The risk factors of colistin methanesulfonate associated nephrotoxicity

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Abstract

**Purpose:** The risk factors of colistin methanesulfonate (CMS) associated nephrotoxicity are important. Our study attempts look into the prevalence of CMS-associated nephrotoxicity in Intensive Care Units (ICUs), and related risk factors. **Materials and Methods:** The study was conducted between September 2010 and April 2012 on 55 patients who underwent CMS treatment. Nephrotoxicity risk was defined based on the Risk Injury Failure Loss End-stage kidney disease criteria. **Results:** Fifty-five patients included in the study. A total of 22 (40%) patients developed nephrotoxicity. The correlation was detected between nephrotoxicity and patients over 65 with a high Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score. APACHE II score was revealed an independent risk factor for nephrotoxicity. **Conclusion:** Advanced age and a high APACHE II score are significant risk factors in the development of nephrotoxicity at ICUs following CMS use. Patient selection and close monitoring are critical when starting CMS treatment.

**Keywords:** Colistin methanesulfonate, nephrotoxicity, risk factors

Introduction

The use of polymyxin antibiotics dates back to the 1950s. In the ensuing years, the use was abandoned due to severe side effects such as neurotoxicity and nephrotoxicity. In recent years, questions are being raised regarding colistin methanesulfonate (CMS)-associated nephrotoxicity as CMS is back in use again for treatment of multiresistant *Acinetobacter* spp. and *Pseudomonas* spp. related infections. Some studies demonstrated that CMS was not as nephrotoxic as it was feared at the outset, while some other studies detected high nephrotoxicity rates. Dose of CMS, treatment duration, patient’s age, and simultaneous use of vancomycin have been identified as independent risk factors in the development of nephrotoxicity. This study seeks to demonstrate CMS-associated nephrotoxicity occurrences and risk factors.

Materials and Methods

The study was conducted between September 2010 and April 2012 on 55 patients over the age of 18, who underwent CMS treatment for over 72 h at a 16-bed Intensive Care Unit (ICU) in a 750-bed tertiary hospital. Nephrotoxicity risk was defined based on the Risk Injury Failure Loss End-stage (RIFLE) criteria. Evaluations included demographic data (age, sex, weight), the number of days at ICU (Acute Physiologic Assessment and Chronic Health Evaluation [APACHE] II score, urea, creatine), RIFLE score, and duration of ICU hospitalization before starting on CMS. Antibiotics and other likely nephrotoxic drugs used along with CMS were noted down. Throughout CMS use, urea, creatine, creatine clearance, APACHE II, and RIFLE scores were monitored.

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evaluated together, and they were recorded separately on the 3rd, 6th, and 9th days at the start of treatment. CMS was administered as colymicine (Koçak Pharma) at 5 mg/kg/day, 2.5–3.8 mg/kg/day, 2.5 mg/kg/day for glomerular filtration rates of > 80, 50–79, 30–49 mL/min, respectively. Patients who are receiving renal replacement treatment (RRT) were not included in the study. It is established that nephrotoxicity begins to develop onward of detecting risk (R) based on RIFLE criteria.

**Statistical analysis**

Statistical analyses were done using the Stata 12.1 (StataCorp, Texas, USA) program. Binary comparisons were performed using Chi-square or Fisher’s test for categorical variables, two-sample t-test for constant variables with normal distribution, and Wilcoxon rank-sum test for those without normal distribution.

Multivariate analyses were carried out by using the logistic regression analysis. Initial model comprised variables that were clinically significant and/or that had a $P < 0.10$ in univariate analyses. Variables were examined for parallelism and interaction. Ultimate model was obtained through the successive elimination of the insignificant variables or those of which elimination did not weaken the model.

**Results**

All of the 55 patients in the study received CMS i.v. treatment; 46 due to growth of multidrug-resistant (MDR) *Acinetobacter* spp., 4 due to the growth of *Pseudomonas* spp., and 5 empirically. Following diagnoses were made in the patients: Ventilator-associated pneumonia (VAP) (microbiologically documented) in 46, suspected VAP in 5, central nervous system infection in 2, soft tissue in 1, and urinary system tract infection in 1.

Table 1 shows the demographics of the 37 male and 18 female patients that were studied. Of those, 19 were over the age of 65 with a median APACHE II score of 18. Based on the RIFLE criteria, a total of 22 (40%) patients developed nephrotoxicity.

Regarding comparison of patients who did or did not develop nephrotoxicity based on the univariate analysis, it was interesting to note that nephrotoxicity developed in patients over 65 with a high APACHE II score [Table 2].

In a comparison of both groups, when the APACHE II score was <17, there was a higher number of patients with a RIFLE score of 1–3.

### Table 1: Characteristics of patients

| Characteristic          | All patients ($n=55$) | Patients without nephrotoxicity ($n=33$) | Patients with nephrotoxicity ($n=22$) | P     |
|------------------------|-----------------------|----------------------------------------|--------------------------------------|-------|
| Age, median (IQR)      | 41.0 (35.0, 60.0)     | 41.0 (35.0, 60.0)                      | 72.0 (44.0, 76.0)                    | 0.043 |
| Age >65 (%)            | 7 (21%)               | 12 (55%)                               | 12 (55%)                             | 0.011 |
| Male                   | 24 (73%)              | 13 (59%)                               | 13 (59%)                             | 0.29  |
| BMI, mean (SD)         | 25.3 (4.8)            | 26.3 (4.2)                             | 26.3 (4.2)                           | 0.39  |
| ICU hospitalization days, median (IQR) | 43.0 (25.0, 54.0) | 38.0 (31.0, 49.0)                      | 38.0 (31.0, 49.0)                    | 0.81  |
| Hospitalization days before colistin, median (IQR) | 16.0 (7.0, 28.0) | 20.5 (13.0, 26.0)                      | 20.5 (13.0, 26.0)                    | 0.27  |
| Kreatinin, median (IQR) | 0.7 (0.5, 0.8)      | 0.8 (0.6, 1.2)                         | 0.8 (0.6, 1.2)                       | 0.20  |
| Mechanical ventilation day (IQR) | 17.0 (14.0, 20.0)    | 22.0 (18.0, 28.0)                      | 22.0 (18.0, 28.0)                    | 0.007 |
| Duration of CMS treatment, days (IQR) | 26 (16, 43)    | 31 (25, 47)                            | 31 (25, 47)                          | 0.22  |
| Total CMS dosage (mg) (IQR) | 10 (8, 18)      | 12 (8, 15)                             | 12 (8, 15)                           | 0.98  |
| Usage of nephrotoxic drug (%) | 0.92 (0.38)    | 0.8 (0.6, 1.2)                         | 0.8 (0.6, 1.2)                       | 0.58  |

**Discussion**

CMS is removed from the body through glomerular filtration. Nephrotoxicity develops with acute tubular necrosis. There are various scores available for evaluation of nephrotoxicity (i.e., RIFLE, acute kidney injury network). RIFLE is a highly specific classification due to its sensitivity in detecting acute renal impairment.
Two recent studies using the RIFLE criteria achieved detecting mild renal impairment to the degree of 43%. In the study, we evaluated nephrotoxicity according to RIFLE criteria as well. We have determined advanced age (>65) and a high APACHE II score to be significant risk factors in development of nephrotoxicity [Figure 1].

A study by Balkan et al. similarly points to advanced age (>60) and OR = 5.19 as a considerable risk factor in development of nephrotoxicity. In parallel with our results, a Rocco et al. study determined the Simplified Acute Physiology Score to be notably high in the group that developed nephrotoxicity. In conclusion, colistin-associated nephrotoxicity is high in ICUs based on the RIFLE criteria. A link has been established between advanced age and high APACHE II score in development of toxicity. Therefore, this patient group must be monitored and treated closely.

The results of our study are analogous with recent studies that link secondary renal impairment to CMS use in critical patient groups. Nephrotoxicity is proven to be greater with high-dose of CMS treatment. Paul et al. demonstrated in their study, the link between colistin treatment and crude mortality rate.

Other studies point out that even though colistin use accompanied with potentially nephrotoxic drugs (i.e., intravenous radiocontrast agents, anti-inflammatory drugs, aminoglycosides, and vancomycin) increases toxicity; this is statistically insignificant. Our study did not establish a meaningful relationship when used in combination with potentially toxic drugs.

Studies reveal that postcolistin AKI is dose-dependent and appears around 13.5 days (8–37 days) after starting colistin treatment. Whereas, in our study, nephrotoxicity began to appear on the 6th and 9th days of treatment in 50% and 27% of the patients respectively.

In conclusion, colistin use is becoming more prevalent with increasing number of MDR-pathogen related infections.
Consequently, more in-depth studies are needed in monitoring and treatment of nephrotoxicity.

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**Conflicts of interest**
There are no conflicts of interest.

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