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Incidence and risk factors of nephrotoxicity associated with intravenous colistin use in the intensive care unit

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Ethics Committee Approval
Ethics committee approval for this study was received from the Ethics Committee of Inonu University following the Declaration of Helsinki (date: 24.07.2019; no: 2019/138).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The most serious side effect of colistin therapy is nephrotoxicity. This study aimed to investigate the incidence of nephrotoxicity (NT) due to intravenous colistin and determine the associated risk factors in critically ill patients in the intensive care unit (ICU).

Methods: This retrospective cohort study was conducted by examining the files of 100 patients who were hospitalized in the ICU and received intravenous colistin therapy. According to the RIFLE criteria, the patients were divided into two groups as those with and without nephrotoxicity. The clinical characteristics of the patients were compared between the groups and the risk factors associated with nephrotoxicity were determined by multivariate linear logistic regression analysis.

Results: The mean age, mean length of stay in the ICU, and mortality rate of 44 patients included in the study were 68±16.36 years, 77.14 (83.03) days, and 56.8%, respectively. NT developed in 22 (50%) patients during colistin therapy. In those with NT, diabetes mellitus, chronic obstructive pulmonary disease, and coronary artery disease were significantly more common (P<0.05 for all), the mean age (P<0.001), Charlson age-adjusted comorbidity index (CACI) scores, APACHE scores (P=0.010) were higher and albumin level was lower (P=0.001). High CACI scores (B=0.532, P=0.002) and low albumin levels (B=-0.323, P=0.023) were significant risk factors for colistin NT according to the regression analysis.

Conclusion: Nephrotoxicity is significantly common among critically ill patients receiving colistin therapy. Patients with high CACI scores and hypoalbuminemia should be followed up closely for nephrotoxicity.

Keywords: Colistin, Nephrotoxicity, Intensive care unit

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Introduction

Nosocomial infections due to multi-drug resistant (MDR) gram-negative bacteria are associated with mortality, morbidity, and long hospitalization, especially in the intensive care units (ICUs) [1]. Colistin (colistimethate sodium) is one of the widely used intravenous (IV) agents in the treatment of these infections [2]. Its use was suspended in the 1970s due to high rates of nephrotoxicity (NT), but it has recently regained popularity because of the increase in MDR nosocomial infections in recent years [2,3].

The most common side effects that limit the use of colistin are nephrotoxicity and neurotoxicity. Both are dose-dependent and reversible, and permanent kidney damage is rarely seen. The rate of colistin-related nephrotoxicity varies between 20-76% in numerous studies [2, 4, 6]. Although the underlying mechanism is not clear, it was reported to cause an increase in membrane permeability and oxidative damage, resulting in acute tubular necrosis [6, 7].

Factors affecting the risk of nephrotoxicity include age, gender, hypoalbuminemia and hyperbilirubinemia, high-dose and long-term use of colistin, use of additional nephrotoxic agents, and various comorbidities [6]. Colistin nephrotoxicity is associated with increased adverse outcomes in critically ill patients [1]. For this reason, determining the risk factors associated with nephrotoxicity is critical in preventing nosocomial infections with MDR in the ICU.

This study aims to investigate the frequency of nephrotoxicity due to IV colistin use in the intensive care unit and determine the associated risk factors.

Materials and methods

Study design and environment

This retrospective observational study was conducted by examining the files of patients hospitalized in a tertiary ICU between May 2018-May 2019. Adult patients who received at least 48 hours of IV colistin therapy were included in this study; while patients followed in the cardiovascular surgery ICU, those with acute or chronic renal failure, those who received hemodialysis, patients under 18 years of age, and pregnant women were excluded. In patients who received colistin therapy more than once, their first use was assessed (Figure 1). This study was performed per Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.

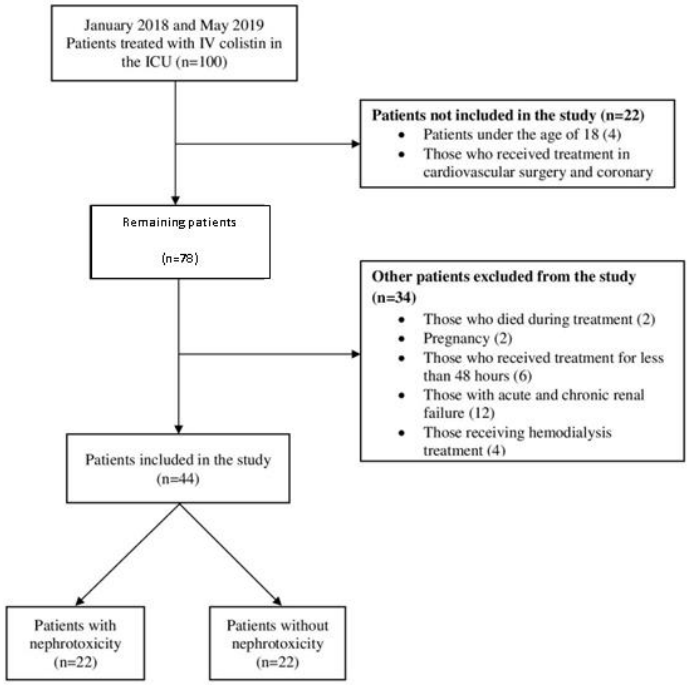
Study data

All included patients were in critical condition and received IV colistin due to gram-negative infections with MDR in the ICU. The data were obtained by scanning the hospital information management system, patient files, and daily ICU follow-up forms. Demographic characteristics of the patients, length of stay in the ICU, comorbid diseases, Charlson age-adjusted comorbidity index (CACI) scores, infection location and causative microorganisms, Acute Physiology and Chronic Health Evaluation (APACHE) II scores at diagnosis and albumin values were recorded. After at least 48 hours of IV colistin therapy, the amount of colistin received, the number of days until nephrotoxicity developed, and mechanical ventilation (MV), hemodialysis requirements, and inotropic agent needs were noted.

RIFLE criteria were used for the evaluation of nephrotoxicity. The patients were divided into two groups as those with and without NT. In cases of nephrotoxicity, nephrology and infectious diseases departments were informed. Recommendations for change in IV the colistin treatment regimen or dose adjustment were followed. Comorbidities of the patients were confirmed by preoperative consultation records. The CACI scores of the patients were calculated on the website http://www.pmidcalc.org/id=7722560&newtest=Y' and their results were noted [8].

Nosocomial infection diagnoses were made according to the “Centers for Disease Control and Prevention” criteria in daily visits performed in the ICU by the infectious diseases department. The analyzed infection-related data were obtained from patient files, the hospital automation system, and the database of the National Hospital Infections Surveillance Network. The use of other nephrotoxic agents (aminoglycoside, carbapenem, vancomycin, tigecycline, sulbactam, contrast agent, etc.) used in combination with colistin was recorded and compared between the groups.

Figure 1: Flow chart of the study



Ethical statement

Ethics committee approval for this study was received from the Ethics Committee of the Inonu University following the Declaration of Helsinki (date: 24.07.2019; no: 2019/138).

Statistical analysis

Statistical analysis was performed using SPSS 20.0 package program. The data were presented as number (%), median and interquartile range (25-75 p). The suitability of the variables to normal distribution was evaluated with the Kolmogorov–Smirnov test. Non-normally distributed continuous variables were compared with the Mann-Whitney U test. Categorical variables were compared using Pearson's Chi-square test and Fisher's exact test, as needed. Risk factors affecting the RIFLE scores were found by the enter method in multivariate

sequential logistic regression analysis. $P<0.05$ was considered statistically significant.

Sample size calculation was based on the study of Kaya et al. [16] on the incidence of colistin-related nephrotoxicity. A total of 40 patients were required for one-sided, 0.05 error and 85% power. Sample size estimation was made using G*Power (version 3.1.9.6; Kiel, Germany) software.

Results

Demographic data and clinical characteristics of the patients

The data of 44 patients who met the inclusion criteria among 100 patients who received IV colistin therapy due to nosocomial infection in the ICU were analyzed retrospectively (Figure 1). Nephrotoxicity developed in 22 (50%) patients (with NT) during colistin therapy, while it was not observed in 22 (50%) (without NT). Twenty-seven (61.4%) patients were male, 17 (38.6%) were female, and the overall mean age was 68 (16.36) (range: 20-92) years. The mean length of stay in ICU was 77.14 (83.03) (range: 10-356) days, and 25 (56.8%) patients died. The demographic characteristics of the patients are presented in detail in Table 1.

Table 1: Comparison of demographic characteristics and prognosis in patients with and without nephrotoxicity

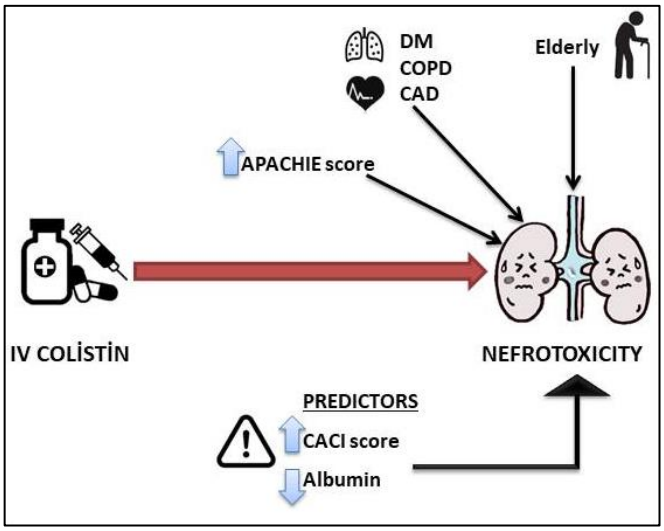
Patient characteristics		Patient without NT (n=22)		Patient with NT (n=22)		All patients (n=44)		*P*-value
Gender	Male	13	59.1%	14	63.6%	27	61.4%	0.757*
	Female	9	40.9%	8	36.4%	17	38.6%	
Age (years)		64	55-70	79	68-84	69	62-80	<0.001‡
Site of infection	Respiratory	13	59.1%	8	36.4%	21	47.7%	0.183†
	Blood circulation	4	18.2%	8	36.4%	12	27.3%	
	Urinary tract	4	18.2%	2	9.1%	6	13.6%	
	Other	1	4.5%	4	18.2%	5	11.4%	
Infectious agent	Acinetobacter	14	63.6%	9	40.9%	23	52.3%	0.406†
	Klebsiella	4	18.2%	7	31.8%	11	25.0%	
	Pseudomonas	3	13.6%	3	13.6%	6	13.6%	
	Others	1	4.5%	3	13.6%	4	9.1%	
Comorbidities	Diabetes mellitus	4	18.2%	11	50.0%	15	34.1%	0.026*
	Hypertension	13	59.1%	18	81.8%	31	70.5%	0.099*
	Neurologic disease	9	40.9%	4	18.2%	13	29.5%	0.498*
	Chronic obstructive pulmonary disease	15	68.2%	17	77.3%	32	72.7%	0.030*
	Cancer	7	31.8%	5	22.7%	12	27.3%	0.698*
	Liver failure	17	77.3%	10	45.5%	27	61.4%	0.664*
	Coronary artery disease	5	22.7%	12	54.5%	17	38.6%	0.026*
Mortality		11	50.0%	14	63.6%	25	56.8%	0.361*
Renal replacement therapy		6	27.3%	13	59.1%	19	43.2%	0.033*
Need for MV		13	59.1%	21	95.5%	34	77.3%	0.045*
Need for inotropic support		13	59.1%	18	81.8%	31	70.5%	0.099*
Length of stay (days)		45	28-100	34	24-96	40	26-98	0.664‡
CACI score		3	2-4	5	4-6	4	3-5	<0.001‡
APACHE score		22	12-24	25	22-36	24	18-26	0.010‡
Duration of treatment, days		8.5	5.75-14	7.5	5-9.25	8	5-10.75	0.062‡
Duration of colistin treatment, days		5.5	4-8	4.5	3-6	5	4-6	0.089‡
Albumin level (g/dl)		2.80	2.55-3.40	2.20	1.90-2.65	2.58	2.15-2.95	0.001‡
Use of additional nephrotoxic agents		19	%86.4	20	%90.4	39	%88.6	0.635*

*Chi-square test; †Fisher exact test; ‡ Mann Whitney U Test, It was presented as n (%) and median (25-75 p.). MV: Mechanic ventilation; CACI: Charlson Age-Adjusted Comorbidity Index

Comparison of clinical characteristics between nephrotoxicity groups

The mean age was significantly higher in the group with NT compared to the group without (77.09 (9.6) vs 58.9 (16.8)) ($P<0.001$), but gender distribution was similar ($P= 0.757$) (Table 1). While diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and coronary artery disease (CAD) were significantly more common in the group with NT ($P=0.026$, $P=0.030$, and $P=0.026$, respectively), there were no significant differences in terms of other comorbidities (each $P>0.05$). In addition, CACI scores were significantly higher in the NT group ($P<0.001$) (Figure 2).

Figure 2: Risk factors associated with nephrotoxicity



The foci of infection in order of frequency were the respiratory tract (47.7%), blood circulation (27.3%), and the urinary tract (13.6%). The most common infectious agents were Acinetobacter (52.3%), Klebsiella (25.0%), and Pseudomonas spp. (13.6%). These results did not differ between the two groups.

Data

Total treatment time of colistin and days until NT development did not differ between the groups. While the hospitalization period was insignificantly shorter, and mortality was insignificantly higher, MV support, hemodialysis need, and APACHE scores were significantly higher, and mean serum albumin level was significantly lower in the group with NT ($P=0.045$, $P=0.033$, $P=0.010$, and $P=0.001$, respectively). The two groups were similar in terms of inotropic agent need ($P>0.05$). Five patients (11.4%) received colistin monotherapy and 39 (88.6%) received combination therapy with other nephrotoxic agents. The rate of those who received additional nephrotoxic agents did not differ between the groups ($P=0.365$).

Independent risk factors for nephrotoxicity

According to the RIFLE scoring system, half (50%) of the patients had no renal damage, 9.1% carried a risk, 15.9% had damage and 25% had renal insufficiency (Table 2). Risk factors affecting RIFLE scores were determined by multivariate logistic regression analysis: High CACI scores (*B:* 0.532, $P=0.002$) and low albumin levels (*B:* -0.323, $P=0.023$) were significant risk factors for colistin nephrotoxicity (Table 3).

Table 2: Nephrotoxicity rates by RIFLE classification

RIFLE criteria	n	%
No	22	50.0%
Risk	4	9.1%
Damage	7	15.9%
Failure	11	25.0%

Table 3: Multivariate ordinal logistic regression analysis of possible factors affecting the RIFLE classification

$R^2=0.510$	ß	SE	Beta	t	*P*-value
Constant	0.891	1.296	-	0.687	<0,001
Age	0.009	0.015	0.109	0.561	0.578
CACI	0.398	0.118	0.537	3.363	0.002
APACHE-II	0.032	0.020	0.201	1.610	0.116
Albumin	-0.605	0.255	-0.323	-2.374	0.023

SE: Standard error; CACI: Charlson age comorbidity index; APACHE: Acute Physiology and Chronic Health Evaluation

Discussion

Colistin-related nephrotoxicity rates vary between 20% and 76% in different studies [5]. This difference may be due to different scoring systems (AKIN, RIFLE, and KDIGO) used for renal failure [9]. In the present study, RIFLE criteria were used to determine the risk of colistin-related nephrotoxicity, as suggested by various studies [1, 7, 12]. Our rate of NT was higher (50% of the patients), which may be because our patient population consists of critically ill patients of advanced age and the right treatment dose of colistin could not be adjusted.

Many factors, including advanced age, male gender, comorbidities (DM, HT, etc.), obesity, hypoalbuminemia, hyperbilirubinemia, nephrotoxic drug use, total colistin dose and duration, and contrast agent administration, are found to increase the risk of colistin-related nephrotoxicity [6, 10-12]. Extensive studies report that advanced age and chronic multiple comorbid diseases are important risk factors for drug-related kidney injury [6, 10, 11]. Conversely, studies are reporting that advanced age does not play a role in NT [12]. In a study investigating the relationship of colistin NT with age, NT was associated with being over 60 years of age and high CACI scores [10]. In our study, the mean age of patients with NT was higher, and DM, COPD, and CAD were more common. CACI index is a widely used clinical scoring system that evaluates the patient's physical condition and age and determines the prognosis depending on the patient's comorbidities [8]. Various studies report that the CACI score is associated with acute kidney injury in critically ill patients [6, 8]. Similarly, in our study, the CACI score was an independent risk factor for colistin-associated NT. However, CACI is not yet fully considered an independent risk factor for colistin-associated NT due to insufficient data.

In numerous studies, the most common site of infection is the respiratory tract, and the infectious agents are Acinetobacter, Klebsiella, and Pseudomonas spp. [1, 13-15], like our findings. The relationship between colistin dose, duration of use and NT are still contradictory [6, 14, 16]. There are studies reporting that the duration and amount of colistin affect NT [13, 17]. Colistin-associated NT usually occurs within the first 5 days of treatment and may be reversible after the treatment is terminated [18]. Jason et al. [16] state that NT developed within the first 7 days in 78% of the patients, Emrah et al. [1] reported that it developed within the first 9 days in 77%, and in the study of Deryke et al. [17], NT developed in the first 5 days in all patients. On the other hand, we found no significant relationship between the duration of colistin use and NT.

Another risk factor associated with NT is the combinational use of nephrotoxic agents with colistin. Despite conflicting reports, the use of additional nephrotoxic agents was associated with kidney damage in most studies [14]. There are also studies reporting that it does not affect NT [10, 11, 13, 16, 17]. Kim et al. [14] stated that the combined use of various NT agents (NSAID, aminoglycoside and diuretic, etc.) is a risk factor for colistin NT. In our study, the combined use of colistin with nephrotoxic agents did not significantly affect NT. However, caution should be exercised in the use of additional nephrotoxic agents (contrast agent, NSAID or aminoglycoside, etc.).

Hypoalbuminemia was the second independent risk factor for NT in our study. The relationship between hypoalbuminemia and NT was demonstrated in many studies [14, 19, 20]. However, there is wide heterogeneity in the literature on this subject as well. In the case of hypoalbuminemia, NT may develop due to reduced binding of colistin to albumin; however, the underlying mechanism is not yet clear. Daniele et al. [19] reported that severe hypoalbuminemia (<2.5 g/dl) at the beginning of colistin therapy was a predictor of nephrotoxicity. In another study, hypoalbuminemia with a cut-off value of 2.65 g/dL was a significant predictor for NT [20]. On the other hand, various studies have shown that albumin level does not affect NT [11, 14]. Another important result in the present study is that the APACHE score, which is an indicator of mortality in critically ill patients, was significantly higher in patients with NT. Similarly, Emrah et al. [1] found that a high APACHE score was associated with colistin NT.

Although colistin nephrotoxicity is reversible, studies are reporting increased mortality [2, 6] and inotropic need, and prolonged hospitalization [1, 13, 20, 21]. We observed that patients with NT insignificantly more frequently needed inotropes, MV, and hemodialysis. Despite these negative results, there was no significant difference in mortality between the NT groups. Conversely, other studies found that colistin-associated NT is associated with high mortality [11]. Based on our results, it can be said that colistin-associated NT disrupts the clinic of critically ill patients but is not an important risk factor for mortality.

The limitations of our study include the small sample size, and its retrospective and single-center nature.

Conclusion

Our results show that nephrotoxicity during colistin therapy is common in critical patients in the ICU. Higher rates of nephrotoxicity were observed in patients with DM, COPD, and CAD. High CACI score and hypoalbuminemia were independent risk factors for colistin-associated nephrotoxicity. During colistin therapy, critical patients with these adverse risk factors should be closely monitored in terms of nephrotoxicity.

Acknowledgment

Figure 2 is original, copyrighted by the authors of this study, and was produced for this article.

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