were also included. The accepted *P* value as statistical significance was < 0.05.

Results

Fifty-nine patients met the inclusion criteria, and 31 (52.5%) developed nephrotoxicity. Although patients infected with any MDR Gram-negative pathogen could be included according to study protocol, all patient received CMS therapy due to infection with *A. baumanni*. The age range of the participants was between 18 and 91 years with a mean age of 58.05 ± 19.09 years. There were 24 female patients (40.7%) and 35 male patients (59.3%). Demographic and clinical

Table 1. Demographic and Clinical Characteristics of Patients and Risk Factors of Nephrotoxicity.

N = 59		**N**	**%**
Age (years) ≥ 65		26	44.1
Gender (male)		35	59.3
APACHE II > 15		48	81.4
Clinical status			
Severe sepsis		8	13.5
Septic shock		29	49.1
30 days mortality		31	52.5
Number of comorbidities ≥ 1		47	79.7
Serum albumin (g/dL) ≤ 2 g/dL		14	23.7
Concomitant antibiotic use			
	Imipenem	11	18.6
	Meropenem	33	55.9
	Sulbactam	12	20.0
	Cefoperazone/sulbactam	2	3.0
	Tigecycline	1	1.0
	Daptomycin	5	8.5
	Linezolid	6	10.2
	Other	7	11.9
Potential nephrotoxic agent			
	Diuretic	31	52.5
	Vasopressor	34	57.6
	Diuretic + vasopressor	22	37.3
	NSAID	7	11.8
	Vancomycin	5	8.5
	Aminoglycoside	1	1.6
Number of potential nephrotoxic agent			
	1 nephrotoxic agent	32	54.2
	≥ 2 nephrotoxic agent	27	45.8

Table 2. Nephrotoxicity Days (RIFLE) and Colistin Doses.

	Mean ± SD	Range
Time to nephrotoxicity (day) (n = 31); (median)	7.81 ± 3.52	3-18
Complete recovery of the renal function (n = 9)	10.67 ± 7.00	2-21
Duration of colistin treatment (day)	11.41 ± 4.29	4-26
Total parenteral + inhaler CMS) dose (mg)	5032 ± 2304	1150-14550
Total parenteral colistin (CMS) dose (mg)	3706 ± 1851	1150-10800

characteristics of patients and risk factors of nephrotoxicity were given in Table1.

The duration of the ICU stay ranged between 2 and 37 days with a mean duration of 13.17 ± 8.73 days. APACHE II scores ranged between 4 and 38 with a mean value of 20.44 ± 7.35. The APACHE-II score at colistin initiation was >15 in 81% (n = 48) of patients.

Hypertension (HT), diabetes mellitus (DM), chronic renal failure (CRF), coronary artery disease (CAD), and immunosuppression was present in 30.5% (n = 18), 13.6% (n = 8), 8.5% (n = 5), 32.2% (n = 19), and 22.0% (n = 13) of the patients, respectively;66% (n = 39) had other comorbid conditions. Twelve patients had no comorbidity (23%). The reasons for ICU admission included pneumonia, respiratory failure, surgery, and other causes in 23.7% (n = 14), 30.4% (n = 18), 32.2% (n = 19), and 39.3% (n = 35) of the cases, respectively.

Table 3. Demographic/Clinical Characteristics of Patients and Risk Factors of Nephrotoxicity Associated with Colistin.

	Patients with nephrotoxicity (n = 31)	Patients without nephrotoxicity (n = 28)	OR (95% CI)	P
Age, years*	63.61 ± 16.03	51.89 ± 20.55	1.036 (1.005-1.067)	0.019
Male sex	17 (54.8)	18 (64.3)	1,482 (0,520-4,227)	0.637
APACHEE II*	20.13 ± 5.78	20.79 ± 8.86	0,988 (0,921-1,060)	0.741
Sepsis or septic shock	20 (64.5)	17 (60.7)	1,176 (0,409-3,384)	0.974
Baseline creatinine, mg/dL*	0.85 ± 0.54	1.27 ± 0.92	0,448 (0,201-0,998)	0.078
Chronic kidney disease	11 (35.5)	8 (28.6)	1,375 (0,457-4,137)	0.773
Hypertension	14 (45.2)	4 (14.3)	4.941 (1.383-17.649)	0.022
Diabetes	5 (16.1)	3 (10.7)	1,603 (0,346-7,423)	0.709
Comorbidities ≥ 2	21 (67.7)	11 (39.3)	3,245 (1,115-9,450)	0.054
Albumin ≤ 2 mg/dL	9 (29.0)	5 (17.9)	1,882 (0,545-6,501)	0.483
Receipt of > 2 concomitant nephrotoxins	18 (58.1)	9 (32.1)	0,763 (0,409-3,384)	0.083
Diuretic + vasopressor	16 (51.6)	6 (21.4)	2.923 (1.006-8.494)	0.034
30 day mortality	18 (58.1)	13 (46.4)	1,598 (0,570-4,474)	0.527
ICU stay during colistin administration (days)*,**	13.84 ± 7.67 (11.00)	12.43 ± 9.86 (10.00)	1,019 (0,960- 1,083)	0.164
Colistin treatment duration (days)*,**	11.42 ± 5.01 (11.00)	11.39 ± 3.41 (12.00)	1,001 (0,888-1,129)	0.620
Colistin dose (CBA), mg/kg/day*	5.40 ± 1.53	5.59 ± 2.24	0,948 (0,721-1,246)	0.706
Total iv colistin dose (CBA) (mg/day)*,**	3663.23 ± 2101.25 (3300.00)	3754.25 ± 1565.45 (3450.00)	1,000 (1,000-1,000)	0.544
Total iv + inhaled colistin dose (CBA) (mg/day)*,**	4999.52 ± 2651.01 (4500.00)	5068.86 ± 1894.08 (4949.50)	1,000 (1,000-1,000)	0.466
The number of days that estimated target plasma concentrations of colistin were ≥ 3.5 mg/L during therapy*,**	3.00 ± 3.15 (2.00)	0.79 ± 1.50 (0.00)	1.577 (1.138-2.187)	0.001
The number of days that estimated target plasma concentrations of colistin were ≥ 3.5 mg/L in the first week of therapy*,**	1.94 ± 2.24 (1.00)	0.50 ± 1.07 (0.00)	1.788 (1.137-2.811)	0.003
Concomitant imipenem	6 (19.4)	5 (17.9)	1,104 (0,296-4,112)	1.000
Concomitant meropenem	15 (48.4)	18 (64.3)	0,521 (0,183-1,482)	0.334
Concomitant sulbactam	9 (29.0)	5 (17.9)	1,882 (0,545-6,501)	0.483
Concomitant daptomycin	3 (9.7)	2 (7.1)	1,393 (0,215-9,011)	1.000
Concomitant linezolid	3 (9.7)	3 (10.7)	0,893 (0,165-4,833)	1.000

Data are n (%) except where indicated *Mean + SD, ** Median.

The patients had ventilator-associated pneumonia (VAP) (49.1%; n = 29), microbiologically-documented non-VAP hospital acquired pneumonia (HAP) (10.1%; n = 6), bacteremia (27.1%; n = 16), soft tissue infections (5.1%; n = 3), or central venous catheter-related infections (3.3%; n = 2) caused by MDR *A. baumanii*.

Bacteriological eradication was achieved in 69.4% of the patients (n = 41) at the end of the therapy while 47.4% (n = 28) had clinical cure. During the follow-up, no patients required discontinuation of therapy due to renal failure, and there were no patients in need of hemodialysis or Continuous Renal Replacement Therapy (CRRT).

According to the RIFLE classification, 52.5% of the patients (n = 31) developed nephrotoxicity. The median time to nephrotoxicity was 7 days (range, 3 to 18) (Table 2). Patients with AKI were in the risk (10.2%), injury (16.9%), and failure (25.4%) categories,and none of the patients developed permanent renal insufficiency at the end of the colistin treatment or there was no need for permanent hemodialysis.

In univariate analysis, age (odds ratio [OR], 1.036; 95% confidence interval (CI) = 1.005-1.067), hypertension (OR = 4.941; 95% CI = 1.383- 17.649), and co-administration of a loop diuretic and vasopressors (OR = 2.923; 95% CI = 1.006- 8.494) increased the risk for development of nephrotoxicity. Colistin nephrotoxicity was not associated with the duration of therapy, total dose, or average daily dose. However, the number of days that estimated target plasma concentrations of colistin were ≥ 3.5 mg/L in the first week of therapy. The number of days that estimated target plasma concentrations of colistin were ≥ 3.5 mg/L during therapy, and these were related to AKI. Receipt of >2 concomitant nephrotoxins, concomitant antimicrobials, and level of sepsis were similar between the groups. There was no significant difference in the 30-day mortality between nephrotoxicity and non-nephrotoxicity groups (58.1% *vs*. 46.4%; p = 0.53). Basal creatinine levels were lower in the nephrotoxicity group than the non-nephrotoxicity group (0.85 ± 0.54 *vs*. 1.27 ± 0.92, OR = 0.448; 95% CI = 0.201-0.998) (Table 3).

Logistic Regression Model

A backward-conditional logistic regression was used for multi-variate analysis. In order to increase the accuracy of percent estimates, cut-off values in logistic regression were identified using ROC (Receiver Operating Characteristics). Clinical variables with a p-value of less than 0.1 in the univariate analysis were included in the multivariate analysis.

A logistic regression model identified three predictors of colistin-associated nephrotoxicity: age (OR = 1.04; 95% CI = 1.01-1.08); the number of days that estimated target plasma concentrations of colistin were ≥ 3.5 mg/L in the first week of therapy (OR = 2.4; 95% CI = 1.25-4.47); and baseline creatinine (OR = 0.2; 95% CI = 0.07- 0.60) (Table 4). Other variables in the analysis lost their significance in the multivariate model despite initial significance in the univariate analysis (the overall explanatory power of the model was 86.4% with a sensitivity of 93.5% and specificity of 78.6%).

Other Adverse Events Observed During Colistin Therapy

Fifty-one patients (86.5%) experienced at least one adverse event. The causative role of colistin in adverse effects observed during the study period could not be assessed. Of the six patients (10%) who developed neurotoxicity during colistin therapy, none had nephrotoxicity. One of these patients (1.6%) had grade 1 peripheral and oropharyngeal paresthesia on day 9 of therapy that improved within 4 days without discontinuation of treatment. Two patients (3.3%) had grade 2 convulsions; in one of these subjects, convulsions started on day 2 of treatment and improved within 6 days without treatment discontinuation; the convulsions were considered to be due to head trauma in the other patient who showed improvement within 4 days with antiepileptic therapy. Three patients (5%) had mental confusion that resolved within 3 days without stopping colistin therapy. Two patients (3.3%) had grade 2 respiratory muscular paralysis (neuromuscular block); this adverse effect occurred on day 7 in one patient and on day 6 in the other. These issues subsided within 3 days without discontinuation of therapy. One

Table 4. Logistic regression analysis of colistin-associated nephrotoxicity.

	P	OR	%95 CI	
			Lower	Upper
Age (years)	**0.042**	1.039	1.001	1.077
The number of days that estimated target plasma concentrations of colistin were ≥ 3.5 mg/L in the first week of therapy	**0.008**	2.362	1.249	4.470
Creatinine at start	**0.004**	0.197	0.065	0.598

patient (1.6%) developed a bronchospasm on day 6 of intravenous + inhaler colistin therapy, and the inhaler therapy was discontinued on the second day. Bronchospasms persisted for 3 days and improved when the bronchodilator doses were increased. This adverse effect was probably related to colistin inhaler therapy. This patient died during the follow-up period. This death was considered unrelated to colistin therapy. Three patients (5%) had urticaria, and all of them consisted of grade 2 reactions that resolved within 5 to 7 days without stopping the treatment. Five patients (8%) had grade 1-2 gastroenteritis that did not require treatment discontinuation and resolved within 2-5 days. Adverse effects such as headache, pruritus, and fatigue could not be assessed in 37 patients (62.7%) because they were unconscious and intubated.

Discussion

The incidence of infections associated with MDR Gram-negative bacteria are increasingly common in intensive care units, and this led to a renewed interest in colistin treatment. In publications through the 1980s, polymyxins were reported to be associated with a high rate of nephrotoxicity. In most of these studies, CMS was mostly administered intramuscularly.

In this cohort of severely ill ICU patients, colistin led to a relatively high rate of nephrotoxicity (52.5%). In the last 15-year period, the reported rate of nephrotoxicity for colistin has shown considerable variation with some studies reporting a nephrotoxicity rate between 6 and 14%; others report values between 32 and 55% [8,9]. The use of different criteria for renal failure accounts for most of these significant inconsistencies between the studies with no consensual criteria utilized for the diagnosis of ARF(Acute Renal Failure). Furthermore, a lack of knowledge on the chemical structure of colistin as well as the absence of a common proposed dose scheme contributed to these controversial results. This makes a proper comparison difficult between these studies.

In a 2010 study by Deryke *et al*. [10] nephrotoxicity was found in 33% of the 30 patients in whom nephrotoxicity was defined as an increment of 0.5 mg/dL in at least two measurements. Hartzell *et al*. [8] reported a nephrotoxicity rate of 45% in 66 patients who were relatively younger (27 ± 12 years) and had a better health status (APACHE II score 8.3 ± 6.5). Again, the reported figure was 43% in a study conducted in 2011 [11]. Kwon *et al*. [12] observed a higher rate of nephrotoxicity than in the other studies, i.e. 53.5%, in a groupof 71 patients who were older (median age 60 years), had longer duration of admission (median 27 days), and had higher burden of comorbidity (43% malignancy).

A colistin treatment scheme was proposed for the first time in a pharmacokinetic/pharmacodynamics study by Garonzik *et al*. in 2011. For CMS, the time to conversion to active form, i.e. colistin, was 7 hours; stable plasma concentrations were reached in 60 hours confirming the need for a loading dose [1]. In accordance with these recommendations, Dalfino *et al*. [13] found a nephrotoxicity rate of 17.8% after a loading dose of CMS 9 MU in 2012. This was followed by maintenance dose of 4.5 MU every 12 hours. However, the sample size was small, and AKIN nephrotoxicity criteria were used rather than the RIFLE criteria.

Here, our objective was to examine the incidence of nephrotoxicity and its associated risk factors in the context of the current recommendations for colistin dosage including the loading dose. Based on the RIFLE criteria, 52.3% (n = 31) of our patients developed nephrotoxicity. This is higher than most other recent reports, and it represents a relatively higher incidence although Kwon *et al*. [12] reported similar figures. A number of factors may account for this high rate of nephrotoxicity in our study including high APACHE II scores, advanced age, presence of more than 2 comorbid conditions in a significant proportion of participants, and the presence of sepsis or septic shock in more than half of the cases. This study involves a loading dose and was conducted by Dalfino *et al*. [13] who identified a nephrotoxicity rate of 17.8%. However, it should be pointed out that the sample size was small in that study (n = 28), and the APACHE II score was 18 versus 20 in this study. Hassan *et al*. [14] reported a nephrotoxicity rate was 46%, which is lower than our study. This is because only 30% of patients got the loading dose; the APACHE II scores were lower (8 ± 6 *vs* 20 ± 7.3), and the patients were younger. Another recent study showed lower nephrotoxicity rates than our study, however the loading dose was not mentioned [15].

Nephrotoxicity categories in our study consisted of risk in 10.2%, injury in 16.9%, and failure in 25.4%. Nephrotoxicity occurred at a median of 7 days of treatment (7.81 ± 3.52). In 11 of the 31 patients (35%), nephrotoxicity resolved at a mean duration of 10.67 ± 7.00 days (range: 2-21 days). De Ryke *et al*. [10] found that nephrotoxicity developed within the first 5 days of treatment, which was earlier than our observations. On the other hand, similar to our study, Poque *et al*. identified nephrotoxicity at 1 week in their patients [11].

Similar to some previous studies, none of our patients required hemodialysis or continuous venovenous hemodiafiltration (CVVHD) [8,11]. Kwon *et al*. [12] reported that 6 patients (15%) required dialysis although death occurred in 5 of these 6 cases within 24 hours of dialysis. This suggests that this might be due to factors such as old age, a high number of comorbidities, or the presence of shock or other factors unrelated to colistin. The absence of permanent renal injury in any of our patients also suggests that nephrotoxicity may be generally reversible with no associated serious parenchymal injury. In our study, patients with CMS-associated nephrotoxicity did not exhibit an increase in crude mortality rates ($p = 0.52$) similar to Pogue *et al*. [11].

In recent years, a number of risk factors have been described for colistin-associated nephrotoxicity including age, concomitant use of nephrotoxic agents, presence of DM, total CMS dose, duration of treatment, and cumulative dose [8,10,11,13,16]. In this study, no significant association was found between nephrotoxicity and DM($p > 0.05$). In contrast, Poque *et al*. [11] identified DM as a significant predictor of nephrotoxicity. Gender had no impact on nephrotoxicity in our cohort similar to previous reports [8,10,11].An examination of the comorbid conditions showed a higher incidence of HT in those who developed nephrotoxicity [odds ratio: 4.941; ($p = 0.022$; $p < 0.05$, 95% CI = 1.383-17.649)].

Pogue *et al*. also considered vancomycin and NSAID use as potential risk factors in nephrotoxicity [11].However, only 7 and 5 patients had concomitant use of NSAIDs and vancomycin, and their effect on nephrotoxicity could not be assessed. Concomitant use of diuretics and vasopressor agents was associated with an increased risk of nephrotoxicity in the univariate analysis but was not statistically significant in logistic regression analysis similar to the study by Lee *et al.*[15].

A strong association between estimated target steady-state plasma concentrations (C-target) for colistin and creatinine clearance was found [1].The doses recommended earlier were unable to reach effective plasma concentrations, and a loading dose followed by maintenance could obtain a steady-state with an associated increase in colistin efficacy in patients with reduced or normal renal functions. Poque *et al*.administered treatment in accordance with the recommendations of Garonzik *et al*. at a daily colistin dose of > 5 mg/kg based on ideal body weight. This was associated with an increased risk of nephrotoxicity [11].In a one-year study by Sorli *et al*. [17] involving 120 patients, CMS serum levels were checked twice daily: once immediately before the administration of CMS (Cmin; minimum plasma colistin concentration at steady-state) and one after 1/2 hours (Cmax; maximum plasma colistin concentration at steady state). Those who developed nephrotoxicity had a higher Cmin and Cmax.

We did not measure the actual serum levels, but the C-target was estimated based on the real dose given and daily creatinine clearance allowing risk assessment. Patients with more estimated days with a C-target of ≥ 3.5 mg/L were likely to develop nephrotoxicity than those with fewer days ($p < 0.01$). Patients with nephrotoxicity in this study had estimated colistin concentrations above this level for a mean duration of 3 days versus 0.79 days in those without nephrotoxicity. Again, considering the occurrence of nephrotoxicity within one week of starting treatment in previous studies, the number of days with a C-target level of ≥ 3.5 mg/L in the first 7 days was explored, and patients with nephrotoxicity had more days at the C-target level ($p = 0.003$; $p < 0.01$). Accordingly, the number of days with a C-target of ≥ 3.5 mg/L during this period was 1.94 days in nephrotoxicity patients *vs*. 0.50 days in those with no nephrotoxicity ($p = 0.003$; $p < 0.01$)

Previously, a link between colistin nephrotoxicity and total CMS dose (cumulative dose) and treatment duration was reported[8,10,13,16].Sorli *et al*. [17]found that while these parameters emerged as significant risk factors in the univariate analysis, their statistical significance disappeared in the multivariate analysis similar to our findings suggesting no effect of cumulative intravenous colistin dose on the development of nephrotoxicity ($p > 0.05$). These results suggest that when higher target concentrations are adopted to increase efficacy for strains with higher MIC values or in critically ill patients, a C-target of ≥ 3.5 mg/L could lead to significantly increased nephrotoxicity. This may be explained by the fact that the low basal creatinine values in the multivariate analyses as a risk factor which may be attributed to the higher doses of colistin given to these patients.

Other factors that were associated with increased risk of nephrotoxicity in the univariate analysis included the presence of ≥ 2 comorbidities and use of > 2 nephrotoxic agents, but these lost their significance in the multivariate analysis. In the pharmacokinetic/pharmacodynamics study by Mohammed *et al*. [18] in 2012, the advised loading dose for fast bacterial eradication was 6-9 MU (480-720 mg) in critically ill patients; however the effect of these

higher doses on nephrotoxicity levels were not evaluated.

One important finding in this work was the low baseline creatinine level in patients who developed nephrotoxicity. Patients who developed nephrotoxicity had a baseline creatinine of 0.85 ± 0.54 mg/dL*vs*. 1.27 ± 0.92 in whom nephrotoxicity did not develop ($p = 0.078$; $p > 0.05$). This observation may suggest a more careful dose adjustment both at the initiation and maintenance phases of therapy in subjects with high baseline creatinine clearance. However, Lee *et al*.[15]found that colistin dose was only significantly associated with the development of nephrotoxicity in patients with eGFR < 60 mL/minute/1.73 m^2 although the rate of nephrotoxicity was higher among patients with higher baseline creatinine levels.

It is known that in low concentrations colistin is not effective, that is because in 2012, optimal dosage regimens for colistin were updated and increased up to three times [1]. Heteroresistance to colistin among MDR acinetobacter strains was known for more than a decade [19,20,21,22]. While lower doses could cause treatment failure and selection of heteroresistant clones, increased dose could become nephrotoxic. Combined therapies have synergistic effects and they could be less toxic due to administration of decreased doses of two antimicrobials. The most frequently studied in-vitro combinations were colistin with rifampicin [21,23], colistin with carbapenems [24] and colistin with tigecycline [21, 25]. All these three combinations have synergistic activity against heteroresistant *A.baumanni* isolates. Synergy was also observed for unusual vancomycin+colistin combination at low doses of colistin [22,26]. Another approach to avoid nephrotoxicity may be the use of polymyxin B instead of colistin. Recent studies suggest that kidney damage is more severe in patients treated with CMS than polymyxin B [27].

Further studies are needed to determine effective doses of available antibiotics that do not cause increased nephrotoxicity and prevent development of resistance until new agents active against MDR acinetobacter strains to be approved for clinical use [28].

Limitations

This study does have some limitations. Since most of the patients admitted to the ICU were unconscious, information on bodyweight had to be gathered from close relatives or caregivers (spouse, children, etc.). In subjects admitted to the surgical ICU only, we assumed that the body weight measurements were accurate because pre- and post-operative weights were recorded in the patient files. On the other hand, patients requiring prolonged ICU stay and receiving subsequent therapy might have an altered number of factors including - intravenous hydration, total parenteral nutrition (TPN), and fluid loss etc. which affects the ideal body weight estimations.

Another limitation relates to the absence of a control group. Therefore, no comparisons with the earlier dose recommendations involving no loading dose could be made; nephrotoxicity rates could be compared with figures reported from other centers in previous years. During the follow up period, direct serum concentrations were not measured and the estimated target concentrations were used, those may be not reflect the real values.

Conclusion

Colistin is one of the limited therapeutic options for the management of MDR gram-negative organisms in the hospital settings. However, nephrotoxicity is a limiting factor for more widespread use of this agent. Dose estimates based on the ideal rather than the actual body weight might minimize the risk of nephrotoxicity. A relatively higher rate of nephrotoxicity (52.5%) was found despite the use of the recent recommendations involving a loading dose and subsequent dose. Studies are needed to evaluate whether measurement of colistin plasma concentrations might help in the determination of effective colistin doses and in minimizing the risk of nephrotoxicity.

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