The Study of Incidence and Risk Factors Associated with Colistin-Induced Nephrotoxicity at Tertiary Hospital, Thailand.

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Abstract

Colistin is an antibiotic against multidrug-resistant Gram-negative bacteria and extensively drug resistant, but it has an important adverse drug reaction such as nephrotoxicity. Thus, monitoring renal function during colistin use is necessary for patient care. The objective of this study is to assess the incidence of nephrotoxicity due to colistin and to evaluate the factors associated with nephrotoxicity. We performed a retrospective survey of patient chart reviews from June 2015 to December 2020 at Tertiary Hospital. The inclusion study included 1) the patients aged over 18 years and 2) patients receiving intravenous colistin for at least 48 hours. The definition of acute kidney injury was based on Risk, Injury, Failure, Loss, and End-stage Kidney Disease (RIFLE) criteria, including serum creatinine rising more than 1.5 times from baseline, decreasing glomerular filtration rate (GFR) by more than 25%, or urine output remaining less than 0.5 ml/kg/hr. According to the inclusion criteria, 219 patients were included. The incidence of nephrotoxicity was 59.4%. The onset of nephrotoxicity was four days after colistin initiation. There were three patients who have to undergo hemodialysis. According to logistic regression analysis, the factors associated with colistin-induced nephrotoxicity were age (OR 1.013; 95% CI 1.002-1.025), furosemide use (OR 1.941; 95% CI 1.087-3.467), and serum albumin (OR 0.747; 95% CI 0.559-0.998). In conclusion, the incidence of nephrotoxicity from colistin use is high. Therefore, healthcare professionals should closely monitor kidney function during the use of colistin, especially in elderly patients, concomitant use of furosemide, and patients with low serum albumin.

Keywords**:** *Colistin, Risk Factors, Acute Kidney Injury, Nephrotoxicity*

1. Introduction

Colistin is an antibiotic against multidrug-resistant Gram-negative bacilli, especially *Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae*. The bactericidal effect of colistin is concentration-dependent killing with a post-antibiotic effect. Nephrotoxicity is a major adverse event of colistin due to an increase in tubular epithelial cell membrane permeability, resulting in anionic, cationic, and water influx, leading to cell swelling and cell lysis. Therefore, colistin causes acute tubular necrosis manifested as a rise in serum creatinine. Acute kidney injury (AKI) remains a treatment-limiting adverse effect of colistin. Strategies to minimize nephrotoxicity in patients receiving colistin have become a challenge for clinicians (Anusornsangiam et al., 2016; Areewattananon, 2021). Most studies classified AKI according to the Risk, Injury, Failure, Loss of Kidney Function, and End-stage Kidney Disease (RIFLE) criteria. However, AKI network criteria (AKIN) were also used for classification (Disease, 2012; Durante-Mangoni et al., 2016). Moreover, clinical practice guidelines from the Kidney Disease Improving Global Outcomes (KDIGO) group provided a uniform definition, staging, and severity of AKI, which can detect AKI earlier

and predict mortality more precisely than the previously used RIFLE criteria (Koksal, Kaya, Gencalioglu, & Yilmaz, 2016).

The prevalence of colistin-induced AKI was widely different among studies based on AKI criteria. The prevalence in Thailand ranged from 30%-50% (Koomanachai, Tiengrim, Kiratisin, & Thamlikitkul, 2007; Miano et al., 2018). The time to AKI during colistin treatment has been reported to range from 5–12 days (Moghnieh et al., 2023; Nation et al., 2019; Ordooei Javan, Shokouhi, & Sahraei, 2015). Several factors associated with nephrotoxicity have been reported, such as dosage regimen, advanced age, liver disease, hypoalbuminemia, hemoglobin level, coadministration of nephrotoxic agents, and baseline renal function (Lopes, & Jorge, 2013; Luo et al., 2014; Miano et al., 2018; Moghnieh et al., 2023; Nation et al., 2019; Ordooei Javan et al., 2015; Ozel, Ergönül, & Korten, 2019; Özkarakaş et al., 2017; Pogue et al., 2011; Rattanaumpawan, Ungprasert, & Thamlikitkul, 2011). Understanding the risk factors for nephrotoxicity is essential for improving treatment outcomes. Therefore, this research aimed to assess the rate of nephrotoxicity due to colistin and to evaluate the factors associated with nephrotoxicity.

2. Objectives

1) To assess the incidence of nephrotoxicity caused by colistin
2) To evaluate the factors associated with nephrotoxicity

3. Materials and Methods

We performed a retrospective study by patient chart review from June 2015 to December 2020 at Tertiary Hospital. The inclusion criteria were 1) the patients aged over 18 years and 2) receiving intravenous colistin for at least 48 hours. The exclusion criteria were 1) the inability to access the information from the patient chart completely and, 2) the patients who were in end-stage kidney disease.

The definition of acute kidney injury (AKI) was based on Risk, Injury, Failure, Loss, and End-stage Kidney Disease (RIFLE) criteria, including serum creatinine raising more than 1.5 times from baseline, decreasing glomerular filtration rate (GFR) more than 25%, or urine output remaining less than 0.5 ml/kg/hr. Clinical information was gathered on patients prescribed colistin regarding age, sex, SCr, eGFR, albumin level, Charlson comorbidity index, nephrotoxic medications, and ventilator use. Acute kidney injury according to RIFLE criteria and factors associated with AKI were subjected to univariate and multivariate statistical analysis. The number of participants was calculated by following Yamane's formula. The total number of participants is 96.

All procedures were performed in accordance with the ethical review committee of the Royal Thai Army Medical Department. The ethics number was Q002h/64.

4. Results and Discussion

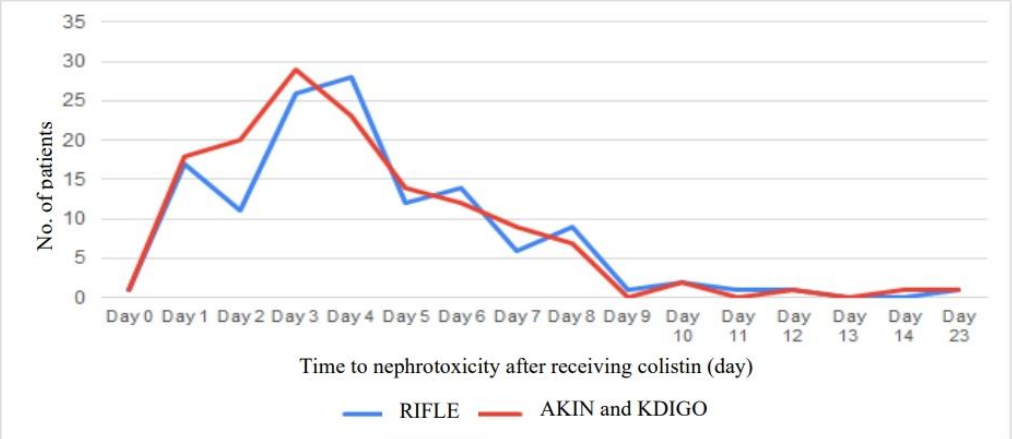
4.1 A total of 219 patients who had colistin between June 2015 and December 2020 were included in the study. Among them, 68.04 % were in the non-ICU, and 73.06 % were mechanically ventilated. They were male, 143 patients (65.3%). The median age of the patients was 75 years old. The three most common reasons for colistin use were pneumonia, sepsis, and urinary tract infection, accounting for 63.01%, 34.25%, and 12.32%, respectively.

Table 1: Baseline Characteristics with Univariate Analysis for Comparison Between Patients With and Without AKI

Variables	All Patients (n=219)	With AKI (n=130)	Without AKI (n=89)	OR (95% CI)	p-value
Age, median (IQR), year	75 (22)	77 (21)	73 (23)	-	0.1
Colistin dose, median (IQR), mg	286 (107)	251.50 (111)	300 (100)	-	0.009
sCr baseline, Median (IQR), mg/dL	0.9 (0.8)	0.9 (0.59)	0.9 (1.07)	-	0.422

Variables	All Patients (n=219)	With AKI (n=130)	Without AKI (n=89)	OR (95% CI)	p-value
eGFR baseline, Median (IQR), ml/min/1.73m^2	81.73 (50.99)	81.04 (41.04)	85.50 (65.23)	-	0.846
Hb baseline, Median (IQR), g/dL	9.25 (2.2)	9.0 (2.0)	9.6 (2.6)	-	0.306
Albumin baseline, Median (IQR), g/dL	2.68 (0.9)	2.6 (0.8)	2.8 (0.86)	-	0.102
Comorbidity diseases					
Diabetes, n (%)	68 (31.05)	40	28	0.968 (0.541-1.733)	0.914
COPD, n (%)	18 (8.22)	11	7	1.083 (0.403-2.910)	0.875
Liver diseases, n (%)	7 (3.2)	7	0	-	0.024
CVA, n (%)	22 (10.05)	16	6	1.942 (0.729-5.173)	0.178
HT, n (%)	146 (66.67)	90	56	1.326 (0.751-2.342)	0.331
Cancer, n (%)	31 (14.16)	19	12	1.098 (0.504-2.394)	0.813
CKD, n (%)	31 (14.16)	18	13	0.940 (0.435-2.030)	0.874
Hematologic malignancy, n (%)	14 (6.39)	7	7	0.667 (0.225-1.972)	0.461
Nephrotoxic medication					
Vancomycin, n (%)	61 (27.85)	38	23	1.185 (0.646-2.174)	0.583
Amikacin, n (%)	12 (5.48)	7	5	0.956 (0.294-3.114)	0.583
Gentamicin, n (%)	2 (0.91)	1	1	0.682 (0.042-11.051)	0.649
Amphotericin B, n (%)	18 (8.22)	9	9	0.661 (0.252-1.737)	0.399
NSAIDs, n (%)	15 (6.85)	8	7	0.768 (0.268-2.2)	0.622
ACEIs, n (%)	6 (2.74)	6	0	-	0.42
ARBs, n (%)	5 (2.28)	3	2	1.028 (0.168-6.278)	0.673
Furosemide, n (%)	86 (39.27)	59	27	1.908 (1.081-3.370)	0.025
Ventilator, n (%)					0.530
No	59 (26.94)	33	26	1.213 (0.663-2.219)	
Yes	160 (73.06)	97	63		
Charlson comorbidity index, n (%)					0.413
0-2	38 (17.35)	18	20	-	
3-5	119 (54.34)	72	47	-	
>5	62 (28.31)	39	23	-	

One hundred and thirty (59.4%) patients had AKI during the hospitalization following colistin administration. The mode incidence time was three days. (figure 1)



RIFLE = Risk Injury Failure Loss End-stage Kidney DiseaseCriteria, AKIN = Acute Kidney Injury Network Criteria, KDIGO = Kidney Disease Improving Global Outcomes Criteria

Figure 1: Time course of colistin-induced nephrotoxicity in the patients who were receiving colistin

Univariate analysis compared All baseline characteristics between patients with and without AKI (Table 1). Significant differences were found in colistin dose (P-value: 0.009), liver diseases (P-value: 0.024),

receiving furosemide (P-value: 0.025), and lower albumin levels (P-value: 0.102). In multivariate analysis, as shown in Table 2, the risk factor associated with acute kidney injury is as follows: age (OR = 1.013, 95% CI; 1.002-1.025), P-value: 0.022, receiving furosemide (OR = 1.941, 95% CI; 1.087-3.467), P-value: 0.025, and albumin baseline (OR = 0.747, 95% CI; 0.559-0.988), P-value: 0.048

Table 2: Multivariate Analysis of Nephrotoxicity Risk Factors

Variables	OR	95% CI	p-value
Age	1.013	1.002 -1.025	0.022
Albumin baseline	0.747	0.559- 0.988	0.048
Furosemide	1.941	1.087-3.467	0.025

4.2 The analysis was performed based on the results of the RIFLE criteria. The current study's findings showed that 59.4% of patients receiving colistin developed AKI based on RIFLE criteria, and 63.0% according to AKIN and KDIGO criteria. These results are consistent with several studies that found nephrotoxicity rates exceeding 50%; 70% were reported from a study using RIFLE criteria14, 57% were reported from a study using AKIN criteria15, and 51% were reported from another one using KDIGO criteria[9]. However, other studies based on RIFLE criteria reported rates of less than 50% (Luo et al., 2014; Nation et al., 2019; Ordooei Javan et al., 2015). Our results showed that the onset of nephrotoxicity was four days after colistin initiation, assessed by the RIFLE criteria, and three days after colistin initiation according to the AKIN and KDIGO criteria. The study of Miano et al. (2018) also found that AKI significantly increased within 72 hours after receiving colistin (Moghnieh et al., 2023). Similarly, Koksal, Kaya, Gencalioglu, & Yilmaz (2016)and Ozkarakas et al. reported that the average onset of nephrotoxicity was five days of dosing (Nation et al., 2019; Özkarakaş et al., 2017). In addition, Anusornseangnim et al. found that AKI occurred within the first week after receiving colistin (Luo et al., 2014). While Durante-Mangoni et al. (2016) reported that a significant increase in AKI had been found on 11 days after receiving colistin (Pogue et al., 2011). The difference in incidence and onset of nephrotoxicity among studies could be explained by variations in diagnostic criteria for AKI, patient characteristics, and factors related to nephrotoxicity.

In multivariate analysis, we found that the factors significantly associated with nephrotoxicity were advanced age, concomitant use of furosemide, and low serum albumin levels. Regarding the patient age, we found a significant relationship between patients aged 75 or older and AKI (OR 1.013; 95% CI, 1.002-1.025). This is consistent with Moghnieh et al. (2023), who found that patients aged≥ 75 years were risk factors for AKI (Rattanaumpawan et al., 2011). Several studies also found that increased age was statistically significantly related to nephrotoxicity (Luo et al., 2014; Moghnieh et al., 2023; Nation et al., 2019; Özkarakaş et al., 2017; Pogue et al., 2011). Generally, older patients were more prone to nephrotoxicity. This age-related susceptibility is attributed to changes in blood vessels, posing a risk of renal tubular damage. Therefore, elderly patients receiving colistin should be closely monitored for renal function, particularly in patients with an age of ≥ 75 years. Concerning serum albumin levels before treatment, Ozkarakas et al. found that low albumin levels before treatment were significantly related to nephrotoxicity. The receiver operating characteristic (ROC) curve showed the discriminative ability with a cut-off value of 2.65 g/dL.[14] While our result showed a slight variation in the median values of albumin levels between the group that experienced nephrotoxicity (median 2.6 g/dL) and the group that did not (median 2.8 g/dL). This factor should not be overlooked and should be closely monitored.

Nevertheless, our results showed that serum creatinine, or eGFR were not correlated with nephrotoxicity from colistin use. On the contrary, Koksal et al. (2016) found that higher levels of serum creatinine before treatment were related to nephrotoxicity from colistin; the baseline in the group with developed nephrotoxicity (0.75 mg/dL) was higher than one in the group without nephrotoxicity (0.33 mg/dL).[11] A possible explanation might be the similarity of median serum creatinine at baseline of both developed nephrotoxicity groups and without nephrotoxicity group (0.90 mg/dL) in this study.

In contrast to other studies, the current study did not find any comorbidities, the dosage of colistin, and hemoglobin levels significantly associated with nephrotoxicity. This finding differs from the previous research, which found that diabetes, chronic obstructive pulmonary disease, cancer, and liver disease were the risk factors (Moghnieh et al., 2023; Nation et al., 2019; Pogue et al., 2011). This result is possibly due to

similarities in the characteristics of study participants. The dosage of colistin did not have a significant risk factor in our study. This could be a result of initiating colistin at lower doses and adjusting the dosage as kidney function declined. Concerning hemoglobin levels, Miano et al. (2018) reported that lower hemoglobin levels increased the risk of nephrotoxicity, possibly due to decreased oxygen transport to the kidneys (Moghnieh et al., 2023). This might be explained by the lower median value of hemoglobin level in Miano et al.'s (2018) study (8.8 g/dL) compared to our study (9.25 g/dL). Thus, colistin-induced toxicity may vary according to baseline hemoglobin levels.

There are some limitations to our study. The first is a retrospective study in which tracking some information was limited. Second, this study is a single-center study, which might not be a generalized finding in another setting. Third, the data for evaluating the colistin dose was not available. Although there are these limitations, the findings highlight the risk factors associated with colistin-induced nephrotoxicity. Future studies should be performed with multiple settings and prospective studies to elucidate risk factors associated with nephrotoxicity in Thailand and explore more risk factors, such as colistin dosing from previous studies.

5. Conclusion

This study showed a high prevalence of colistin-induced nephrotoxicity. Our findings suggest that renal function should be monitored early when patients receive colistin, especially elderly patients, concomitant use of furosemide, and patients with low serum albumin levels, in order to improve the quality of care.

6. References

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