

# Evaluation of risk of nephrotoxicity with high dose, extended-interval colistin administration

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## Abstract

**Aim:** The aim was to evaluate the risk of nephrotoxicity with high-dose, extended-interval regimen of colistin administration in critical ill patients. **Materials and Methods:** This prospective study was conducted on patients suffering from sepsis due to Gram-negative infection susceptible only to colistin. The dosing schedule for colistin was 9 million units stat followed by 4.5 million units at 12 hourly interval (adjusted as per body weight and renal functions). The serum creatinine and creatinine clearance were estimated at the start of therapy and daily during therapy. **Results:** Thirty-one patients suffering ventilator associated pneumonia (61.29%), blood stream infections (29.03%) and urinary tract infections (9.67%) due to Gram-negative multiple drug resistance organisms were assessed. Most commonly isolated organism were *Acinetobacter baumannii* (54.83%), *Klebsiella pneumonia* (16.12%) and *Pseudomonas* (29.03%). Five patients (16.12%) developed acute kidney injury within 4-5 days of start of therapy and returned to baseline after 6 days with no patient requiring renal replacement therapy or discontinuation of colistin. **Conclusion:** Our study showed that high-dose, extended-interval colistin can be given to critically ill patients without any significant risk of nephrotoxicity.

**Keywords:** Extended interval, High-dose colistin, nephrotoxicity

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## Introduction

Despite the recent advances in the management of patients, severe nosocomial infections due to multi-drug resistant (MDR) Gram-negative bacteria (GNB) account for high morbidity and mortality in intensive care unit (ICU).<sup>[1]</sup> With no new antibiotics in pipeline after carbapenams, there has been renewed interest in colistin, the drug “forgotten” for several decades.<sup>[2]</sup>

Colistin (also called polymyxin E) was first isolated in Japan in 1949 from *Bacillus polymyxa* var. colistinus and became available for clinical use in 1959.<sup>[3]</sup> Colistin was given as an intramuscular injection for the treatment of Gram-negative infections, however, the parenteral use of the drug was abandoned approximately 20-30 years

ago in most countries after aminoglycosides became available, because of reports of common and serious nephrotoxicity and neurotoxicity. It was later used as topical therapy as part of selective digestive tract decontamination and aerosolized form for patients with cystic fibrosis.<sup>[4]</sup>

With the renewed interest in colistin in treating MDR-GNB infections, the benefit of using the right drug has often been negated by a suboptimal concentration at the infection site as the consensus on the most effective colistin dosage has not yet been reached.<sup>[5]</sup>

The therapeutic efficacy of colistin strictly depends on peak/minimum inhibitory concentration (MIC) or area under the curve/MIC ratio as it exhibits a concentration-dependent bactericidal activity.<sup>[6,7]</sup> To obtain an optimum concentration at infection site for effective killing a loading dose along with high-dose at extended dosage interval sounds logical.

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However, the main concern among most clinicians with using loading dose and high-dose of colistin is nephrotoxicity, especially in critically ill patients with other comorbid conditions.

The purpose of our study was to critically evaluate the renal toxicity with a loading dose followed by high-dose and extended-interval dosing regimen of colistin, in a cohort of critically ill patients with nosocomial infections due to MDR-GNB.

## Materials and Methods

This prospective, observational, cohort study was performed in a 13-bedded medical ICU of a tertiary care hospital from March 2013 to September 2013. Thirty-one critically ill patients with sepsis due to GNB, who were only susceptible to colistin were enrolled in the study.

Exclusion criteria for the study included age <18 years old, pregnant or breast-feeding, or if the patient is already on hemodialysis therapy. Patients were followed-up until ICU discharge or death.

Primary outcome was to study nephrotoxicity due to high-dose of colistin therapy.

A proforma was made to record patient characteristics (including age, gender, weight, underlying comorbidities, Acute Physiology and Chronic Health Evaluation-II [APACHE-II] score on admission), type of infection, causative organism and *in vitro* susceptibility, daily doses and duration of colistin therapy, cumulative dose of colistin, co-administered antibiotics and other nephrotoxic agents (e.g. aminoglycosides, vancomycin, nonsteroidal anti-inflammatory drugs, intravenous radiocontrast agent, diuretics, mannitol etc.).

Identification and susceptibility of all causative microorganisms was based on routine microbiological methods as defined by the Clinical and Laboratory Standards of the Hospital.

An isolate was defined as colistin sensitive only if it was fully susceptible to colistin, but resistant to other drugs.

According to recent data,<sup>[8-12]</sup> 9 MU of colistin (adjusted to body weight) was administered as colistimethate sodium (CMS) dissolved in 100-ml sterile saline, and administered over 45-50 min as a loading dose in all patients irrespective of creatinine clearance (CrCl), followed by a maintenance dose of 4.5 MU every 12 h after 24 h of loading dose in patients with CrCl >50 ml/min.

In patients with renal impairment (CrCl 20-50 ml/min), maintenance doses of 4.5 MU/24 h was administered and for CrCl in the <20 ml/min 4.5 MU/48 h was administered.

Serum creatinine and estimated CrCl were recorded on 1<sup>st</sup> day of CMS therapy followed by daily serum creatinine until discharge or death.

Nephrotoxicity was defined as increase in serum creatinine measurements of 0.5 mg/dl from baseline. Criteria needed to be at least two consecutive determinations 24 h apart, after 2 or more days of CMS therapy.<sup>[13]</sup> The RIFLE criteria were used to evaluate the severity of acute kidney injury (AKI).<sup>[14]</sup>

## Statistical analysis

All statistical analyses were performed using IBM SPSS software. Continuous variables were analyzed using either the *t*-test or the Mann-Whitney U-test; categorical data were compared using either the  $\chi^2$  or Fisher's exact test when appropriate. In all comparisons, a *P* < 0.05 was considered as statistically significant.

## Results

### Characteristics of the whole sample

Of 31 critically ill patients who were prescribed colistin for Gram-negative infections 78% were male with mean age of 65 ( $\pm$ 15) years.

Main comorbid conditions were hypertension 14 (50.6%), ischemic heart disease 3 (10.8%), diabetes mellitus 7 (30%), chronic obstructive pulmonary disease 5 (25.5%), and chronic kidney disease 2 (9%). Mean APACHE-II score was 20 ( $\pm$ 4).

9 (29.03%) patients were having BSI, 19 (61.29%) VAP and 3 (9.67%) patients were having urosepsis.

Most common isolated pathogens was *A. baumannii* seen in 17 (54.83%) patients, followed by *P. aeruginosa* in 9 (29.03%), *K. pneumoniae* in 5 (16.12%) patients. All strains isolated were fully susceptible to colistin. In all the cases, colistin was administered as combination therapy with carbapenems or cefoperazone-sulbactam.

Out of 31 patients 24 patients (77.41%) were having normal baseline renal functions (serum creatinine level  $0.8 \pm 0.2$ ) and 7 patients (22.58%) were having deranged renal functions (serum creatinine levels  $3 \pm 1.4$ ) who received modified colistin dose after loading dose as per protocol. Median duration of therapy in both the groups were 14 days (12-16 days).

### Colistimethate sodium nephrotoxicity

No deterioration in renal functions were observed in 26 patients (83.87%) during treatment which included 5 patients (71.42%) with preexisting renal disease. In this group, the increase in serum creatinine level was <0.5 mg/dl. The nonsignificant increase in serum creatinine levels returned to baseline at 5-6 days of therapy [Table 1].

Acute kidney injury developed in 5 (16.12%) patients within 3-5 days of starting of therapy with colistin, out of which 2 (40%) patients had preexisting renal disease. The mean serum creatinine level in patients without preexisting renal disease was 0.8 mg/dl (0.6-1 mg/dl) at start and peaked at 3.5 mg/dl (2.8-4.5 mg/dl [ $P = 0.035$ ]) in a mean time of 4 days (3-5 days). The serum creatinine at the end of colistin therapy was 3 mg/dl (2-4 mg/dl) and returned to baseline after 10 days (8-13 days) of stopping of colistin therapy [Table 2].

The base line serum creatinine level in patients with preexisting renal disease was 2 mg/dl and 2.5 mg/dl which peaked at 4 mg/dl and 4.5 mg/dl ( $P = 0.022$ ) respectively in a average time of 3-5 days. The serum creatinine at the end of colistin therapy was 3.6 mg/dl and 2.9 mg/dl respectively, which returned to baseline after 6-8 days of stopping of colistin therapy [Table 2].

All the patients who developed AKI had nonoliguric renal failure and no patient required renal replacement therapy. Two, two and one patients met the criteria for Stages I, II and III AKI respectively. All the patients completed colistin therapy by dose modification as per protocol and in no patients colistin therapy was discontinued.

### Discussion

Today's intensivists are faced with the growing problem of emergence of organisms like *A. baumannii*, *P. aeruginosa*, and *K. pneumonia* that are sensitive only to colistin resulting in severe nosocomial infections.<sup>[15]</sup>

Clinical cure rates improved from 51% to 70% by increasing daily dose of colistin from 2 to 9 MU.<sup>[16]</sup>

A loading dose to rapidly achieve target drug concentration and a dosing schedule using high single doses at longer intervals has been proposed,<sup>[17-19]</sup> rather than 9 MU three-daily fractioned colistin regimen, currently prescribed in ICU practice, which is associated with suboptimal and delayed steady-state concentration.<sup>[18,19]</sup>

**Table 1: Patients on colistin with and without renal dysfunction**

	Number	%
Total number of patients	31	
Number of patients who did not develop renal dysfunction	26	83.87
Number of patients who developed AKI	5	16.12

AKI: Acute kidney injury

**Table 2: AKI during colistin therapy**

AKI	Baseline serum creatine mg/dl	Peak serum creatine mg/dl	Serum creatine at end of therapy mg/dl
Patients without preexisting renal disease	0.8 (0.6-1)	3.5 (2.8-4.5)	3 (2-4)
Patients with preexisting renal dysfunction	2 and 2.5	4 and 4.5	3.6 and 2.9

AKI: Acute kidney injury

We adopted a dosing schedule based on a 9 MU loading colistin dose and a 4.5 MU/12 h maintenance dose based on the pharmacokinetic/pharmacodynamic profile of the colistin which is consistent with study by Garonzik *et al.*<sup>[18]</sup>

One of the major concerns in using colistin at high-doses is nephrotoxicity. Colistin induces tubular damage by increasing the epithelial cell membrane permeability, leading to leakage of contents and cell death.<sup>[20]</sup>

Acute kidney injury was observed only in 16.12% of patients in our study, which is similar to the studies using lower individual doses and more fractioned regimens of CMS.<sup>[15,21]</sup> Moreover, AKI in our patients was not severe, did not require discontinuation of colistin and subsided rapidly as reported previously.<sup>[21]</sup> Patients who developed renal dysfunction, dose titration was done by prolonging dosing interval instead of reducing single dose (according to colistin concentration-dependent pharmacodynamic behavior), which may have contributed to the low rate and moderate severity of AKI.<sup>[18]</sup>

Even in presence of other factors such as age, race and comorbidities, severity of critical illness, hemodynamic status and other potentially co-administered nephrotoxic agents, such as radiocontrast medium, which may have played a crucial role in affecting kidney function the percentage of renal dysfunction in patients was low.

The main limitation of our study was small number of patients studied and absence of control group apart from nonevaluation of other side-effects of high-dose extended colistin regimen.

## Conclusion

Our study demonstrates that a loading dose of colistin of 9 MU followed by high-dose extended-interval regimen of 4.5 MU 12 hourly can be safely used in critically ill patients with prolongation of time interval rather than dose reduction in patients with renal dysfunction.

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