RESEARCH ARTICLE / ARAŞTIRMA

DOI: 10.4274/mjima.galenos.2021.2021.53
Mediterr J Infect Microb Antimicrob 2021;10:53
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2021.2021.53

Colistin-induced Nephrotoxicity: Experience from a University Hospital

Kolistin ile İndüklenen Nefrotoksisite: Bir Üniversite Hastanesi Deneyimi

Pınar BAKIR EKİNCİ[1], Melek KURTARAN[1], Emre KARA[1], Hanife AVCI[2], Kutay DEMİRKAN[1], Gökhan METAN[3]

[1]*Hacettepe University Faculty of Pharmacy, Department of Clinical Pharmacy, Ankara, Turkey*
[2]*Hacettepe University Faculty of Medicine, Department of Biostatistics, Ankara, Turkey*
[3]*Hacettepe University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*

Abstract

Introduction: Colistin has been widely used in the treatment of infections caused by multidrug-resistant bacteria. This study aimed to determine the frequency and risk factors of colistin-related nephrotoxicity.
Materials and Methods: Patients who received colistin between October 2018 and August 2019 in a tertiary care hospital were analyzed retrospectively. Kidney Disease Improving Global Outcome criteria were used for the staging of nephrotoxicity.
Results: A total of 100 patients who were treated with colistin were included in this study. The median patient age was 64 years, and 43% were female. Nephrotoxicity was detected in 52% of patients at Week 1 of colistin therapy, and 59% of the patients on colistin therapy experienced nephrotoxicity at any time. Serum creatinine increased to ≥1.5 times the baseline in a median of four (1-11) days, and the estimated glomerular filtration rate decreased below 60 ml/min in a median of five (1-42) days. After Week 1 of colistin therapy, 48% of the patients preserved "normal" kidney functions. Of the patients who experienced nephrotoxicity in Week 1 of colistin therapy: 85% had stage 1, 56% had stage 2, and 35% had stage 3. The length of hospitalization [Odds ratio (OR): 1.009, 95% confidence interval (CI): 1.001-1.017], age (OR: 1.036, 95% CI: 1.005-1.068), duration of colistin therapy (OR: 1.115, 95% CI: 1.023-1.216), and use of vasopressors (OR: 3.012, 95% CI: 1.003-9.042) were significantly associated with nephrotoxicity at any time during colistin therapy.
Conclusion: This study showed a high rate of colistin-related nephrotoxicity. Regular monitoring of renal functions, appropriate dosing, and limiting the duration of colistin therapy as much as possible may be useful to avoid nephrotoxicity in older patients particularly when administered with vasopressors.
Keywords: Polymyxins, acute kidney injury, nephrotoxicity, risk factor, colistin dosage

Öz

Giriş: Kolistin, çok sayıda ilaca dirençli bakterilerin neden olduğu enfeksiyonların tedavisinde yaygın olarak kullanılmaktadır. Bu çalışmada, kolistin ilişkili nefrotoksisitenin sıklığı ve risk faktörlerinin belirlenmesi amaçlanmıştır.
Gereç ve Yöntem: Bu çalışmada Ekim 2018 ile Ağustos 2019 arasında, üçüncü basamak bir hastanede kolistin alan hastalar geriye dönük olarak incelenmiştir. Nefrotoksisitenin evrelenmesinde Kidney Disease: Improving Global Outcomes-Böbrek Hastalıkları: Küresel Sonuçların İyileştirilmesi kriterleri kullanılmıştır.
Bulgular: Çalışmaya kolistin ile tedavi edilen 100 hasta dahil edilmiştir. Hastaların ortanca yaşı 64 yıl ve %43'ü kadındır. Hastaların %52'sinde kolistin tedavisinin ilk haftasında nefrotoksisite saptanmıştır ve hastaların %59'unda kolistin tedavisinin herhangi bir anında nefrotoksisite saptanmıştır. Serum kreatinin ortanca dört (1-11) günde normal seviyenin ≥1,5 katına yükselmiştir ve ortanca beş (1-42) günde tahmini glomerüler filtrasyon hızı 60 ml/dakikanın altına düşmüştür. Kolistin tedavisine başlandıktan sonraki ilk haftanın sonunda hastaların %48'i "normal" böbrek fonksiyonlarını korumuştur. Kolistin tedavisine başladıktan sonraki ilk hafta nefrotoksisite gözlenen hastaların %20'si "evre 1", %17'si "evre 2", %15'i "evre 3" olarak

Cite this article as: Bakır Ekinci P, Kurtaran M, Kara E, Avcı H, Demirkan K, Metan G. Colistin-induced Nephrotoxicity: Experience from a University Hospital. Mediterr J Infect Microb Antimicrob. 2021;10:53.

Address for Correspondence/Yazışma Adresi: Pınar Bakır Ekinci MD, Hacettepe University Faculty of Pharmacy, Department of Clinical Pharmacy, Ankara, Turkey
Phone: +90 544 246 19 04 **E-mail:** pinar.bakir55@gmail.com **ORCID ID:** orcid.org/0000-0003-0694-6078
Received/Geliş Tarihi: 17.03.2021 **Accepted/Kabul Tarihi:** 01.09.2021

Published: 2 September 2021

Öz

saptanmıştır. Hastanede kalış süresi [Odds oranı (OR): 1,009; %95 güven aralığı (GA): 1,001-1,017], yaş (OR: 1,036; %95 GA: 1,005-1,068), kolistin tedavisi süresi (OR: 1,115, %95 GA: 1,023-1,216) ve vazopressör kullanımı (OR: 3,012, %95 GA: 1,003-9,042) kolistin tedavisinin herhangi bir anında nefrotoksisite ile ilişkilidir.

Sonuç: Bu çalışma, kolistin ile ilişkili nefrotoksisite oranının yüksek olduğunu göstermiştir. Özellikle vazopressörlerle birlikte uygulandığında böbrek fonksiyonlarının düzenli monitörizasyonu, uygun dozlama ve kolistin tedavi süresini mümkün olduğunca sınırlandırmak, yaşlı hastalarda nefrotoksisiteden kaçınmak için faydalı olabilir.

Anahtar Kelimeler: Polimiksinler, akut böbrek hasarı, nefrotoksisite, risk faktörü, kolistin dozu

Introduction

Treatment of infections caused by multi-drug resistant (MDR) infections is challenging. Carbapenems are the most effective option for the treatment of MDR Gram-negative bacilli infections. However, colistin (polymyxin E) has become the most common choice in the treatment of carbapenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* infections[1].

Colistin is a polymyxin antibiotic consisting of a cationic polypeptide structure. It was discovered in 1949 and introduced to clinical use in the 1960s, but it was replaced by other antibiotics because of its nephrotoxicity potential[2]. Colistin is eliminated primarily by the kidneys, and it is secreted through tubular cells[3]. Aminobutyric and fatty acid components of colistin damage the epithelial cells of the proximal tubule[4]. Colistin-induced nephrotoxicity develops as a result of acute tubular necrosis[5]. Colistin has two forms, namely, colistimethate sodium (CMS) and colistin sulfate. Of those, CMS is a prodrug, and it is preferred because of its low risk for nephrotoxicity[6].

The antibacterial effect and nephrotoxicity are dependent on the dose of colistin[2]. A pharmacokinetic trial showed the importance of a loading dose to overcome the slow conversion of CMS to its active form[7]. These approaches helped achieve the pharmacokinetic targets, but the effect on colistin-related adverse effects is largely unknown[8,9]. Increasing colistin doses can also increase the risk of acute kidney injury (AKI)[10]. The incidence of nephrotoxicity during colistin therapy has been reported various studies[11,12].

In the present study, we aimed to determine the rate of colistin-induced nephrotoxicity by using the Kidney Disease Improving Global Outcome (KDIGO) criteria and to assess the risk factors for colistin-induced nephrotoxicity.

Materials and Methods

This study was conducted as a retrospective cross-sectional and observational study in a university hospital between October 31, 2018, and August 01, 2019. The study protocol was approved by the Hacettepe University Local Ethics Committee (date: 01.10.2019; GO 19/853). This study retrospectively evaluated data of patients aged ≥18 years who received intravenous (with or without inhaled/intrathecal) colistin. Demographic and laboratory features of the patients such as age, gender, body mass index, infection site, causative bacteria, daily creatinine values, comorbidities, indication for colistin therapy, colistin dose (milligrams), treatment duration (days), concomitant nephrotoxic agent(s) use, and need for vasopressors were recorded from the local hospital database. Patients with body mass index ≥30 kg/m^2 were considered obese[13].

According to the Infectious Diseases Society of America guideline, in case of carbapenemase-producing *Klebsiella pneumoniae* suspicion in patients with neutropenic fever, CMS may be added to empiric antimicrobial treatment[14]. Colistimethate sodium which contains 150 mg of colistin base activity in each vial was the only form that used in the hospital during the study period. The recommendations of International Consensus Guidelines for the Optimal Use of the Polymyxins were followed for colistin dosing in the entire study period (Supplementary Table 1)[15].

Assessment of renal functions and grading of colistin-induced nephrotoxicity were determined by using the KDIGO criteria. Nephrotoxicity was defined as an increase in serum creatinine (SCr) by ≥0.3 mg/dl within 48 h or an increase in SCr to ≥1.5 times the baseline within seven days after initiation of colistin according to the KDIGO criteria. The stage of nephrotoxicity was determined according to KDIGO guidelines. Stage 1 refers to an increase in SCr to 1.5-1.9 times the baseline or an increase in SCr of >0.3 mg/dl. Stage 2 refers to an increase in SCr to 2.0-2.9 times the baseline. Stage 3 refers to an increase in SCr to ≥3.0 times the baseline or to >4.0 mg/dl or initiation of renal replacement therapy[16].

Any increase in SCr that exceeds 1.5 times higher than the baseline SCr value was defined as nephrotoxicity regardless of the KDIGO classification. Nephrotoxicity that occurred at Week 1 of colistin therapy (according to KDIGO) and at any time during colistin therapy were evaluated separately.

Statistical Analysis

Statistical analysis was performed on IBM Statistical Package for the Social Sciences Statistics 23. The Shapiro-Wilk goodness-of-fit test were used to test whether the distributions related to the numerical variables match the normal distribution. Descriptive statistics such as mean, standard deviation, minimum, and maximum were used for numerical variables that conform to normal distribution. Percentage values and frequency tables were given for categorical variables. Categorical variables were compared with the x^2 tests. The Mann-Whitney U nonparametric test was used for comparing two independent groups. Logistic regression analysis was used for risk factor assessment. To investigate the risk factors associated with the causes of diagnosis, univariate and multivariate backward logistic regression were applied. In addition, the Odds ratio (OR) and confidence intervals (CI) of the ORs of each factor separately or in combination were calculated. All statistical tests were performed at the statistical significance level of 5%.

Results

A total of 110 patients who received colistin were included in this study. One patient was excluded because of missing data, and 9 were excluded because of the presence of chronic renal insufficiency when colistin was started. One hundred patients were evaluated in the final analysis. The median age of the patients was 64 (minimum-maximum: 18-93) years, and 43% were female. The leading comorbidity was malignancy (48%), and the patients had a median of 3 (0-8) different comorbidities. The mean weight was 71±16 kg, and obesity was detected in 22% of the patients. The 7-, 14- and 30-day fatality rates after initiation of colistin therapy were 13%, 16%, and 23%, respectively.

Colistin indications were bacteremia (32%), pneumonia (29%), intra-abdominal infections (13%), empirical treatment of patients with febrile neutropenia (11%), central nervous system infections (5%), urinary tract infection (4%), soft tissue infections (4%), and others (2%). The most frequent bacteria that triggered colistin therapy were carbapenem-resistant *Acinetobacter baumannii* (39%) and *Klebsiella pneumoniae* (34%). Empirical treatment was administered in 28% of the patients, and colistin-resistant bacteria was detected in 8% of the patients (Figure 1). The median duration of colistin therapy was 10 days (interquartile range, 6-14). The most commonly used antibiotic in combination with colistin was meropenem (Table 1). Colistin was used with a loading dose of 300 mg in 92% of the patients. Intrathecal or inhaled colistin was administered concomitantly with intravenous colistin in 2% and 5% of patients, respectively.

Nephrotoxicity was detected in 52% of the patients at Week 1 of colistin therapy, and 59% of the patients experienced nephrotoxicity at any time. Serum creatinine increased >1.5 times in a median of 4 (1-11) days, and glomerular filtration rate (GFR) decreased below 60 ml/min in a median of 5 (1-42) days. After Week 1 of colistin therapy, 48% of the patients preserved "normal" kidney functions. Of the patients who experienced

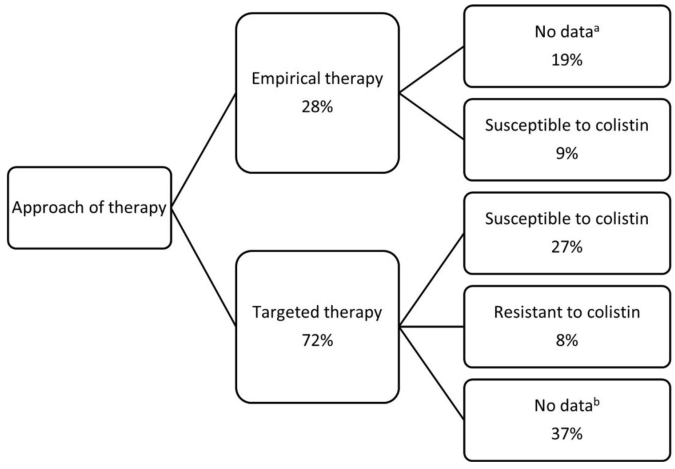

Figure 1. Indications of colistin therapy and susceptibility of relevant bacteria against colistin. [a]Any microorganism was not identified. [b]Colistin susceptibility was not tested

Table 1. Comparison of the demographic characteristics of the patients according to occurrence of nephrotoxicity

Risk factors	Number of patients (n=100)	Nephrotoxicity in Week 1			Nephrotoxicity at any time		
		Yes (n=52)	No (n=48)	p value	Yes (n=59)	No (n=41)	p value
Age (years), median	61 (18-93)	64 (19-93)	52 (18-85)	**0.001**	64 (18-93)	53 (18-85)	**0.016**
Length of hospitalization (days), median	88 (8-336)	103 (13-336)	86 (8-336)	0.070	99 (13-336)	74 (8-336)	**0.027**
Number of comorbidities, median	3 (0-8)	3 (0-8)	2 (0-7)	0.088	3 (0-8)	2 (0-7)	0.200
Number of medications, median	13 (5-29)	13 (5-26)	13 (5-29)	0.959	13 (5-26)	12 (5-29)	0.384
Duration of colistin therapy (days), median	10 (2-51)	10 (2-27)	10 (2-51)	0.487	11 (2-51)	8 (2-36)	**0.013**
Body mass index (kg/m^2), median	25.71 (5.67-37.46)	25.39 (16.07-37.46)	25.98 (5.67-35.26)	0.997	25.39 (16.07-37.46)	25.73 (5.67-35.26)	0.978
Number of other nephrotoxic agents, median	2 (1-9)	2 (1-9)	2 (1-5)	0.406	2 (1-9)	2 (1-5)	0.406
Discordance of colistin dose, n (%)	45 (45)	21 (40.4)	31 (64.6)	**<0.001**	24 (40.7)	35 (85.4)	**<0.001**

nephrotoxicity in Week 1 after starting colistin therapy: 85% had stage 1, 56% had stage 2, and 35% had stage 3. Many patients have different stages of AKI during follow-up (Figure 2) and have often experienced progressive deterioration in renal function. The risk of nephrotoxicity was not significantly different between female and male patients. Coadministration of intravenous colistin with intrathecal or inhaled colistin was not associated with the risk of nephrotoxicity according to the logistic regression analysis.

The clinical characteristics of the patients and anticipated risk factors of nephrotoxicity are shown in Tables 1 and 2. Patients who experienced nephrotoxicity in Week 1 of colistin therapy were older, and they had lower albumin levels and higher serum levels of conjugated bilirubin. Logistic regression analysis showed that not reducing colistin dosage in patients with impaired renal function significantly affected the development of nephrotoxicity in Week 1 (OR: 47.59, 95% CI: 5.55-407.6; p<0.001). Based on the results, the risk of nephrotoxicity was approximately 48 times higher in patients whose colistin dose was not adjusted according to renal function.

Nephrotoxicity at any time during colistin therapy were more common in older patients (p=0.016) and patients with hypoalbuminemia (p=0.014). Patients who experienced nephrotoxicity had a longer duration of hospital stay (p=0.027). The duration of colistin therapy was longer (p=0.013), and the rate of inappropriate colistin dosage was higher (p<0.001) in this group. According to logistic regression analysis, duration of hospitalization, age, duration of colistin therapy, and use of vasopressors were significantly associated with the development of nephrotoxicity at any time during colistin therapy (Table 3).

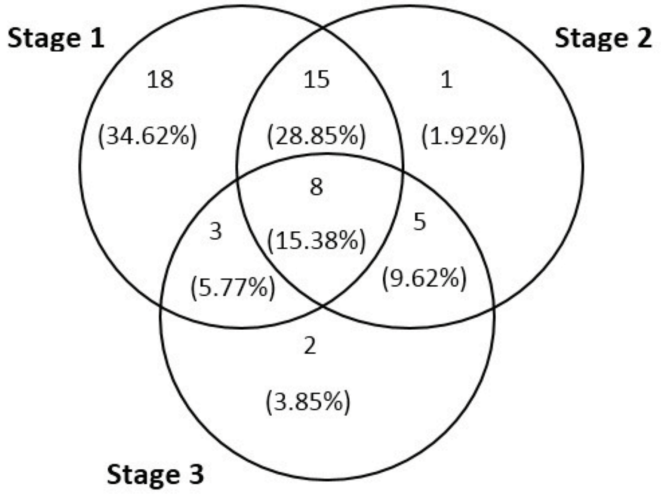

Figure 2. Staging of nephrotoxicity based on KDIGO classification. The intersection region of the clusters shows patients that are involved in multiple stages at Week 1 of colistin therapy

Discussion

This study assessed the incidence of colistin-related nephrotoxicity by using KDIGO definitions of AKI and identified certain risk factors. Colistin remains the last drug for infections caused by MDR microorganisms. However, its nephrotoxicity is still a concern. For this reason, investigation of the true incidence and confounding factors of colistin nephrotoxicity could lead to more proper management of antimicrobial therapy. A few studies have used the KDIGO criteria for assessing the nephrotoxicity of colistin[17,18]. Different classification criteria such as KDIGO and Risk, Injury, Failure, Loss and End Stage (RIFLE) classification can be preferred in determining the rate of AKI and the choice of classification criteria affect the AKI rate. In this study, the KDIGO criteria for determining the AKI were preferred because it was considered more sensitive than the RIFLE criteria[19].

In previous studies, the frequency of nephrotoxicity during colistin therapy ranged from 16.1% to 60.4%[9,20-22]. In this study, the incidence of nephrotoxicity was 52% and 59% at Week 1 and at any time during colistin therapy, respectively. In the present study, rates of nephrotoxicity were similar to those reported in the study using RIFLE criteria by Kwon et al.[23] (53.5%) and Ko et al.[24] (54.6%). Another recent retrospective study reported 49.2% of renal toxicity with colistin according to the RIFLE criteria[25]. In a retrospective study, Shields et al.[17] reported 29% as the prevalence of colistin-related nephrotoxicity according to the KDIGO criteria at Week 1. The loading dose was not given in more than half of the patients, which can explain the lower rate of nephrotoxicity in this study than in the present study. In a study by Gunay et al.[19], frequency of nephrotoxicity was 64.4% according to the KDIGO criteria, and a loading dose was administered in 77% of the patients. These variations in findings can arise from the differences in the definitions of AKI, nephrotoxicity, dosage of colistin, patient characteristics, and other confounding factors. In a prospective study, Sorlí et al.[26] reported 25% and 49% as the prevalence of colistin-related nephrotoxicity using the RIFLE criteria at day seven and at the end of colistin therapy, respectively. After the treatment, the rate of nephrotoxicity doubled. In contrast to this study, the rates of colistin nephrotoxicity at Week 1 and at any time are comparable in our study as most renal dysfunction is determined early in the therapy.

The length of hospitalization, advanced age, duration of colistin therapy, and concomitant administration of vasopressors were determined as independent predictors of nephrotoxicity at any time during colistin therapy. Other researchers have reported some triggers of colistin-related AKI, such as advanced age, comorbidities, preexisting renal impairment, concomitant use of nephrotoxic agents, daily dose of colistin, and duration of colistin therapy[22,23,26,27]. Some of them are concordant with our

Table 2. Clinical characteristics and baseline laboratory findings of the patients according to the occurrence of nephrotoxicity, n (%)

Factors		Patients (n=100)	Nephrotoxicity in Week 1	p value	Nephrotoxicity at any time	p value
Comorbidities						
COPD	Yes	14	9 (64.3)	0.482	10 (71.4)	0.467
	No	86	43 (50.0)		49 (57.0)	
CHF	Yes	14	9 (64.3)	0.482	9 (64.3)	0.888
	No	86	43 (50.0)		50 (58.1)	
Diabetes mellitus	Yes	28	18 (64.3)	0.190	19 (67.9)	0.370
	No	72	34 (47.2)		40 (55.6)	
Hypertension	Yes	41	24 (58.5)	0.375	26 (63.4)	0.588
	No	59	28 (47.5)		33 (55.9)	
Obesity	Yes	22	13 (59.1)	0.609	14 (63.6)	0.799
	No	78	39 (50.0)		45 (57.7)	
Malignancy	Yes	48	24 (50.0)	0.854	26 (54.2)	0.459
	No	52	28 (53.8)		33 (63.5)	
Abdominal surgery	Yes	25	16 (64.0)	0.248	17 (68.0)	0.411
	No	75	36 (48.0)		42 (56.0)	
Hematopoietic stem cell transplantation	Yes	14	5 (35.7)	0.305	5 (35.7)	0.106
	No	86	47 (54.7)		54 (62.8)	
Concomitant nephrotoxic agents						
Concurrent nephrotoxic medications	Yes	80	37 (46.3)	**0.040**	44 (55.0)	0.170
	No	20	15 (75.0)		15 (75.0)	
Contrast agents	Yes	28	17 (60.7)	0.387	20 (71.4)	0.177
	No	72	35 (48.6)		39 (54.2)	
Nephrotoxic chemotherapies	Yes	14	6 (42.9)	0.653	6 (42.9)	0.302
	No	86	46 (53.5)		53 (61.6)	
Combined antibiotic therapy	Yes	95	51 (53.7)	0.192	58 (61.1)	0.156
	No	5	1 (20.0)		1 (20.0)	
Glycopeptide antibiotics	Yes	46	22 (47.8)	0.568	27 (58.7)	1.000
	No	54	30 (55.6)		32 (59.3)	
Vasopressor agents	Yes	36	22 (61.1)	0.246	25 (69.4)	0.167
	No	64	30 (46.9)		34 (53.1)	
Carbapenems	Yes	67	35 (52.2)	1.000	41 (61.2)	0.675
	No	33	17 (51.5)		18 (54.5)	
Fluoroquinolones	Yes	15	6 (40.0)	0.466	7 (46.7)	0.442
	No	85	46 (54.1)		52 (61.2)	
Antivirals	Yes	18	6 (33.3)	0.136	7 (38.9)	0.099
	No	82	46 (56.1)		52 (63.4)	
Antifungals	Yes	23	9 (39.1)	0.242	11 (47.8)	0.317
	No	77	43 (55.8)		48 (62.3)	
Aminoglycoside	Yes	5	3 (60.0)	1.000	4 (80.0)	0.646
	No	95	49 (51.6)		55 (57.9)	
NSAIDs	Yes	28	17 (60.7)	0.387	19 (67.9)	0.370
	No	72	35 (48.6)		40 (55.6)	

Table 2. Continued

Factors		Patients (n=100)	Nephrotoxicity in Week 1	p value	Nephrotoxicity at any time	p value
Diuretic agents	Yes	34	18 (52.9)	1.000	22 (64.7)	0.537
	No	66	34 (51.5)		37 (56.1)	
PPI	Yes	79	40 (50.6)	0.776	47 (59.5)	1.000
	No	21	12 (57.1)		12 (57.1)	
Laboratory values						
Serum albumin level <3.50 mg/dl	Yes	90	50 (55.6)	**0.045**	57 (63.3)	**0.014**
	No	10	2 (20.0)		2 (20.0)	
Serum albumin level <3.00 mg/dl	Yes	73	43 (58.9)	**0.041**	48 (65.8)	**0.042**
	No	27	9 (33.3)		11 (40.7)	
TB elevation	Yes	27	18 (66.7)	0.119	19 (70.4)	0.239
	No	73	34 (46.6)		40 (54.8)	
CB elevation	Yes	53	33 (62.3)	**0.048**	36 (67.9)	0.053
	No	47	19 (40.4)		23 (48.9)	
Others						
7-day fatality	Yes	13	9 (69.2)	0.300	9 (69.2)	0.616
	No	87	43 (49.4)		50 (57.5)	
14-day fatality	Yes	16	10 (62.5)	0.519	10 (62.5)	0.973
	No	84	42 (50.0)		49 (58.3)	
30-day fatality	Yes	23	15 (65.2)	0.227	15 (65.2)	0.653
	No	77	37 (48.1)		44 (57.1)	

COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, BMT: Bone marrow transplantation, NSAIDs: Non-steroidal anti-inflammatory drugs, TB: Total bilirubin, CB: Conjugated bilirubin; nephrotoxic concurrent medications, liposomal amphotericin B, diuretic, NSAIDs, voriconazole, acyclovir, valacyclovir, tenofovir, trimethoprim-sulfamethoxazole, vancomycin, aminoglycosides, meropenem, cyclosporine, zoledronic acid, levofloxacin, ciprofloxacin, oseltamivir, ACE inhibitor, intravenous immunoglobulin; contrast agent, gadobutrol; carbapenem, meropenem; nephrotoxic chemotherapy, ifosfamide, carboplatin, oxaliplatin, cisplatin, gemcitabine, and methotrexate; glycopeptide, vancomycin and teicoplanin; fluoroquinolone, ciprofloxacin and levofloxacin; antiviral, acyclovir and valacyclovir; aminoglycosides, amikacin and gentamicin; diuretic agents, furosemide, acetazolamide, indapamide, hydrochlorothiazide, and spironolactone; PPI, proton pump inhibitors (pantoprazole); vasopressor agent: mostly norepinephrine

Table 3. Predictors for at any time nephrotoxicity according to the logistic regression analysis

Factors	Nephrotoxicity at any time			
	OR	95% CI		p value
		Lower	Upper	
Age (years)	1.036	1.005	1.068	0.023
Length of hospitalization (days)	1.009	1.001	1.017	0.023
Duration of colistin therapy (days)	1.115	1.023	1.216	0.013
Vasopressor therapy	3.012	1.003	9.042	0.049

OR: Odds ratio, CI: Confidence interval

study, but vasopressor use is a novel finding for colistin-related AKI. Septic shock is a condition of systemic vasodilation and generally requires vasopressor therapy, which can cause AKI in patients with critical illness[28]. Although septic shock is an independent risk factor for AKI, there is controversy regarding the effect of norepinephrine use on AKI in septic shock. Norepinephrine was thought to induce vasoconstriction through α-adrenergic stimulation, and this may decrease renal blood flow. However, the findings of a study strongly suggested that vasopressor therapy is possibly beneficial for renal perfusion in patients with septic shock[29]. There are conflicting observations from previous studies. Although two studies did not show any difference in the rate of nephrotoxicity regarding vasopressor infusion, a high rate of nephrotoxicity was reported in patients who received vasopressors when compared with patients who did not receive vasopressors (40% vs 0%, p=0.008) according to the RIFLE criteria[11]. Teicoplanin was the mostly preferred glycopeptide in patients under colistin therapy in the study hospital. This approach is based on studies showing a lower risk of nephrotoxicity in teicoplanin therapy[30].

Patients with nephrotoxicity were older in our study. Advanced age was observed as a predictor of colistin-related nephrotoxicity similar to findings of some studies. Lee et al.[27] reported that age (OR: 1.02; 95% CI: 1.01-1.04) was an independent risk factor in patients with estimated GFR ≥60 ml/min/1.73 m^2 according to

univariable and multivariable logistic regression analyses. Balkan et al.[22] described that nephrotoxicity occurs significantly more frequently in patients aged >60 years, and it is related to low initial GFR estimations and high comorbidity burden, which are determined by age. Another recent study showed that age >65 years was an important risk factor for AKI[19]. Contrary to these studies, some other studies did not report any relationship between older age and colistin nephrotoxicity[26,31].

AKI due to colistin correlated with the duration of therapy. Hartzell et al.[31] demonstrated a 4-fold higher risk of AKI for patients receiving colistin >14 days. We revealed similar results about the duration of colistin therapy as a predictor of nephrotoxicity (OR: 1.115; 95% CI: 1.023-1.216). Prolonged courses of colistin therapy should be considered an important risk factor for nephrotoxicity, renal functions should be followed closely, and timely cessation of therapy with an antimicrobial stewardship program appeared to be essential to avoid adverse outcomes.

Kwon et al.[23] reported hypoalbuminemia (serum albumin level <2.0 g/dl) as an independent predictor of AKI (HR=6.29, 95% CI: 2.04-19.39). In this study, baseline serum albumin levels of patients who developed AKI were lower in patients on intravenous colistin therapy. There are assumptions about the relationship between hypoalbuminemia and AKI. A study suggested that AKI may be associated with higher unbound colistin concentrations because of lower protein binding[10].

Nephrotoxicity is a common adverse effect of colistin; however, this adverse effect is usually reversible[9,22,32]. In our study, renal functions recovered in 16 (27.1%) patients who experienced nephrotoxicity during the colistin therapy. In a prospective, observational study, the reversal of nephrotoxicity was reported in 75% (18 of 24) of patients after Week 1[32]. In another prospective, observational cohort study, renal recovery was observed in 64.5% (20 of 31) of patients, and recovery appeared a median (IQR) of 10.5 (8-13) days after the beginning of AKI[9].

In this study, the discordance of colistin dose according to renal function has been evaluated by using an international recommendation[15]. Discordance of dose with this guideline is an important factor for the development of nephrotoxicity. Although coadministration of intravenous colistin with intrathecal or inhaled colistin was not associated with the risk of nephrotoxicity, the rate of nephrotoxicity was higher in patients whose colistin dosage was not adjusted according to the international guideline.

The risk of nephrotoxicity increased significantly with the simultaneous use of aminoglycosides and colistin. However, in this study, no difference was found between patients treated with aminoglycosides or not[33].

This study has certain limitations. No standard laboratory monitoring schedule was established for renal functions because of the retrospective nature of the study, and 10 patients were excluded from the study because of missing data. Another KDIGO criterion—urinary output—was not accessible from the electronic records of the patients. Serum colistin levels may influence the development of nephrotoxicity, but therapeutic drug monitoring for colistin is not available in our hospital.

Conclusion

The use of colistin has become widespread because of the worldwide increase in infections caused by MDR bacteria. By contrast, nephrotoxicity is an important complication to be considered for the safe use of colistin. Consequently, this study showed the relevance of colistin nephrotoxicity with independent factors, including length of hospitalization, advanced age, discordance of colistin dose, duration of colistin therapy, and concomitant administration of vasopressors. Information obtained from this study may be useful for clinicians to manage the possible risk factors for colistin nephrotoxicity. Regular monitoring of renal functions, adequate dosing, and limiting the duration of colistin therapy as much as possible may avoid nephrotoxicity in older patients, particularly those administered with vasopressors.

Ethics

Ethics Committee Approval: The study protocol was approved by the Hacettepe University Local Ethics Committee (date: 01.10.2019; GO 19/853).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.D., Design: G.M., Data Collection or Processing: P.B.E., M.K., Analysis or Interpretation: P.B.E., M.K., E.K., H.A., K.D., G.M., Literature Search: P.B.E., M.K., E.K., H.A., Writing: P.B.E., M.K., E.K., H.A., K.D., G.M.

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

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Suay-García B, Pérez-Gracia MT. Present and Future of Carbapenem-resistant *Enterobacteriaceae* (CRE) Infections. Antibiotics (Basel). 2019;8:122.
2. Evans ME, Feola DJ, Rapp RP. Polymyxin B sulfate and colistin: old antibiotics for emerging multiresistant gram-negative bacteria. Ann Pharmacother. 1999;33:960-7.

3. Zavascki AP, Nation RL. Nephrotoxicity of Polymyxins: Is There Any Difference between Colistimethate and Polymyxin B? Antimicrob Agents Chemother. 2017;61:e02319-16.

4. Falagas ME, Fragoulis KN, Kasiakou SK, Sermaidis GJ, Michalopoulos A. Nephrotoxicity of intravenous colistin: a prospective evaluation. Int J Antimicrob Agents. 2005;26:504-7.

5. Ordooei Javan A, Shokouhi S, Sahraei Z. A review on colistin nephrotoxicity. Eur J Clin Pharmacol. 2015;71:801-10.

6. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis. 2005;40:1333-41.

7. Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, Silveira FP, Forrest A, Nation RL. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother. 2011;55:3284-94.

8. Nation RL, Garonzik SM, Li J, Thamlikitkul V, Giamarellos-Bourboulis EJ, Paterson DL, Turnidge JD, Forrest A, Silveira FP. Updated US and European Dose Recommendations for Intravenous Colistin: How Do They Perform? Clin Infect Dis. 2016;62:552-8.

9. Dalfino L, Puntillo F, Ondok MJ, Mosca A, Monno R, Coppolecchia S, Spada ML, Bruno F, Brienza N. Colistin-associated Acute Kidney Injury in Severely Ill Patients: A Step Toward a Better Renal Care? A Prospective Cohort Study. Clin Infect Dis. 2015;61:1771-7.

10. Omrani AS, Alfahad WA, Shoukri MM, Baadani AM, Aldalbahi S, Almitwazi AA, Albarrak AM. High dose intravenous colistin methanesulfonate therapy is associated with high rates of nephrotoxicity; a prospective cohort study from Saudi Arabia. Ann Clin Microbiol Antimicrob. 2015;14:3.

11. Deryke CA, Crawford AJ, Uddin N, Wallace MR. Colistin dosing and nephrotoxicity in a large community teaching hospital. Antimicrob Agents Chemother. 2010;54:4503-5.

12. Levin AS, Barone AA, Penço J, Santos MV, Marinho IS, Arruda EA, Manrique EI, Costa SF. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Clin Infect Dis. 1999;28:1008-11.

13. Purnell JQ. Definitions, Classification, and Epidemiology of Obesity. 2018 Apr 12. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Grossman A, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000.

14. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011;52:e56-93.

15. Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, Giacobbe DR, Viscoli C, Giamarellou H, Karaiskos I, Kaye D, Mouton JW, Tam VH, Thamlikitkul V, Wunderink RG, Li J, Nation RL, Kaye KS. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy. 2019;39:10-39.

16. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013;17:204.

17. Shields RK, Anand R, Clarke LG, Paronish JA, Weirich M, Perone H, Kieserman J, Freedy H, Andrzejewski C, Bonilla H. Defining the incidence and risk factors of colistin-induced acute kidney injury by KDIGO criteria. PLoS One. 2017;12:e0173286.

18. Giacobbe DR, di Masi A, Leboffe L, Del Bono V, Rossi M, Cappiello D, Coppo E, Marchese A, Casulli A, Signori A, Novelli A, Perrone K, Principe L, Bandera A, Vender LE, Misin A, Occhilupo P, Melone M, Ascenzi P, Gori A, Luzzati R, Viscoli C, Di Bella S. Hypoalbuminemia as a predictor of acute kidney injury during colistin treatment. Sci Rep. 2018;8:11968.

19. Gunay E, Kaya S, Baysal B, Yuksel E, Arac E. Evaluation of prognosis and nephrotoxicity in patients treated with colistin in intensive care unit. Ren Fail. 2020;42:704-9.

20. Akajagbor DS, Wilson SL, Shere-Wolfe KD, Dakum P, Charurat ME, Gilliam BL. Higher incidence of acute kidney injury with intravenous colistimethate sodium compared with polymyxin B in critically ill patients at a tertiary care medical center. Clin Infect Dis. 2013;57:1300-3.

21. Phe K, Lee Y, McDaneld PM, Prasad N, Yin T, Figueroa DA, Musick WL, Cottreau JM, Hu M, Tam VH. *In vitro* assessment and multicenter cohort study of comparative nephrotoxicity rates associated with colistimethate versus polymyxin B therapy. Antimicrob Agents Chemother. 2014;58:2740-6.

22. Balkan II, Dogan M, Durdu B, Batirel A, Hakyemez IN, Cetin B, Karabay O, Gonen I, Ozkan AS, Uzun S, Demirkol ME, Akbas S, Kacmaz AB, Aras S, Mert A, Tabak F. Colistin nephrotoxicity increases with age. Scand J Infect Dis. 2014;46:678-85.

23. Kwon JA, Lee JE, Huh W, Peck KR, Kim YG, Kim DJ, Oh HY. Predictors of acute kidney injury associated with intravenous colistin treatment. Int J Antimicrob Agents. 2010;35:473-7.

24. Ko Hj, Jeon Mh, Choo Ej, Lee Ej, Kim Th, Jun JB, Gil HW. Early acute kidney injury is a risk factor that predicts mortality in patients treated with colistin. Nephron Clin Pract. 2011;117:c284-8.

25. Katip W, Uitrakul S, Oberdorfer P. The effectiveness and nephrotoxicity of loading dose colistin combined with or without meropenem for the treatment of carbapenem-resistant *A. baumannii*. Int J Infect Dis. 2020;97:391-5.

26. Sorlí L, Luque S, Grau S, Berenguer N, Segura C, Montero MM, Alvarez-Lerma F, Knobel H, Benito N, Horcajada JP. Trough colistin plasma level is an independent risk factor for nephrotoxicity: a prospective observational cohort study. BMC Infect Dis. 2013;13:380.

27. Lee YJ, Wi YM, Kwon YJ, Kim SR, Chang SH, Cho S. Association between colistin dose and development of nephrotoxicity. Crit Care Med. 2015;43:1187-93.

28. Chen YY, Wu VC, Huang WC, Yeh YC, Wu MS, Huang CC, Wu KD, Fang JT, Wu CJ; NSARF; CAKS Group. Norepinephrine Administration Is Associated with Higher Mortality in Dialysis Requiring Acute Kidney Injury Patients with Septic Shock. J Clin Med. 2018;7:274.

29. Bellomo R, Wan L, May C. Vasoactive drugs and acute kidney injury. Crit Care Med. 2008;36(4 Suppl):S179-86.

30. Bugano DDG, Cavalcanti AB, Goncalves AR, Almeida CSD, Silva E. Meta-análise Cochrane: teicoplanina versus vancomicina para infecções suspeitas ou confirmadas. Einstein (São Paulo). 2011;9:265-82.

31. Hartzell JD, Neff R, Ake J, Howard R, Olson S, Paolino K, Vishnepolsky M, Weintrob A, Wortmann G. Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. Clin Infect Dis. 2009;48:1724-8.

32. Aggarwal R, Dewan A. Comparison of nephrotoxicity of Colistin with Polymyxin B administered in currently recommended doses: a prospective study. Ann Clin Microbiol Antimicrob. 2018;17:15.

33. Temocin F, Erdinc S, Tulek N, Demirelli M, Bulut C, Ertem G. Incidence and Risk Factors for Colistin-Associated Nephrotoxicity. Jpn J Infect Dis. 2015;68:318-20.

Supplementary Table 1. 'International Consensus Guidelines for the Optimal Use of the Polymyxins' recommendations for colistin dosing according to creatinine clearance

Creatinine clearance, ml/minute	mg CBA/day
0	130
5 to <10	145
10 to <20	160
20 to <30	175
30 to <40	195
40 to <50	220
50 to <60	245
60 to <70	275
70 to <80	300
80 to <90	340
≥90	360

CBA: Colistin base activity