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Original Article

Septic shock is an independent risk factor for colistin-induced severe acute kidney injury: a retrospective cohort study

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Abstract: Introduction: Colistin, a last-line therapeutic agent for the treatment of multidrug-resistance gram-negative infections, is limited in its use due to nephrotoxicity. This retrospective cohort study evaluates risk factors for colistin-induced severe acute kidney injury (AKI) in critically ill patients. Methods: Patients admitted to a university hospital ICU, were without pre-existing kidney injury, and received colistin therapy 72 or more hours were included. Patient demographics, the source of infection and outcome were collected. AKI was evaluated by using the RIFLE criteria. Risk factors for the development of AKI were analyzed via logistic regression analysis. Results: One-hundred and two patients were included in the study. The overall incidence of AKI was 77.5% (n=79), and that of severe AKI was 34.3% (n=35). On univariate analysis, age and septic shock correlated significantly with severe AKI patients (P=0.042, P=0.001, respectively). By multivariate logistic regression analysis, septic shock was the only independent risk factor for colistin-induced severe AKI (OR 8.580 [1.868-39.417]; P=0.006). Conclusions: A high incidence of colistin-induced AKI defined by RIFLE criteria is observed in critically ill patients. Septic shock is the only variable independently associated with severe AKI induced by colistin therapy.

Keywords: Colistin, acute kidney injury, septic shock, critically ill

Introduction

Multidrug-resistant (MDR) gram-negative bacterial infections are a serious problem especially for an intensive care unit (ICU) patient population with high mortality rates. Colistin (polymyxin E), a cationic cyclic polypeptide, is a last line therapeutic agent for the treatment of these MDR gram-negative infections [1]. The most common adverse effect of colistin is nephrotoxicity, reported in 25%-60% of patients in recent studies [2, 3]. This variability is considered due to the differences in the study populations, as well as the definitional criteria for acute kidney injury (AKI). Risk factors for colistin-induced nephrotoxicity, such as male gender, high dose of colistin administration, concomitant administration of nephrotoxic agents, the severity of patient illness, and septic shock have been described in different patient populations [2, 4-6].

Acute kidney injury (AKI)-defined by the clinically validated RIFLE criteria, Risk, Injury, Failure, Loss, End-stage renal disease [7]-incidence is noted in greater than 50% of the critically ill; increasing AKI severity is associated with increased mortality. For example, patients with mild AKI had a 1.6 fold higher mortality than patients without AKI, while severe AKI patients had a 6.8 fold higher mortality than patients without [8]. As the mortality increases with the severity of AKI, the identification of risk factors may be of utility.

The objective of this study was to define the incidence of and to evaluate the risk factors for, severe AKI induced by colistin therapy in critically ill patients.

Materials and methods

Study design, setting, patients

This retrospective cohort study was conducted in a 16-bed University medical-surgical ICU. The Institutional Research and Ethics Committee of Marmara University approved this study. Our

institutional ethics committee waived informed consent due to the retrospective design of the study. Data were collected from identified ICU patient's medical records. Patients were included if they were in the ICU receiving intravenous (IV) colistin for ≥ 72 hours. Exclusion criteria were patients < 18 years old, pre-existing AKI or AKI developed within two days of initiation of colistin therapy, congestive heart failure, liver failure, hypoalbuminemia, and patients who received colistin before ICU admission. Administration of colistin was based upon the results of in vitro antimicrobial susceptibility tests, and duration determined by the clinical response. Intravenous colistin dosing in the face of a normal renal function is 5 mg/kg ideal body weight/day; the daily dosage was modified for cases of renal impairment.

Definitions

AKI was defined by the RIFLE criteria according to serum creatinine: AKI Risk-increased creatinine × 1.5 above baseline; AKI Injury-increased creatinine × 2; AKI Failure-increased creatinine × 3 or creatinine ≥ 4.0 mg/dL with an acute rise > 0.5 mg/dL; AKI Loss-persistent acute renal failure with complete loss of kidney function for more than 4 weeks. Severe AKI was defined as at least failure category by RIFLE. Threshold serum creatinine values were 1.5 mg/dL for men and 1.3 mg/dL for women [9]. IBW (kg) was calculated as follows: 50 kg + 2.3 kg for each inch over 5 feet for men; 45.5 kg + 2.3 kg for each inch over 5 feet for women. Septic shock was diagnosed as a state of acute circulatory failure characterized by persistent arterial hypotension (mean arterial pressure less than 70 mmHg) despite adequate fluid resuscitation or by the tissue hypoperfusion in the presence of proven or suspected infection [10].

As the mortality increases with the severity of AKI, the primary outcome was the development of severe AKI (at least failure of kidney function by RIFLE) during colistin treatment. Case patients were defined as patients who developed severe AKI following colistin administration, and control patients were those who did not develop AKI and those who were classified as risk and injury according to RIFLE criteria after colistin treatment.

Data collection

The medical records for each patient in the cohort were reviewed, and the following data were collected: demographic variables, acute physiology and chronic health evaluation (APACHE) II score, presence of diabetes mellitus, hypertension on admission, site of infection, concomitant nephrotoxic drugs such as non-steroidal anti-inflammatory drug, other nephrotoxic antimicrobials (i.e: aminoglycosides, vancomycin), radiocontrast agents, mannitol, length of ICU stay, duration of colistin therapy, need for mechanical ventilation and renal replacement therapy (RRT), daily serum creatinine levels, and discharge status. Patients were classified daily using the RIFLE criteria during the colistin treatment period or until death if it occurred during therapy.

Statistical analysis

Number Cruncher Statistical System (NCSS 2007, Kaysville, Utah, USA) was used for all statistical analyses. Categorical variables were compared using Fisher's exact test and Yates' continuity correction test. Normally distributed continuous data are expressed as the mean ± standard deviation and were compared by independent sample t-test. For non-normally distributed continuous data, values are presented as a median and interquartile range (IQR) and were compared by using Mann-Whitney U test. *P*-values of < 0.05 were regarded as significant. Multivariate analysis of risk factors for colistin-induced severe AKI was constructed by using logistic regression.

Results

During the two-year study period (January 2013-January 2015), there were 1,675 consecutively admitted ICU patients; 172 of these received colistin therapies and 102/172 (59.3%) of these met inclusion criteria. Patient median age was 56.5 years (IQR 18-90), median ICU length of stay was 17 days (IQR 3-97), median duration of colistin therapy was 9 days (IQR 3-40), and median APACHE II score was 21 (IQR 10 31). The respiratory tract was the leading site of infection (77.5%, n=79), followed by the abdomen (12.7%, n=13), blood stream (8.8%, n=9) and urinary tract (1%, n=1). All patients had sepsis, and 75 (73.5%) of these had septic shock; overall mortality was 66.7%. RIFLE criteria-defined AKI occurred in 79 (77.5%) patients. Patients developing AKI after colistin administration were in the Risk (25.5%, n=26), Injury (17.7%, n=18), and Failure (34.3%,

Table 1. Comparison of the baseline characteristics of study patients stratified by the severity of acute kidney injury

		Non-AKI n (%)	Risk n (%)	Injury n (%)	Failure n (%)
Gender	Female	13 (56.5)	13 (50.0)	11 (61.1)	16 (45.7)
	Male	10 (43.5)	13 (50.0)	7 (38.9)	19 (54.3)
Septic Shock	(-)	10 (43.5)	9 (34.6)	6 (33.3)	2 (5.7)
	(+)	13 (56.5)	17 (65.4)	12 (66.7)	33 (94.3)
RRT	(-)	23 (100)	26 (100)	18 (100)	28 (80.0)
	(+)	0 (0)	0 (0)	0 (0)	7 (20.0)
Nephrotoxic Agent	(-)	14 (60.9)	18 (69.2)	8 (44.4)	20 (57.1)
	(+)	9 (39.1)	8 (30.8)	10 (55.6)	15 (42.9)
Diabetes Mellitus	(-)	19 (82.6)	17 (65.4)	13 (72.2)	25 (71.4)
	(+)	4 (17.4)	9 (34.6)	5 (27.8)	10 (28.6)
Hypertension	(-)	17 (73.9)	15 (57.7)	14 (77.8)	20 (57.1)
	(+)	6 (26.1)	11 (42.3)	4 (22.2)	15 (42.9)
Site of infection	Abdominal	3 (13.0)	4 (15.4)	1 (5.6)	5 (14.3)
	RTI	17 (73.9)	19 (73.1)	16 (88.9)	27 (77.1)
	Blood	3 (13.0)	2 (7.7)	1 (5.6)	3 (8.6)
	UTI	0 (0)	1 (3.8)	0 (0)	0 (0)
MV	(-)	2 (8.7)	0 (0)	0 (0)	0 (0)
	(+)	21 (91.3)	26 (100)	18 (100)	35 (100)
ICU Mortality	Survived	16 (69.6)	8 (30.8)	4 (22.2)	6 (17.1)
	Died	7 (30.4)	18 (69.2)	14 (77.8)	29 (82.9)

RRT: renal replacement therapy, RTI: respiratory tract infection, UTI: urinary tract infection, MV: mechanical ventilation, ICU: intensive care unit.

n=35) categories; no patients fulfilled the criteria for AKI Loss or End stage kidney disease. Seven patients who received RRT were in Failure category. Septic shock was present in 13 (56.5%) non-AKI patients, 17 (65.4%) of Risk patients, 12 (66.7%) of Injury patients, and 35 (94.3%) of Failure patients. Mortality was 30,4% in non-AKI, 69.2% in Risk, 77.8% in Injury, 82.9% in Failure patients; mortality increased with the severity of the kidney injury. Concomitant use of nephrotoxic agents was similar among the groups; 39.1% in non-AKI, 30.8% in Risk, 55.6% in Injury, 42.9% in Failure. The characteristics of the cohort stratified according to the severity of kidney injury are presented in **Tables 1** and **2**.

The study cohort was grouped as case and control; the case group consisted of patients with severe AKI (defined above), and control group consisted of patients with mild kidney injury (defined as Risk and Injury by RIFLE) and non-AKI patients. The two groups were similar regarding gender, concomitant nephrotoxic drugs, comorbidities, site of infection, APACHE II score, daily serum creatinine levels, ICU length of stay, duration of colistin therapy, and mechanical ventilation. RRT was used significantly more frequently in the case group (P= 0.002). Case group patients were significantly older than the controls (P= 0.042). ICU mortality and presence of septic shock were significantly higher in the case group (P=0.022, P=0.001, respectively, **Tables 3** and **4**).

By Univariate analysis, age and the presence of septic shock were associated with the development of colistin-induced severe AKI. Binary logistic regression analysis was conducted, where risk factors found statistically significant in univariate analysis (age and the presence of septic shock) were introduced as independent variables and development of colistin-induced severe AKI as the dependent variable. The logistic regression model was statistically significant (χ^2=15.866; P= 0.001), had 37.1% sensitivity and 86.6% specificity. The presence of septic shock (odds ratio [OR] 8.580; 95% CI 1.868-39.417; P=0.006) was the only independent risk factor for the development of colistin-induced severe AKI.

Discussion

This retrospective cohort study was designed to evaluate the incidence of severe AKI and the associated risk factors in sepsis patients, without pre-existing renal impairment, receiving ≥ 72 hours colistin treatment for the MDR gram (-) negative infections. The overall incidence of colistin-induced AKI was 77.5%, and the incidence of severe AKI was 34.3%. Septic shock was the only independent risk factor for colistin-induced severe AKI.

The incidence of AKI-related to colistin varies widely, ranging 0% to 53.5% in the literature [6, 11]. This wide variety is likely due to differences

Table 2. Baseline characteristics of study patients stratified by the severity of acute kidney injury

		Non-AKI	Risk	Injury	Failure
Age (years)	Min-Max	18-64	18-90	20-81	18-89
	Mean ± SD	43.22±15.54	54.81±19.61	53.72±17.10	58.63±19.99
APACHE II	Min-Max	11-29	12-31	12-31	10-31
	Mean ± SD	19.57±4.80	21.65±5.05	21.83±5.15	20.83±5.42
SCr on admission (mg/dl)	Min-Max	0.25-1.24	0.21-1.45	0.29-1.47	0.39-1.49
	Mean ± SD	0.74±0.28	0.88±0.34	0.88±0.35	0.91±0.32
Weight (kg)	Min-Max	50-90	51-90	50-90	60-95
	Mean ± SD	71.09±11.96	72.58±8.78	70.00±9.07	73.69±10.64
Duration of colistin therapy	Min-Max	4-40	3-22	3-26	3-18
	Mean ± SD	11.13±7.37	8.77±3.96	9.28±5.33	9.69±3.93
Length of stay in ICU	Min-Max	8-97	6-32	5-43	3-76
	Mean ± SD	24.26±19.86	15.31±6.69	19.06±10.09	21.51±16.05

SCr: serum creatinine, ICU: intensive care unit, AKI: acute kidney injury.

Table 3. Characteristics of case and control patients

		Case patients (n=67) n (%)	Control patients (n=35) n (%)	P
Gender	Female	37 (55.2)	16 (45.7)	[a]0.481
	Male	30 (44.8)	19 (54.3)	
Septic Shock	(-)	25 (37.3)	2 (5.7)	[a]0.001**
	(+)	42 (62.7)	33 (94.3)	
RRT	(-)	66 (98.5)	28 (80.0)	[b]0.002**
	(+)	1 (1.5)	7 (20.0)	
Nephrotoxic Agent	(-)	40 (59.7)	20 (57.1)	[a]0.970
	(+)	27 (40.3)	15 (42.9)	
Diabetes Mellitus	(-)	49 (73.1)	25 (71.4)	[a]0.999
	(+)	18 (26.9)	10 (28.6)	
Hypertension	(-)	46 (68.7)	20 (57.1)	[a]0.349
	(+)	21 (31.3)	15 (42.9)	
Site of infection	Abdominal	8 (11.9)	5 (14.3)	[b]0.955
	RTI	52 (77.6)	27 (77.1)	
	Blood	6 (9.0)	3 (8.6)	
	UTI	1 (1.5)	0 (0.0)	
MV	(-)	2 (3.0)	0 (0)	[b]0.545
	(+)	65 (97.0)	35 (100)	
ICU Mortality	Survived	28 (41.8)	6 (17.1)	[a]0.022*
	Died	39 (58.2)	29 (82.9)	

[a]Yates' continuity correction test. [b]Fisher's exact test. *P < 0.05. **P < 0.01. RRT: renal replacement therapy, RTI: respiratory tract infection, UTI: urinary tract infection, MV: mechanical ventilation, ICU: intensive care unit.

in study populations, severity of illness, dose and duration of colistin treatment, and the defining criteria of AKI. Those of the above studies, which did not use a consistent definition of AKI tended to report incidences ranging from 14% to 18.6% [12, 13]. Recent studies using the RIFLE classification to define AKI reported the incidence as 43% to 53.5% [5, 6, 14-18]. Another study defined AKI by Acute Kidney Injury Network (AKIN) criteria, reporting AKI incidence as 25.8% [2]. These AKI classifications use creatinine values to identify AKI mostly below the critical levels compared to other studies, which use 2 mg/dl as the threshold for a creatinine value.

We report rather high overall AKI incidence compared to those reported in the literature, even compared with the studies using RIFLE criteria to define AKI. This high occurrence can be explained by the differences in the study population and the severity of illness. In this study, all patients were admitted to the ICU, 98% were mechanically ventilated, the median APACHE II score was 21, all were diagnosed as septic and, of these, 73.5% were in septic shock. Pogue, et al. [15] retrospectively reviewed 126 patients who received colistin for ≥ 48 hours to determine the rate of colistin-associated nephrotoxicity defined by RIFLE cri-

Table 4. Characteristics of case and control patients

		Case patients (n=67)	Control patients (n=35)	P
Age (years)	Min-Max	18-90	18-89	[c]0.042*
	Mean ± SD (Median)	50.54±18.17	58.63±19.99	
APACHE II	Min-Max	11-31	10-31	[c]0.885
	Mean±SD (Median)	20.99±5.03	20.83±5.42	
SCr on admission (mg/dl)	Min-Max	0.21-1.45	0.39-1.49	[c]0.271
	Mean ± SD (Median)	0.83±0.33	0.91±0.32	
Weight (kg)	Min-Max	50-90	60-95	[c]0.279
	Mean ± SD (Median)	71.37±9.96	73.69±10.64	
Duration of colistin therapy	Min-Max	3-40	3-18	[d]0.627
	Mean ± SD (Median)	9.72±5.70 (8)	9.69±3.93 (9)	
Length of stay in ICU	Min-Max	5-97	3-76	[d]0.579
	Mean ± SD (Median)	19.39±13.77 (16)	21.51±16.05 (17)	

[c]Independent sample t testi. [d]Mann-Whitney U test *P < 0.05. SCr: serum creatinine, ICU: intensive care unit, AKI: acute kidney injury.

teria. AKI incidence was 43%, 75% of the cohort was admitted to ICU, 62% were mechanically ventilated, sepsis and severe sepsis were diagnosed in 66% of the patients, and the rate of septic shock was 14% [15]. Their cohort consisted of less severely ill patients compared to our cohort, only 66% of their patient population was critically ill. Another study defining AKI by RIFLE criteria for colistin-induced nephropathy reported a 45% AKI incidence. The APACHE II score was 8.3 in this study, and no other data were given as to the severity of illness in their cohort [16]. In severely ill ICU patients, without preexisting renal disease, who receive colistin for more than seven days, a 40% AKI rate was observed, 43% of the patients were diagnosed with sepsis at ICU admission, and AKI was strongly correlated with the presence of septic shock [5]. Even though this study noted the importance of septic shock, only 46% of the cohort experienced septic shock, a much lower rate compared to our study population. A recent study indicated septic shock as a risk factor for colistin-induced AKI in patients with pneumonia treated with colistin more than 72 hours; AKI occurred in 51% of the patient population. Septic shock was diagnosed in 30% of their cohort and APACHE II score was 12 in the nephrotoxicity group; the authors did not mention ICU admission rate [14]. This study cohort likely did not consist only of critically ill patients and had a lower severity score, implying less severe illness. An AKI incidence of 53.5% was reported in a study designed to identify predictors of AKI associated with IV colistin treatment, defining AKI with RIFLE criteria. The study cohort contained patients who admitted to hospital and received colistin treatment for more than 72 hours. The authors did not give any data on ICU admission or the severity of illness; sepsis occurred in 80.3% of the cohort [6].

The studies classifying AKI by RIFLE criteria reported 6% to 44% incidence of severe AKI [5, 6, 14-16] consistent with our findings. Septic shock was an independent risk factor for colistin-induced severe AKI in our study. The presence of septic shock had an 8.5 fold higher incidence of severe AKI. The septic shock incidences in non-AKI, Risk, and Injury patients were similar (56.5%, 65.4%, 66.7% respectively), and significantly lower than the Failure (94.3%) patients. In a recent study by Kwon, et al. [14] septic shock was a significant risk factor for colistin-associated nephrotoxicity, with a 3.16 fold higher risk. The overall occurrence of septic shock was 41% in nephrotoxicity group; septic shock rate for the severe AKI was not stated. The development of AKI was strongly correlated with the presence of septic shock but not colistin therapy in a study consisting severely ill ICU patients [5].

Multiple risk factors for colistin nephrotoxicity are specified: dose and duration of colistin therapy, concomitant administration of other nephrotoxic drugs, and patient-related factors such as age, gender, hypoalbuminemia, hyperbiliru-

binemia, comorbidities and severity of the patients' illness [2, 4, 6, 18-21].

The duration of colistin therapy was similar among the groups of our study. Instead of actual body weight, ideal body weight is recommended for calculation of daily dose to avoid overdose [18, 20]. In our study, the given daily dose was calculated per IBW, and the daily dosage was adjusted according to serum creatinine levels recommended by the manufacturer. As hypoalbuminemia and hyperbilirubinemia were determined as risk factors for colistin-associated AKI, we excluded patients with these for a more homogenous cohort. The concomitant administration of several nephrotoxic agents such as antibiotics, non-steroidal anti-inflammatory drugs were found to be risk factors for colistin-induced nephropathy [2, 4, 21]. There were no significant differences among non-AKI and each of the severity levels of AKI groups in our study regarding concomitant administration of nephrotoxic drugs. The severity of illness was evaluated by APACHE II score in our patient' population, and the median APACHE II scores were similar among both cases and controls.

This study has several limitations. It is retrospective and a single center design. The lack of a control group who did not receive colistin limits the true effect, but a randomized trial would not be appropriate since colistin is the only treatment option for many multi-drug resistance infections. Also, the doses and duration of concomitant nephrotoxic agents were not collected, so we are unable to comment on the effects of those variables.

Given the degree of critical illness, there are multiple factors that may contribute to AKI, and it is very difficult to generate a homogenous patient population consisting of critically ill patients. Sepsis is the leading cause of AKI in the critically ill [22]. As the leading cause of AKI in ICU, sepsis is the major confounding factor when determining the risk factors for AKI. All the patients in our cohort were diagnosed as septic, hence forming as homogenous a patient population as possible. Additionally, a standardized dosing regime for IV colistin utilized in our institution, helping to limit another risk factor. Use of a classification criteria for AKI such as RIFLE allowed an assessment of both the degree of acute nephrotoxicity and the patient characteristics and the risk factors for different severity levels of AKI.

Conclusion

In conclusion, the overall incidence of colistin-induced acute kidney injury is high in critically ill patients receiving colistin more than 72 hours. Septic shock is an independent risk factor for colistin-induced severe AKI. Close monitoring by daily evaluation with standardized and validated AKI classification systems for kidney function in patients receiving colistin therapy, especially in concomitant septic shock is recommended.

Disclosure of conflict of interest

None.

Authors' contribution

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: BB, MH, FG, IC. Acquisition of data: BB, MH, FG, IC. Analysis and interpretation of data: BB, MH. Drafting of the manuscript: BB, MH, IC. Critical revision of the manuscript for important intellectual content: BB, IC. All authors have read and approved the final manuscript.

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