

Comparisons of Colistin-Induced Nephrotoxicity Between Two Different Formulations of Colistin in Critically Ill Patients: A Retrospective Cohort Study

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Research

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Abstract

Background

Colistin is widely used for the treatment of nosocomial infections caused by carbapenem-resistant gram-negative bacilli (CR-GNB). Colistin-induced nephrotoxicity is one of the major adverse reactions during colistin treatment. Comparisons of colistin-induced nephrotoxicity between different formulations of colistin are rarely reported.

Methods

We conducted a retrospective cohort study that enrolled ICU-admitted patients with cultured isolates of CR-GNB and treatment with intravenous colistin. Occurrences of acute kidney injury (AKI) during treatment with intravenous colistin were recorded. Colistin-induced nephrotoxicity between two formulations of colistin, Locolin® and Colimycin®, were compared. The treatment outcomes associated with the occurrence of colistin-induced nephrotoxicity were also investigated.

Results

A total of 195 patients, 95 treated with Locolin® and 100 treated with Colimycin®, were included for analysis. Patients treated with Locolin® had a higher rate of occurrence of stage 2 (46.3% vs. 32%, $p=0.040$) and stage 3 (29.5% vs. 13%, $p=0.005$) AKI than did those treated with Colimycin®. In multivariate analysis, the presence of septic shock (adjusted odds ratio (aOR) 2.07, 95% confidence interval (CI) 1.05–4.06), and inappropriate colistin dosage (aOR 2.49, 95% CI 1.01–60.16) were clinical factors associated with colistin-induced nephrotoxicity. Treatment with Colimycin® was an independent factor associated with a lower risk of colistin-induced nephrotoxicity (aOR 0.36, 95% CI 0.17-0.74). Other clinical factors associated with colistin-induced nephrotoxicity included the presence of septic shock (aOR 2.17, 95% CI 1.10-4.26) and inappropriate colistin dosage (aOR 2.52, 95% CI 1.00-6.33). A comparable mortality rate was noted between patients with and without colistin-induced nephrotoxicity.

Conclusions

The risk of colistin-induced nephrotoxicity significantly varied in different formulations of colistin in critically ill patients. Colistin-induced nephrotoxicity was not associated with increased mortality.

Background

The emergence of multidrug-resistant organisms (MDRO) in nosocomial infections is a growing threat to the global health system. Carbapenem-resistant gram-negative bacilli (CR-GNB), including CR-*Acinetobacter baumannii* complex (CRAB), CR-enterobacteriaceae (CRE), and CR-*Pseudomonas aeruginosa* (CRPA), are common MDRO in nosocomial infections and are associated with increased morbidity and mortality [1–3]. Colistin is one of the key agents against CR-GNB-induced nosocomial infections, especially in hospital-acquired pneumonia [4].

Colistin is a polypeptide antibiotic with specific action against gram-negative bacteria [5]. Despite the increasing use in the management of nosocomial infection, the use of intravenous colistin is frequently limited by its adverse reactions, including nephrotoxicity and neurotoxicity [6–9]. It is proposed that the interaction between colistin and phospholipid in the cell membrane can lead to increased membrane permeability of tubular epithelial cells and acute tubular necrosis [10]. The presentations of colistin-induced nephrotoxicity include a decrease in creatinine clearance, proteinuria, cylindruria, or oliguria and usually occur in the first 5–7 days of treatment [11–14]. If discontinued early, the acute kidney injury (AKI) is mostly alleviated within 10 days from discontinuation [13].

Several clinical factors, including old age, hypoalbuminemia, baseline renal function impairment, underlying comorbidities, concomitant nephrotoxins, higher colistin dose, and presence of septic shock, have been proposed to be related to colistin-induced nephrotoxicity [15–18]. However, the risk of nephrotoxicity by different brands of colistin has rarely been compared until now. Different products of colistin may have their specific pharmacological characteristics. Their lipopeptide components may also be different, which may lead to a different risk of nephrotoxicity. In the present study, we retrospectively enrolled critically ill patients who were treated with two different formulations of intravenous colistin. The occurrence of AKI between patients who were administered with the two different formulations of colistin and the clinical factors associated with AKI were investigated. The effect of AKI on treatment outcomes of critically ill patients was explored as well.

Methods

Patients and settings

This was a retrospective study conducted in a referral medical center in Taiwan. From Jan 2016 to Oct. 2018, intensive care units (ICU)-admitted patients were enrolled if CR-GNB, including CRAB, CRE, and CRPA isolates was cultured from their clinical specimens and if they received intravenous colistin for \geq 48 hours. In patients with more than one treatment course, only the first treatment course was included for analysis. Patients were excluded if $<$ 20 years old, with a history of ESRD, under regular dialysis when initiation of intravenous colistin, missing baseline creatinine results, without at least three follow-up creatinine data, and treated with different brands of colistin in one treatment course. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital and informed consents were waived. (IRB Nos: 2019-11-009AC).

Data collection

The demographic characteristics (age, gender, BMI, smoking status) and underlying comorbidities (diabetes, malignancies, renal insufficiency, chronic liver disease, and heart failure) were obtained from hospital chart review. The infection sources were determined according to the site of specimens collected. In patients with multiple samples with CR-GNB, the sample which was obtained most close to the date of prescription of colistin was used to define infection source. The disease severity was evaluated by Acute

Physiology and Chronic Health Evaluation (APACHE) II score on the day of ICU admission. The presence of respiratory failure and septic shock on the day of specimen collection were also recorded.

Intravenous colistin administration and concomitant nephrotoxins

All the enrolled patients received intravenous colistin for ≥ 48 hours. The intravenous colistin was initiated within seven days of CR-GNB cultured from clinical specimens. For patients with multiple intravenous colistin treatment courses, only the first treatment course was recorded. Two formulations of colistin, Locolin® (Gentle, Taiwan) and Colimycin® (T.T.Y., Taiwan), were available during the study period. Both the formulations were supplied as 66.8mg of colistin base activity per vial, which was considered equivalent to 2 million IU of sodium colistin methanesulfonate. The recommended loading and maintenance dosing of intravenous colistin was based on previous suggestion [19], and adjusted based on body weight and renal function (**Supplementary Table 1**). Estimated glomerular filtration rate (eGFR) was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation [20]. Maintenance dose of intravenous colistin above the recommended dose was determined as inappropriate colistin dosage.

Concomitant nephrotoxins, including aminoglycoside, vancomycin, and intravenous contrast, that were administered within 28 days of colistin treatment were also recorded.

Outcome definition

The primary outcome evaluated in the present study was colistin-induced nephrotoxicity, which was defined as the occurrence of AKI during colistin treatment. Serum creatinine levels were recorded at baseline (day 1 of intravenous colistin administration) and thereafter until the end of colistin treatment or death. AKI was determined based on the definition of KDIGO recommendation by creatinine criteria [21]. The occurrence of stage 1 (with 1.5–1.9 fold increase or ≥ 0.3 mg/dL increase in serum creatinine), stage 2 (with 2-2.9 fold increase in serum creatinine than baseline) and stage 3 (≥ 3 fold increase in creatinine than baseline, or ≥ 4.0 mg/dl) AKI, and newly-onset dialysis were recorded.

Other clinical outcomes evaluated in the present study included mechanical ventilator days, ICU stays, hospital stays, and all-cause mortality at day-28 and upon discharge.

2.5 Statistical analysis

Statistical analyses were performed using SPSS version 20.0 software (SPSS, Inc., Chicago, IL, USA). Participants were categorized into Locolin and Colimycin groups, and analyzed accordingly. Continuous variables such as APACHE II and hospital stays between sub-groups were compared using the Mann-Whitney U test, and categorical variables were compared using Pearson's chi-square or Fisher's exact tests, as appropriate. We used mean imputation for missing data.

The occurrences of KDIGO stage 2, stage 3 AKI, and newly onset dialysis, were compared between patients treated with Locolin® and Colimycin®. Kaplan-Meier curves were constructed to evaluate

difference in occurrence of AKI between subgroups of patients. Cox regression analysis was performed to identify independent variables associated with KDIGO 3 AKI. Treatment outcomes, including mechanical ventilator days, ICU stays, hospital stays, and all-cause mortality were also compared between patients with and without the occurrence of KDIGO stage 3 AKI. All tests were two-tailed and p -value < 0.05 was considered statistically significant.

Results

Patient characteristics

During the study period, the medical records of 195 ICU-admitted patients who were administered with intravenous colistin were analyzed. Among these patients, 95 received Locolin® and 100 received Colimycin®. A flow diagram of the case numbers and reasons for exclusion is shown in Fig. 1. The demographic characteristics and disease severities of the enrolled cases are summarized in Table 1. The mean age of the enrolled patients was 73.8 ± 13.5 years old and 70.8% (138/195) were male. Diabetes is the most common comorbidity (57/195, 29.2%) and 10.8% (21/195) of the enrolled cases had renal insufficiency. The median APACHE II score of the patients at ICU admission was 24 (IQR 19–30). At the time of colistin administration, 89.7% (175/195) had respiratory failure and 31.3% (61/195) had septic shock. Approximately 80% of the CR-GNB isolates were cultured from respiratory specimens. The proportions of CRAB, CRE, and CRPA were 72.3%, 23.1%, and 4.6% respectively. The median daily colistin maintenance dose was 8 MIU (IQR 4–10), and the median treatment duration of colistin was 7 days (IQR 4–12). Twenty-three patients (11.8%) were administered with colistin at an inappropriate maintenance dosage. Comparatively, patients who were administered with Locolin® had higher serum albumin level (2.8 g/dL vs. 2.6 g/dL, $p = 0.017$) and were more likely to receive concomitant aminoglycoside treatment (15.8% vs. 7%, $p = 0.052$) and less likely to have colistin at inappropriate dosage (7.4% vs. 16%, $p = 0.062$) than those administered with Colimycin. Otherwise, the two groups of patients, had similar demographic characteristics, underlying comorbidities, and disease severities. There were no significant differences in the dosage and duration of colistin treatment between the two groups of patients.

Table 1
Demographic characteristics of ICU-admitted patients treated with two different formulations of intravenous colistin^a

	Overall patients	Intravenous colistin		
		Locolin®	Colimycin®	P-value
Case numbers	195	95	100	
Age (SD)	73.8 (13.5)	75.2 (12.3)	72.4 (14.6)	0.142
Male gender	138 (70.8%)	73 (76.8%)	65 (65%)	0.069
BMI (SD)	22.3 (4.6)	21.7 (4.8)	22.8 (4.3)	0.106
Smoking	78 (40%)	40 (42.1%)	38 (38%)	0.559
Comorbidities				
Diabetes	57 (29.2%)	28 (29.5%)	29 (29%)	0.942
Malignancies	33 (16.9%)	24 (25.3%)	9 (9%)	0.002
Renal insufficiency (CCr < 30)	21 (10.8%)	10 (10.5%)	11 (11%)	0.915
Chronic liver diseases	16 (8.2%)	3 (3.2%)	13 (13%)	0.017
Heart failure	17 (8.7%)	8 (8.4%)	9 (9%)	0.886
CR-GNB culture sources				0.752
Respiratory specimens	157 (80.5%)	75 (78.9%)	82 (82%)	
Urine	11 (5.6%)	6 (6.3%)	5 (5%)	
Blood	10 (5.1%)	4 (4.2%)	6 (6%)	
Others	17 (8.7%)	10 (10.5%)	7 (7%)	
CR-GNB species				0.092
CRAB	141 (72.3%)	64 (67.4%)	77 (77%)	

^aData are presented as n (%)

^bIncluding abscess, ascites, CSF, and pericardial effusion

^cEvaluated on the day of ICU admission

^dPresent on the day of sample collection

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; CCr, creatinine clearance; CR-GNB, carbapenem-resistant gram-negative bacteria; SD, standard deviation.

	Overall patients	Intravenous colistin		
		Locolin®	Colimycin®	P-value
CRE	45 (23.1%)	28 (29.5%)	17 (17%)	
CRPA	9 (4.6%)	3 (3.2%)	6 (6%)	
Albumin level (median, IQR)	2.7 (2.4–3.0)	2.8 (2.5–3.1)	2.6 (2.3–2.9)	0.017
Concomitant nephrotoxins				
Aminoglycoside	22 (11.3%)	15 (15.8%)	7 (7%)	0.052
Vancomycin	20 (10.3%)	13 (13.7%)	7 (7%)	0.124
Intravenous contrasts	39 (20.0%)	17 (17.9%)	22 (22%)	0.474
Disease severity				
APACHEII scores (median, IQR) ^b	24 (19–30)	25 (20–30)	24 (19–30)	0.768
Respiratory failure ^d	175 (89.7%)	83 (87.4%)	92 (92%)	0.287
Septic shock ^d	61 (31.3%)	33 (34.7%)	28 (28%)	0.310
Intravenous colistin				
Daily dosage (MIU)(median, IQR)	8 (4–10)	8 (4–10)	8 (4–10)	0.814
Treatment duration (median, IQR)	7 (4–12)	7 (4–12)	7 (4–12)	0.782
Accumulated dosage (MIU)(median, IQR)	48 (28–80)	48 (28–64)	48 (24–88)	0.956
Inappropriate colistin dosage	23 (11.8%)	7 (7.4%)	16 (16%)	0.062
^a Data are presented as n (%)				
^b Including abscess, ascites, CSF, and pericardial effusion				
^c Evaluated on the day of ICU admission				
^d Present on the day of sample collection				
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; CCr, creatinine clearance; CR-GNB, carbapenem-resistant gram-negative bacteria; SD, standard deviation.				

Rate of occurrence of AKI

The rates of occurrence of various severities of AKI and newly initiated dialysis within 28 days after colistin administration are shown in Fig. 2. Overall, the rate of occurrence of KDIGO stage 1, stage 2, stage 3 AKI, and newly initiated dialysis was 49.7%, 39%, 21%, and 9.2%, respectively. Comparatively, patients who were administered with Colimycin® had a significantly lower occurrence rate of KDIGO stage 2 AKI (32% vs. 46.3%, $p = 0.040$) and KDIGO stage 3 AKI (13% vs. 29.5%, $p = 0.005$) than those administered with Locolin®. The rate of occurrence of newly initiated dialysis was comparable between the two groups of patients.

Kaplan-Meier analysis of the occurrence of KDIGO stage 2 and stage 3 AKI in both groups of patients is shown in Fig. 3. Patients who were administered with Colimycin® had a significantly lower occurrence of KDIGO 3 AKI than those administered with Locolin® (log rank $p = 0.008$). The curves separated early after the onset of colistin treatment.

Clinical factors associated with AKI

A total of 41 (2%) enrolled patients had KDIGO stage 3 AKI. The comparisons of clinical factors between patients with and without KDIGO stage 3 AKI are shown in Table 2. Patients with KDIGO stage 3 AKI were more likely to have CR-GNB cultured from respiratory specimens (95.1% vs. 76.6%, $p = 0.035$), concomitant vancomycin treatment (19.5% vs. 7.8%, $p = 0.028$), septic shock (53.7 vs. 25.3%, $p = 0.001$), higher daily colistin dose (8 MIU, interquartile range (IQR) 7.4–10 MIU vs. 8 MIU, IQR 4–10 MIU, $p = 0.036$), and inappropriate colistin maintenance dosage (22% vs. 9.1%, $p = 0.023$).

Table 2

Clinical characteristics of ICU patients with and without the occurrence of KDIGO 3 acute kidney injury^a

	≥ KDIGO 3 AKI		P-value
	Yes, n = 41	No, n = 154	
Age (SD)	71.4 (12.2)	74.4 (13.8)	0.138
Male gender	26 (63.4%)	112 (72.7%)	0.421
BMI (SD)	22.2 (5.6)	22.3 (4.3)	0.788
Smoking	15 (36.6%)	63 (40.9%)	0.363
Comorbidities			
Diabetes	12 (29.5%)	45 (29.2%)	0.958
Malignancies	10 (24.4%)	23 (14.9%)	0.243
Renal insufficiency	6 (14.6%)	15 (9.7%)	0.211
Chronic liver diseases	3 (7.3%)	13 (8.4%)	1.000
Heart failure	3 (7.8%)	14 (9.1%)	0.767
CR-GNB culture sources			0.035
Respiratory specimens	39 (95.1%)	118 (76.6%)	
Urine	0	10 (6.5%)	
Blood	2 (4.9%)	9 (5.8%)	
Others ^b	0	17 (11.0%)	
CR-GNB species			0.229
CRAB	34 (82.9)	107 (69.5%)	
CRE	6 (14.6%)	39 (25.3%)	

^aData are presented as n (%)^bIncluding abscess, ascites, CSF, and pericardial effusion^cEvaluated on the day of ICU admission^dPresent on the day of sample collection

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; CCr, creatinine clearance; CR-GNB, carbapenem-resistant gram-negative bacteria; SD, standard deviation.

	\geq KDIGO 3 AKI		P-value
CRPA	1 (2.4%)	8 (5.2%)	
Albumin level	2.8 (2.5–3.1)	2.7 (2.4–3.0)	0.217
Concomitant nephrotoxins			
Aminoglycoside	5 (12.2%)	17 (11.0%)	0.835
Vancomycin	8 (19.5%)	12 (7.8%)	0.028
Intravenous contrasts	9 (22%)	30 (19.5%)	0.725
Disease severities			
APACHEII scores (median, IQR) ^c	23 (18–31)	25 (20–30)	0.454
Respiratory failure ^d	40 (97.6%)	135 (87.7%)	0.081
Septic shock ^d	22 (53.7)	39 (25.3%)	0.001
Colistin treatment			
Daily dose (MIU)(median, IQR)	8 (7.4–10)	8 (4–10)	0.036
Treatment duration (days)(median, IQR)	7 (4–11)	7 (4–12)	0.403
Accumulated dose (MIU)(median, IQR)	46.5 (30.5–87.2)	48 (24–80)	0.594
Inappropriate colistin dose	9 (22.0%)	14 (9.1%)	0.023
^a Data are presented as n (%)			
^b Including abscess, ascites, CSF, and pericardial effusion			
^c Evaluated on the day of ICU admission			
^d Present on the day of sample collection			
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; CCr, creatinine clearance; CR-GNB, carbapenem-resistant gram-negative bacteria; SD, standard deviation.			

Univariate and multivariate analyses of the clinical factors associated with the occurrence of KDIGO stage 3 AKI are shown in Table 3. In the multivariate analysis, the independent factors associated with KDIGO stage 3 AKI included septic shock (adjusted odds ratio (aOR) 2.07, 95% confidence interval (CI) 1.05–4.06) and inappropriate colistin dosage (aOR 2.49, 95% CI 1.01–60.16). In contrast, when compared to Locolin®, Colimycin® treatment was an independent factor associated with a lower risk of KDIGO stage 3 AKI (aOR 0.36, 95% CI 0.17–0.74).

Table 3
Univariate and multivariate Cox-regression analysis of clinical factors associated with the occurrence of KDIGO 3 acute kidney injury

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	aOR (95% CI) ^a	P-value
Age	0.99 (0.97–1.01)	0.236	0.99 (0.96–1.02)	0.463
Male sex	0.72 (0.38–1.36)	0.312	0.70 (0.34–1.46)	0.346
Baseline eGFR < 30	1.65 (0.69–3.91)	0.260	1.41 (0.48–4.14)	0.536
Diabetes	0.93 (0.47–1.82)	0.824	1.16 (0.56–2.41)	0.681
APACHII \geq 25	0.64 (0.34–1.20)	0.162	0.53 (0.24–1.17)	0.118
Albumin \leq 3 g/dL	0.81 (0.42–1.54)	0.522	0.66 (0.34–1.28)	0.221
CRAB	0.61 (0.29–1.29)	0.197	0.53 (0.24–1.17)	0.118
Aminoglycoside	1.01 (0.40–2.58)	0.982	0.99 (0.34–2.86)	0.979
Vancomycin	1.99 (0.92–4.3)	0.082	1.59 (0.65–3.89)	0.310
Intravenous contrast	1.07 (0.51–2.23)	0.865	0.89 (0.37–2.12)	0.785
Septic shock ^b	2.79 (1.51–5.16)	0.001	2.17 (1.10–4.26)	0.025
Daily colistin > 10 MIU	1.75 (0.94–3.26)	0.077	1.32 (0.61–2.83)	0.482
Colistin treatment duration	0.98 (0.92–1.03)	0.411	0.99 (0.93–1.04)	0.617
Inappropriate colistin dosage	2.29 (1.09–4.80)	0.028	2.52 (1.00–6.33)	0.049
Colistin formulation				
Locolin®	1.00	-	1.00	-
Colimycin®	0.42 (0.22–0.82)	0.011	0.37 (0.18–0.77)	0.008
^a Adjusted odds ratio (aOR) and 95%CI were derived from cox regression analysis				
^b Present on the day of sample collection				

Effect of AKI on treatment outcomes

We further explored the impact of KDIGO stage 3 AKI on treatment outcomes. As shown in Table 4, patients with KDIGO stage 3 AKI had longer ventilator using days (36 days, IQR 17–52 days vs. 22 days, IQR 13–42 days, $p = 0.036$). Otherwise, patients with and without KDIGO stage 3 AKI had comparable hospital stays, ICU stays, and all-cause mortality.

Table 4
Treatment outcomes of patients with and without KDIGO 3 acute kidney injury

	KDIGO 3 AKI		
	Yes, n = 41	No, n = 154	P-value
Ventilator days (Median, IQR)	36 (17–52)	22 (13–42)	0.036
ICU stay (days)(Median, IQR)	31 (19–47)	30 (20–51)	0.889
Hospital stay (days)(Median, IQR)	60 (38–94)	53 (31–80)	0.133
Mortality			
Day 28	14 (34.1%)	62 (40.3%)	0.476
Discharge	28 (68.3%)	91 (59.1%)	0.283
Abbreviations: AKI, acute kidney injury; ICU, intensive care unit; IQR, interquartile range.			

Discussion

This retrospective study involved critically ill patients who underwent intravenous colistin treatment for CR-GNB and evaluated the occurrence of AKI. During the colistin treatment period, the occurrence of KDIGO stage 1, stage 2, stage 3 AKI was 49.7%, 39%, and 21%, respectively. Meanwhile, 9.2% of the patients had newly initiated dialysis. Comparatively, patients who were administered with Colimycin® had a lower rate of occurrence of KDIGO stage 2 and stage 3 AKI than those administered with Locolin®. In the multivariate analysis, we found that independent factors associated with KDIGO stage 3 AKI included the presence of septic shock and inappropriate colistin dosage. In contrast, Colimycin® use was an independent factor associated with a lower rate of occurrence of KDIGO stage 3 AKI. We also found that the occurrence of KDIGO stage 3 AKI during colistin treatment was associated with longer mechanical ventilator using days, but not related to increased all-cause mortality.

Nephrotoxicity and neurotoxicity are well-documented adverse reactions associated with the treatment with intravenous colistin. Nephrotoxicity in colistin is dose-dependent and usually reversible [16, 18, 22, 23]. The nephrotoxicity of colistin is mainly related to its d-aminobutyric acid and fatty acid component. Similar to its bactericidal effects, colistin increases the membrane permeability of tubular epithelial cells, which in turn leads to cell swelling and lysis [10]. Colistin is a multicomponent lipopeptide that contains colistin A and colistin B, which differ in the fatty acid chain attached to the cyclic decapeptide moiety of the drug [24]. The proportion of colistin A and colistin B can have a large difference in commercial preparations of colistin [25]. Although there are comparable bactericidal effects between colistin A and colistin B, colistin A has been shown to have a higher nephrotoxic effect than colistin B in an animal model study [24]. The different compositions of colistin A and colistin B in various formulations of colistin might lead to different risks of colistin-induced nephrotoxicity. In the present study, we demonstrated a significant difference in the rate of occurrence of AKI between two different formulations

of colistin. To our knowledge, this is the first study to evaluate the nephrotoxicity between different formulations of colistin. Although the exact mechanisms remain uncertain, we speculate that the composition of colistin A and B in various colistin products could play a pivotal role. Clinicians should therefore be aware of the possible difference in the risks of nephrotoxicity in various formulations of colistin. Further studies are also warranted to verify our findings.

The rate of occurrence of AKI reported in previous studies ranged from 27–51% and varied with the different study methodology and definition of nephrotoxicity used [7, 15, 16, 22, 26, 27]. In the present study, the overall rate of occurrence of KDIGO stage 2 and stage 3 AKI were 39% and 21%, which were consistent with previous reports. It is worth noting that all the enrolled patients were ICU-admitted cases and 90% of them had respiratory failure, which may further increase the rate of occurrence of nephrotoxicity during colistin treatment. We found that patients with KDIGO stage 3 AKI were more likely to have CR-GNB isolated from respiratory specimens and have a septic shock at the onset of colistin treatment. It may imply that patients with a respiratory infection and unstable hemodynamic status are more vulnerable to the nephrotoxicity of colistin. In addition, we found that more than 10% of our patients had inappropriate colistin dosage, which was rarely analyzed in previous studies, and it was an independent factor associated with AKI in the multivariate analysis. In contrast, both the accumulated dose and treatment duration of colistin were not significantly associated with AKI. Our findings suggest that the nephrotoxicity of colistin is more likely correlated with the disease severity and inappropriate colistin dose adjustment according to renal function. Clinicians should therefore monitor renal function rigorously at the onset and during colistin treatment and adjust colistin dose carefully to keep the risk of nephrotoxicity as low as possible. Some strategies, including N-acetylcysteine (NAC) treatment and plasma volume expansion, have been proposed to prevent or ameliorate colistin-related AKI and deserve further verification [28, 29].

We further evaluated the impact of the occurrence of colistin-related AKI on treatment outcomes, which have rarely been evaluated until now. We found that patients with colistin-induced AKI may have prolonged mechanical ventilator dependence; there were no differences in mortality and hospital stays between patients with and without colistin-related AKI. Our findings were consistent with a previous study, which prospectively enrolled patients infected by extensively drug-resistant *Acinetobacter baumannii* and treated by colistin [30]. However, ventilator dependence and hospital stays were noted in that study. A study involving patients infected by drug-resistant *Pseudomonas aeruginosa* reported the presence of AKI as an independent factor associated with increased mortality [31]. Another study reported that patients who experienced AKI had higher mortality if kidney function failed to return to the baseline level [6]. Although the findings remain controversial, we believe that close monitoring of renal function during colistin treatment and discontinuation of colistin early in patients with AKI is the best way to reduce the effect of AKI on treatment outcomes in these critically ill patients.

There are some limitations to this study. First, as a retrospective study, the demographic characteristics and disease severities were not equal between patients who were treated with Colimycin® and Locolin®. Although we had used multivariate analysis to adjust the effects from clinical factors, our findings still

should be interpreted with caution. Second, all the enrolled patients had CR-GNB isolated from clinical specimens and some of them may have colonization, rather than true infection. However, its effect on our analysis was limited because the present study aimed to investigate colistin-induced nephrotoxicity, rather than treatment effectiveness. Third, exposure to concomitant nephrotoxins, including vancomycin, aminoglycosides, and contrast, were not rare in our patients. Therefore, the risk of colistin-induced nephrotoxicity could be overestimated. Finally, we enrolled critically ill patients with ICU admission and high APACHE II scores. Most of them had respiratory failure and nearly one-third of them received inotropic agents. Therefore, the findings in our study may not be applicable in patients with low disease severities.

Conclusion

This retrospective study involved critically ill patients who were treated with intravenous colistin. We found significant differences in the rate of occurrence of colistin-induced nephrotoxicity between two formulations of colistin. Other clinical factors associated with colistin-induced nephrotoxicity included septic shock and inappropriate colistin maintenance dosage. Our findings suggest that the risk of nephrotoxicity in colistin could be affected by the manufacturing protocol and compositions in various formulations, which deserves verification in further clinical studies. Meanwhile, close monitoring of renal function in high-risk populations and appropriate dosage adjustment during colistin treatment is crucial to decrease the risk of colistin-induced nephrotoxicity in critically ill patients.

Abbreviations

MDRO: multidrug-resistant organisms; CR-GNB: carbapenem-resistant gram-negative bacilli; CRAB: carbapenem-resistant-Acinetobacter baumannii complex; CRE: carbapenem-resistant enterobacteriaceae; CRPA: carbapenem-resistant Pseudomonas aeruginosa; AKI: acute kidney injury; ICU: intensive care units; APACHE: Acute Physiology and Chronic Health Evaluation; eGFR: estimated glomerular filtration rate; NAC: N-acetylcysteine.

Declarations

Author's contributions

JYF, YTL, FDW conceptualise the study design. JYF, YTL wrote the manuscript draft

with input from all authors. JYF performed the data analysis. JYF, YTL, SWP, KYY, YMC, DHTY, SYL, FDW collected all the data. All authors read and approved the final manuscript.

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None

Availability of data and aterials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by local institutional review board. (IRB Nos: 2019-11-009AC)

Consent for publications

Not applicable.

Competing interests

The authors declared no competing interests.

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Figures

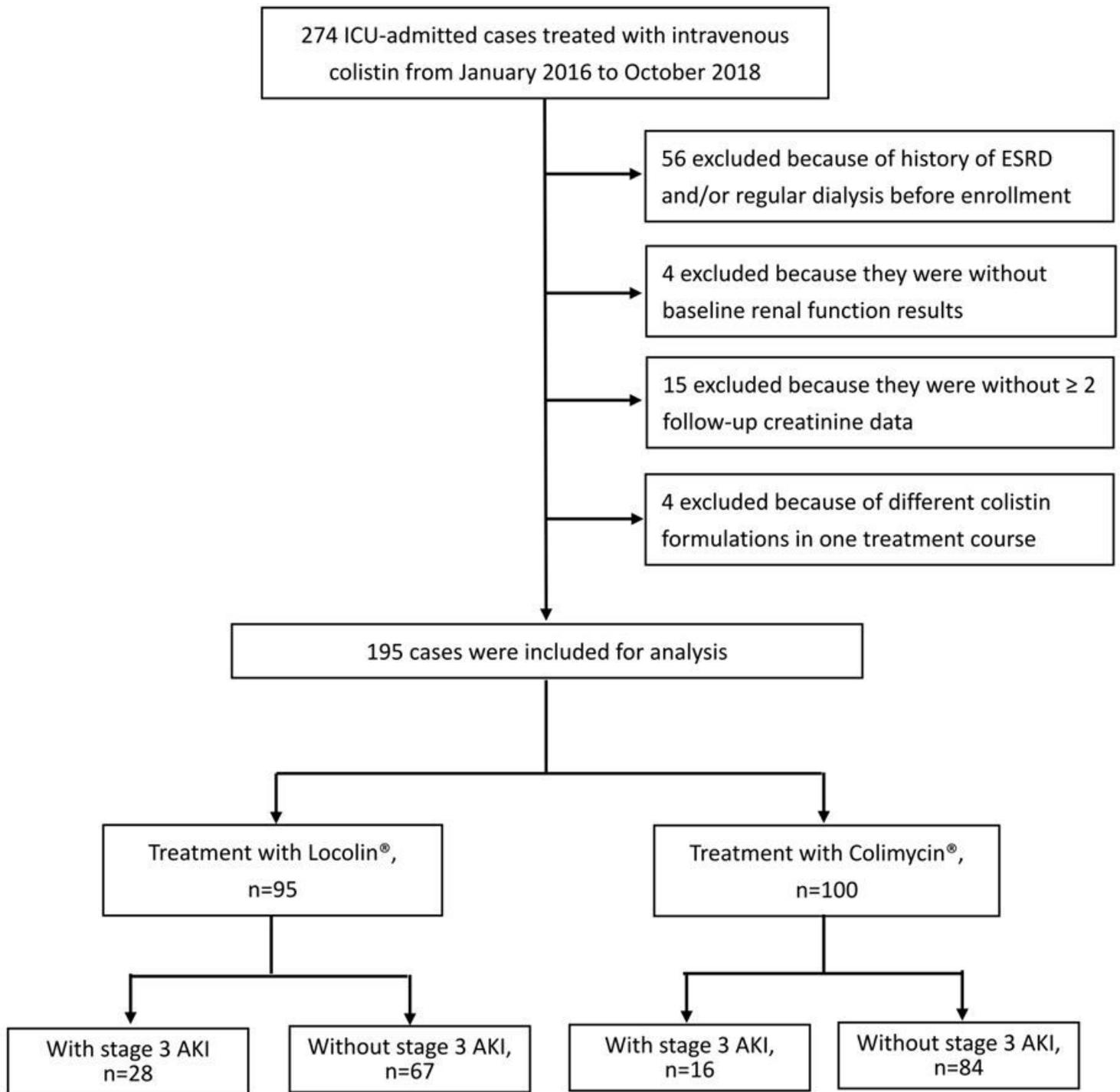


Figure 1

Study flow diagram and reasons for patient exclusions. ESRD, end stage renal diseases; AKI, acute kidney injury.

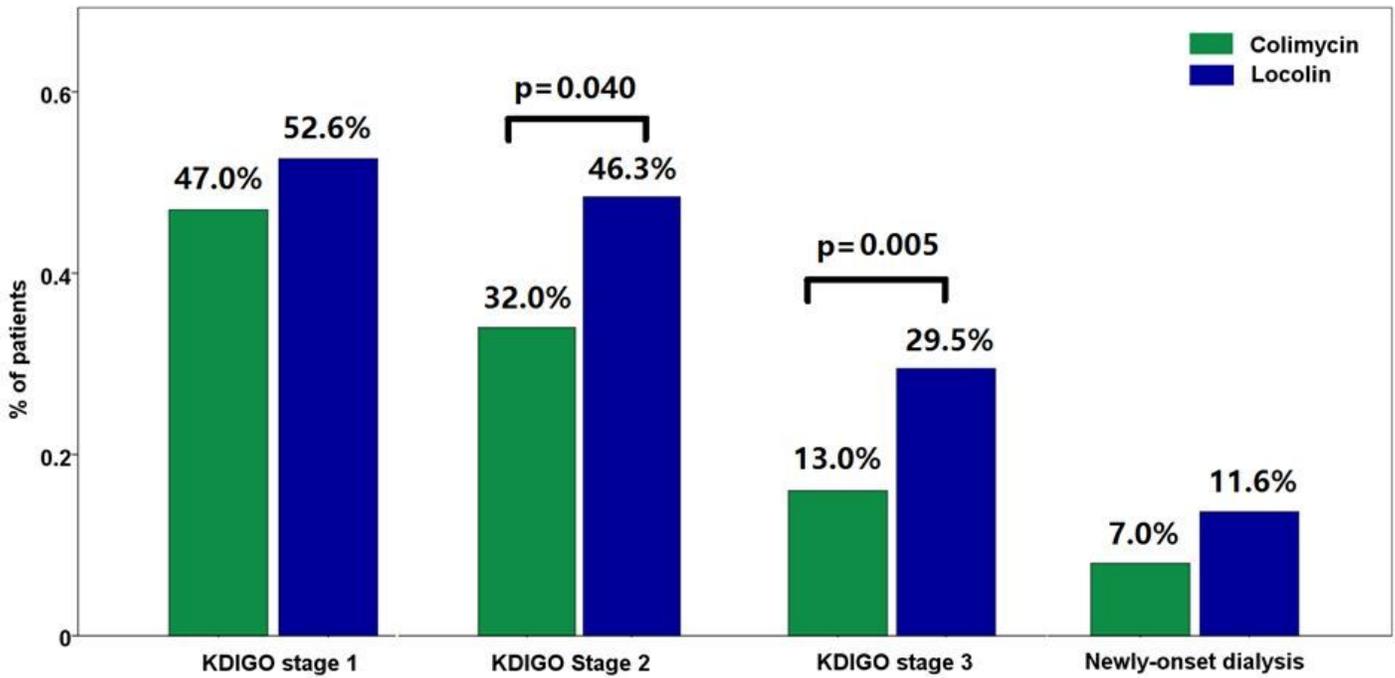


Figure 2

Rate of occurrence of acute kidney injury in ICU-admitted patients treated with intravenous colistin. KDIGO stage 1, stage 2, stage AKI, and newly initiated dialysis are presented respectively.

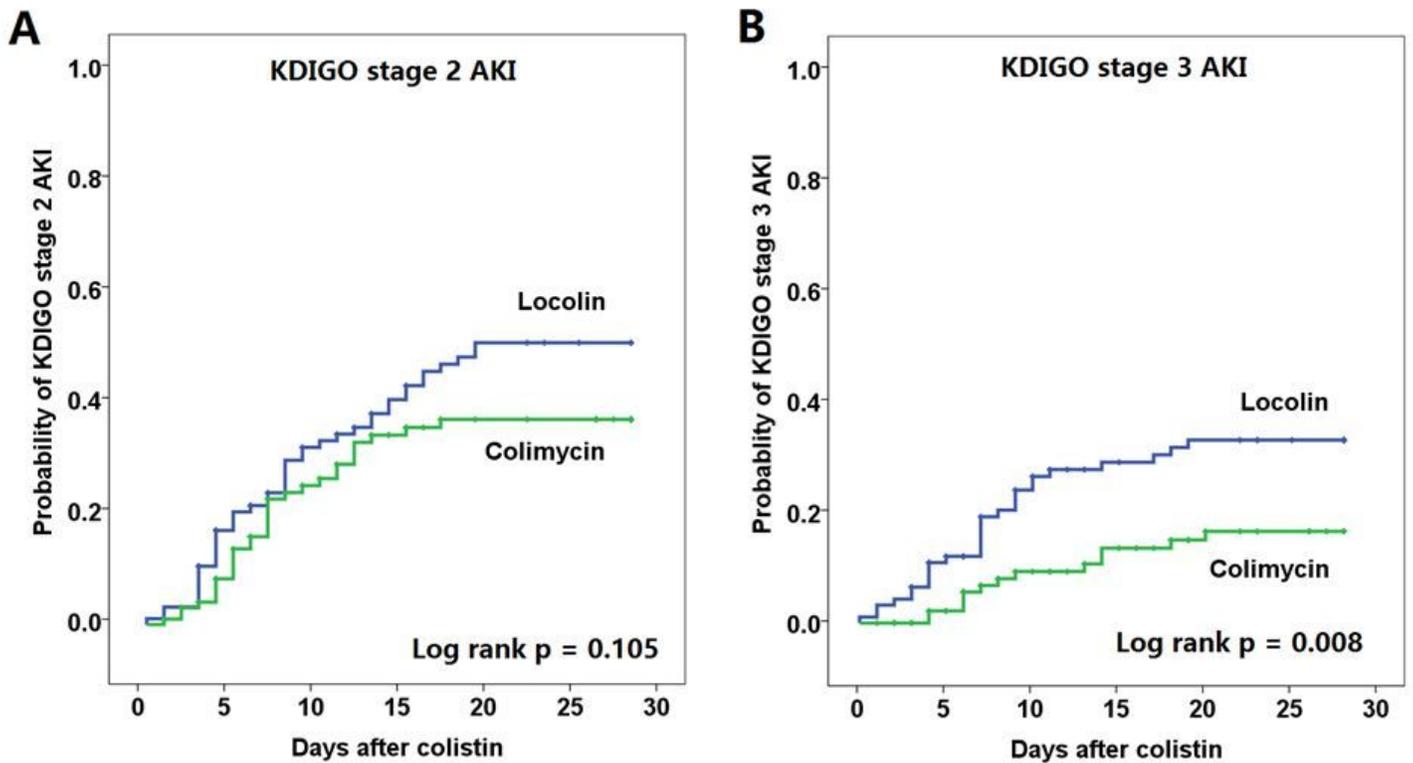


Figure 3

Kaplan-Meier analysis of (A) stage 2 AKI and (B) stage 3 AKI between patients treated with Locolin® and Colimycin®. AKI, acute kidney injury.

Supplementary Files

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- [SupplementaryTable1.docx](#)