

Determination of colistin-related nephrotoxicity and risk factors in intensive care unit

Ayşe İnci,¹ Melike Korkmaz Toker,² İlhan Güney Bicer,² Abdurrahim Derbent,² Ziya Salihoglu²

¹Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Istanbul Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey

²Department of Anesthesiology and Reanimation, University of Health Sciences, Istanbul Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey

ABSTRACT

OBJECTIVE: Colistin is a cationic polypeptide antibiotic with a cyclic structure that belongs to the polymyxin group. It was banned from clinical use because of its significant renal side effects, such as nephrotoxicity. However, the administration of colistin has recently been initiated again in the treatment of multi-drug resistant pathogens, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Nephrotoxicity and neurotoxicity are the main problems encountered in the clinical use of polymyxins. The aim of this study was to determine the frequency and risk factors of colistin-related nephrotoxicity in the adult intensive care unit (ICU).

METHODS: In this study, a retrospective review of patients who were followed up between January 1 and December 31, 2016 and who received colistin treatment in the adult ICU was performed. Retrospective computer records of age, sex, site of infection and microorganism breeding, daily creatinine values, and additional diseases were recorded and examined. Nephrotoxicity was assessed using the Risk, Injury, Failure, Loss, and End-stage kidney disease criteria.

RESULTS: A total of 48 patients were included in the study. Of these, 50% were male. The mean age of the patients with nephrotoxicity was 59.73±22.38 years, and the mean age of those without nephrotoxicity was 58.00±22.39 years. *A. baumannii* was observed to be the causative microorganism in all patients, and the most frequent infection was pneumonia. Nephrotoxicity was investigated in 54.2% (n=26) of the patients. In this study, when risk factors for nephrotoxicity were evaluated, it was found that the presence of nephrotoxicity was greater in cases with chronic obstructive pulmonary disease, malignancy, or abdominal surgery in patients older than 65 years. In addition, mortality was greater in those who developed nephrotoxicity, although it was not statistically significant.

CONCLUSION: In this study, the rate of nephrotoxicity was 54.2% in patients who received colistin in the ICU. Therefore, patients in the adult ICU receiving colistin therapy should be carefully monitored for the development of nephrotoxicity as a side effect.

Keywords: Colistin; end-stage kidney disease criteria; failure; injury; loss; multi-drug resistant pathogens; nephrotoxicity; risk.

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Intensive care units (ICUs) are the units in which invasive procedures are performed, mechanical ventilation (MV) is applied, and patients who receive intensive drug therapy are followed up; in these units, the hospital-ac-

quired infections (HAIs) and mortality rates are also high [1].

Approximately 25% of HAIs occur in ICU. The frequency of hospital infection and antibiotic susceptibil-

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Correspondence: Dr. Melike KORKMAZ TOKER, Department of Anesthesiology and Reanimation, University of Health Sciences, Istanbul Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey.

Phone: +90 505 474 70 98 e-mail: meltoker@gmail.com

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TABLE 1. RIFLE classification (serum creatinine and GFR criteria)

Category	Criteria
Risk (R)	Increased creatinine level x1.5 or GFR decrease >25%
Injury (I)	Increased creatinine level x2 or GFR decrease >50%
Failure (F)	Increased creatinine level x3, GFR decrease >74% or creatinine level >4mg/dl
Loss (L)	Persistent acute renal failure or complete loss of function for >4 weeks
ESKD (E)	ESKD for >3 months

ESKD: End stage kidney disease.
GFR: Glomerular filtration rate.

ity may vary from country to country, from hospital to hospital, and within different units of the same hospital. Reduction in resistance of patients followed up in ICU, long-term hospitalization, MV, and invasive procedures such as catheterization lead to an increase in the incidence of infections in these units. Multiple antimicrobial resistances occur with the widespread use of broad-spectrum antibiotics in these units [2-4].

Colistin is a cationic polypeptide antibiotic that was introduced in the 1960s. Its use had been banned due to its potential side effects, particularly owing to the nephrotoxicity rates approaching 50% and subsequent use of other antimicrobials. Recently, its administration has been reinitiated in the treatment of multi-drug resistant pathogens (MDRP) such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and carbapenem-resistant Enterobacteriaceae. Nephrotoxicity and neurotoxicity are the main problems encountered in the clinical use of polymyxins [5-8]. In this study, our aim was to determine the frequency and risk factors of colistin-related nephrotoxicity in the adult ICU.

MATERIALS AND METHODS

This was a retrospective cohort analysis to assess nephrotoxicity in critically ill patients receiving colistin at a university-affiliated tertiary research and training hospital. In this study, patients who received intravenous colistin during follow-up in the adult ICU of University of Health Sciences Istanbul Kanuni Sultan Suleyman Research and Training Hospital between January 01 and December 31, 2016 were retrospectively evaluated. Computer records of age, sex, site of infection and microorganism breeding, daily creatinine values, comorbidities such as diabetes mellitus (DM), cerebrovascular disease (CVD), chronic obstructive pulmonary disease (COPD), malig-

nancy, trauma, and presence of abdominal surgery were recorded and examined.

Concurrent use of nephrotoxic antibiotics such as aminoglycoside, vancomycin, and carbapenem has been identified in patients who have received colistin. Patients were excluded if they received colistin therapy for less than 72 hours, had a diagnosis of chronic renal failure according to documented medical history, or were younger than 18 years of age. If a patient received recurrent colistin treatment, only the first treatment was evaluated.

The primary outcome was the occurrence of nephrotoxicity according to the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria. The RIFLE criteria (Table 1) represent a valuable validated tool for evaluation of acute kidney injury (AKI) based on both change in glomerular filtration rate (GFR) and serum creatinine concentration [9]. These criteria have been validated and continue to be used in literature describing colistin-associated nephrotoxicity [10].

For statistical analysis, SPSS 15.0 package program, chi-square test, and T-test were used. In the analysis results, a p value less than 0.05 were considered to indicate a statistically significant difference.

RESULTS

A total of 48 patients met the inclusion criteria and were included in the study. Of these, 50% were male. *A. baumannii* was observed to be the causative microorganism in all patients and the most frequent infection was pneumonia. Patients were treated for pneumonia (73%), blood stream infection (23%), soft tissue infection (2%), and urinary system infection (2%) (Table 2). Nephrotoxicity was investigated in 54.2% (n=26) of the patients. Overall, the 26 patients with nephrotoxicity were classi-

TABLE 2. Distribution of infections in patients

	N	%
Pneumonia	35	73
Blood stream infection	11	23
Soft tissue infection	1	2
Urinary system infection	1	2

TABLE 3. Distribution of patients according to RIFLE criteria

Criteria (Patient)	N	(%)
No risk	22	(45.8)
Risk (R)	7	(14.5)
Injury (I)	10	(20.8)
Failure (F)	9	(18.7)

fied as risk (7 patients), injury (10 patients), and failure (9 patients) (Table 3).

The mean age of the patients with nephrotoxicity was 59.73 ± 22.38 years and of those without nephrotoxicity was 58.00 ± 22.39 years.

Demographic features of the patients and clinical characteristics are listed in Table 4. The incidence of nephrotoxicity was not affected by other variables.

DISCUSSION

Hospital infections are one of the major causes of mortality and morbidity in hospitalized patients and cause serious problems particularly in patients in ICU. Inflammatory infections caused by resistant microorganisms are frequent in ICU due to invasive interventions, prolonged hospitalization, and frequent use of broad-spectrum antibiotics [11].

This retrospective cohort study was designed to evaluate the incidence of severe AKI and the associated risk factors in ICU patients, without pre-existing renal impairment, receiving colistin treatment for the MDRP infections.

Colistin is a cyclic structured polypeptide. Nowadays, the increase of multi-drug resistant gram-negative pathogens has attracted interest with respect to colistin. The most important disadvantage of this drug is its nephrotoxic effect, which is the only option in patients with *P. aeruginosa* and *A. baumannii* infections, particularly in their last few years. *A. baumannii* has been iden-

TABLE 4. Demographic and clinical characteristics of patients who received colistin

	Patients with nephrotoxicity (n=26)	Patients without nephrotoxicity (n=22)	P
Age (years) (mean±SD)	59.73±22.38	58.00±22.39	0.39
Gender (M/F)	15/11 (58/42)	9/13 (41/59)	0.24
>65 years, N. (%)	13 (50)	9 (41)	0.52
Diabetes Mellitus, N. (%)	9 (35)	9 (41)	0.65
COPD, N. (%)	11 (42)	4 (18)	0.72
Malignancy, N. (%)	3 (12)	1 (4)	0.38
Cerebrovascular disease, N.(%)	5 (19)	2 (9)	0.32
Postoperative visceral surgery, N. (%)	12 (46)	7 (32)	0.31
Creatinin level before therapy (mg/ dL) (mean±SD)	0.66±0.24	0.70±0.18	0.51
Concomitant aminoglycoside use	1 (4)	3 (14)	0.22
Concomitant vancomycin use	12 (46)	10 (45)	0.56
Concomitant carbapenem use	26 (100)	20 (91)	0.11
Concomitant tigecycline use	0 (0)	3 (14)	0.52
Duration of treatment (day) (mean±SD)	13.38±7.17	15.18±7.12	0.39
Mortality, N. (%)	19 (73)	14 (64)	0.48

COPD: Chronic Obstructive Pulmonary Disease.

tified as the most frequent cause of hospital infections in elderly patients followed up in ICU [12-14]. Nephrotoxicity and neurotoxicity are the main problems encountered in the clinical use of polymyxins. Nephrotoxicity ratios differ in studies conducted on the subject, and it is thought that this difference may be due to different patient populations and the use of different criteria. In recent years, for obtaining more standardized data, varying criteria have been used, and the RIFLE criteria provide a useful framework for nephrotoxicity [8, 14]. Ricci et al [15] defined the RIFLE classification as a simple, readily available clinical tool to classify AKI in different populations. Authors concluded their review by stating that the RIFLE classification seems to be a good outcome predictor.

Due to the high sensitivity of the RIFLE criteria with respect to determining acute renal failure, in our study, we decided to use RIFLE as a degree of measuring nephrotoxicity.

In our study, the rate of nephrotoxicity was detected to be 54.2% in patients who received colistin in ICU. The rate of nephrotoxicity varies widely throughout the published literature. A total of 11 relevant study results [5-20] have been identified in Table 5.

The incidence of AKI related to colistin varies widely, ranging from 16.2% to 77.5% in the literature [5-20]. This wide variety is likely due to differences in study populations. Bilgili et al. reported a rather high overall AKI incidence, and they explained this high occurrence by the severity of illness. Their median Apache score was 21. The lack of Apache scores of our patients in this study is insufficient to compare our outcome with this study.

In the current study, among the 26 patients with nephrotoxicity, 14.6% were classified as risk, 20.8% as injury, and 18.7% as failure. Pogue et al. presented similar rates of nephrotoxicity in a cohort of 126 patients: 13% as risk, 17% as injury, and 17% as failure.

A. baumannii was observed to be the causative microorganism in all patients, and the most frequent infection was pneumonia. Similar to our study, it was determined that *A. baumannii* is the most common agent in other studies [8, 18, 22], and the most frequent infection is pneumonia [8, 12, 18, 19].

When risk factors for nephrotoxicity were evaluated, it was found that nephrotoxicity was higher in the presence of COPD, malignancy, and abdominal surgery in those older than 65 years, and mortality was higher in those who developed nephrotoxicity, although the toxicity was not statistically significant.

Pogue et al. [5] reported that higher colistin doses led to a relatively high rate of nephrotoxicity. Tuon et al. [7] concluded their study stating that vancomycin co-administration likely increases the risk of AKI.

In our country, Köksal et al. [8] showed that older age, presence of COPD, and DM increased the risk of nephrotoxicity. There are several studies that revealed the association between COPD and renal failure. Gadani et al. [23] reviewed prospective and retrospective observational studies that reported the prevalence of chronic kidney disease (CKD) in patients with COPD. They found that patients with COPD have increased odds of developing CKD. The mechanism by which COPD potentiates the development of CKD remains unclear. COPD has been associated with systemic inflammation. This inflammation is also potentially related to development of kidney disease. Mapel et al. [24] examined renal disease in a population-based cohort of persons with COPD. They found that COPD patients have a substantially increased prevalence of renal diseases as well as abnormal renal and hepatic laboratory values. Our results revealed that COPD patients have more nephrotoxicity as studies mentioned above. This result can be explained by stating that COPD patients are also more likely to be prescribed medications with potentially toxic renal side effects.

Other studies on the subject have reported that the presence of malignancy, hypotension, simultaneous vancomycin use, high dose, advanced age, and septic shock are factors that increase nephrotoxicity [13, 14, 17, 18, 20-22].

In conclusion, nephrotoxicity seems to be an important adverse effect in our study because of the fact that the risk factors affecting nephrotoxicity were not statistically determined but the rate of development of nephrotoxicity was 54.2% in patients using colistin. Therefore, periodic assessment of serum creatinine levels, modification of the colistin dose according to renal function, avoidance of coadministration of other nephrotoxic agents (if possible), and shortening the duration of antimicrobial treatment will minimize the potential for nephrotoxic effects of this valuable old antibiotic.

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