ORIGINAL ARTICLE

PREDICTORS AND OUTCOMES OF ACUTE KIDNEY INJURY ASSOCIATED WITH COLISTIN

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Background: Colistin is a nephrotoxic drug. We aimed to determine factors predictive of acute kidney injury amongst patients on colistin and study its impact on mortality. **Methods:** This observational study was done on adult patients receiving colistin in intensive care unit. Exclusion criteria included use of colistin before shifting to intensive care unit, presence of acute kidney injury before starting colistin or unwillingness. Complete blood counts, serum creatinine, albumin, C-reactive protein and lactate were checked at admission. Renal function tests were repeated daily and urine output was regularly monitored. Sequential Organ Failure Assessment score was calculated after 24 hours of admission. Primary outcome was development of acute kidney injury based on KDIGO criteria. **Results:** There were 150 patients aged 45.17±13.24 years, with a median length of stay of 12 (10–15) days. Mortality rate in intensive care unit was 39.33% (59 patients). Acute kidney injury developed in 78 (52.00%) patients after a mean of 4.26±1.48 days. Serum C-reactive protein (OR=1.011; 95% confidence interval 1.000, 1.023) and lactate (OR=1.714; 95% confidence interval 1.015, 2.895) levels at admission were predictive of acute kidney injury. Serum C-reactive protein ≥92 mg/dl and lactate ≥2.15 mg/dl had sensitivity of 64.10% and 76.92% respectively, and specificity of 75.00% each for predicting acute kidney injury. Patients with AKI were 3.324 (95% confidence interval 1.660,6.656) times more likely to die. **Conclusion:** Acute kidney injury associated with colistin is a significant problem, and is predicted by serum C-reactive protein and lactate levels at admission.

Keywords: Acute kidney failure; Acute kidney injury; Anti-bacterial agents; Colistin; Drug toxicity; Intensive care unit; Polymyxins; Risk factors

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INTRODUCTION

Sepsis is a leading cause of death and probably the most common indication for admission to medical intensive care units (ICU).[1] It is associated with a high degree of morbidity and mortality in the short term, and could even have long term sequelae.[2] It is thus not surprising to note a lot of effort being put into identifying strategies for early diagnosis and appropriate management of sepsis. There is more aggressive monitoring and management of patients in the ICUs.

The invasive nature of some of these interventions, such as central line placement and mechanical ventilation, places these patients at a much higher risk of acquiring nosocomial infections. As compared to general wards, patients cared for in ICUs often have more severe infections with pathogens likely to be highly resistant to conventional antibiotics.[3] This coupled with the fact that multiorgan dysfunction is commonly seen in intensive care settings, means that the management of such patients is very resource intensive.

Colistin was first used in clinical practice about 80 years ago, but this was later stopped because of safety concerns.[4] During the last decade or two, there has been another surge in its use as it is frequently employed as a last resort against many multidrug resistant gram-negative bacilli, such as Acinetobacter baumannii, Pseudomonas aeruginosa and Klebsiella pneumoniae. Concerns regarding the emergence of resistance to colistin as well in these organisms in the near future are absolutely legitimate.

Yet, on the other hand, this drug still has significant side effects as well. Notable amongst these are nephrotoxicity and neurotoxicity.[5]

Renal effects of colistin could range from mild phenomena such as acquired Bartter-like syndrome to severe manifestations like acute tubular necrosis.[6] Colistin is excreted mainly through the kidneys, hence the need to adjust dose for the degree of impairment in renal excretory function. Colistin causes acute tubular necrosis by altering the permeability of tubular epithelial cells, leading to water influx, cell swelling and subsequent lysis.[7]

Oxidative stress damaging the mitochondria in proximal tubular cells may also be contributory.[8]

Acute kidney injury (AKI) per se is a major problem in ICUs, with significant negative impact on

patient outcomes, particularly longer ICU/hospital stay and higher probability of death.[9] Use of colistin is an independent risk factor for the development of AKI in ICUs.[10] It is thus important to limit its use.

Whereas most of the data on this subject comes from Western countries, local data is scarce. It is very difficult to interpolate currently available evidence to our settings, keeping in view the difference in resources as well as patient characteristics. This study was thus carried out to collect data from our institute. We aimed to determine the frequency of AKI with colistin, to identify risk factors that could predict this and to determine the impact of AKI on mortality in ICU. The results would help both the individual physicians and policy makers alike. For doctors, it would mean countering each of the identified risk factors, so as to improve patient outcomes. The results of this study would guide policy makers in tailoring approach towards attainment of specific goals of antibiotics stewardship programs.

MATERIAL AND METHODS

This observational study was carried out at Intensive Care Unit, Department of Medicine of Pak Emirates Military Hospital Rawalpindi from February to November 2023. The research protocol was approved prospectively by Ethics Review Committee of the hospital. A minimum of 131 patients were required for this study. This calculation was done using Free Statistics Calculator version 4, available online. Assumptions included a medium effect size, 13 predictor variables, desired power of 0.8 and probability level of 0.05. Consent was taken from all the study participants at the time of admission. For patients with altered level of sensorium or on mechanical ventilation, consent was obtained from next of kin. All adult patients receiving colistin in the ICU were included in this study. Key exclusion criteria included use of colistin prior to shifting to ICU, presence of AKI before starting colistin or unwillingness expressed by the patients/next of kin for inclusion in this study. Eligible patients were consecutively enrolled into this study.

Patient demographics and co-morbid conditions were noted down. Blood sampling for complete blood counts, serum creatinine, albumin, C-reactive protein and lactate was done as a part of baseline investigations within an hour of admission. Serum urea and creatinine were repeated daily and the urine output was regularly monitored. Sequential Organ Failure Assessment (SOFA) score was calculated after 24 hours of admission to ICU. The use of other nephrotoxic drugs, including amikacin, vancomycin, non-steroidal anti-inflammatory drugs and meropenem was also recorded. Body mass index (BMI) was calculated using last known height of the patients, as communicated by the patients or their attendants. Colistin was used in different doses amongst various patients. Intravenous doses of 6 gm/ day or higher, before the development of AKI and subsequent adjustment based on renal dysfunction, were classified as high dose. The primary outcome was the development of AKI as defined by KDIGO criteria. Patients were followed up throughout the course of ICU stay to document outcome, which could be either death or discharge from ICU alive. SPSS 22 was used for data analysis, with descriptive statistics presented as mean±standard deviation or median and interquartile range for continuous variables and proportions for categorical variables. Binary logistic regression was used to identify risk factors associated with the development of AKI. For statistically significant factors identified on multivariate stage, ROC curve analysis was done to find out the best cut-offs for prediction of AKI. Chi square test with risk estimation was used to evaluate the relationship of AKI with survival in the ICU.

RESULTS

Included in this study were 150 patients having a mean age of 45.17±13.24 years. There were 90 (60.00%) males and 60 (40.00%) females. Baseline characteristics of these patients are shown in Table-1.

The median length of stay in ICU was 12 (10-15) days. AKI developed in 78 (52.00%) patients after a mean of 4.26±1.48 days of admission. The severity of AKI was stage 1 in 21 (26.92%), stage 2 in 31 (39.74%) and stage 3 in 26 (33.33%) patients respectively. AKI was oliguric in 62 (79.49%) patients. 59 (39.33%) patients died in the ICU, whereas the rest (91;60.67%) were shifted to step down facilities. The former group developed AKI much earlier than the latter (Figure-1). As shown in Table-2, serum CRP and lactate levels at the time of admission were predictive of AKI, with odds ratios of 1.011 (95% confidence interval 1.000, 1.023) and 1.714 (95% confidence interval 1.015, 2.895) respectively.

Most of the other parameters lost significance on multivariate stage. Receiver operating characteristic (ROC) curve analysis revealed areas under the curve of 0.736 (95% confidence interval 0.656, 0.816, $p<0.001$) and 0.779 (95% confidence interval 0.701, 0.856, $p<0.001$) for serum CRP and lactate respectively. Serum CRP ≥92 mg/dl had a sensitivity of 64.10% and specificity of 75.00% for predicting AKI. Similarly, serum lactate ≥2.15 mg/dl had a sensitivity of 76.92% and specificity of 75.00% for predicting AKI. Patients developing AKI were 3.324 (95% confidence interval 1.660, 6.656) times more likely to die as compared to those not developing AKI (Table-3).

The comparison of survival amongst patients with and without AKI is graphically represented in Figure-3.

Table-1: Baseline characteristics

Parameter		Value
Clinical characteristics	Body mass index (kg/m^2)	26.21±2.53
	Central venous pressure (cm of H_2O)	9.58±2.52
	SOFA score	11.20±4.11
Co-morbidities	Diabetes mellitus	32 (21.33%)
	Hypertension	51 (34.00%)
	Heart failure	14 (9.33%)
	Chronic obstructive pulmonary disease	20 (13.33%)
	Pre-existing chronic kidney disease	10 (6.67%)
Laboratory parameters	Baseline serum creatinine (µmol/L)	70.00 (58.00, 85.00)
	Maximum serum creatinine (µmol/L)	142.00 (84.75, 210.00)
	Haemoglobin (g/dl)	11.77±2.15
	Total leucocyte count (/µl)	15917.93±3692.10
	Platelets count (/µl)	218625.21±77077.43
	C-Reactive protein (mg/dl)	85.00 (56.75, 126.25)
	Serum albumin (g/L)	30.63 (28.00, 34.00)
	Serum lactate (mg/dl)	2.39 (1.68, 2.90)

Table-2: Binary Logistic regression for predicting development of acute kidney injury

	Unadjusted Odds Ratio	*p*	Adjusted Odds Ratio	*p*
Age	1.029 (1.003, 1.055)	0.027	1.002 (0.968, 1.037)	0.904
Gender[@]	0.818 (0.425, 1.576)	0.548	-	-
Body mass index	1.110 (0.974, 1.265)	0.118	1.119 (0.939, 1.332)	0.210
Preexisting chronic kidney disease	9.261 (1.143, 75.052)	0.037	4.745 (0.505, 44.618)	0.173
Diabetes mellitus	1.724 (0.774, 3.843)	0.183	1.680 (0.648, 4.356)	0.286
Smoking	3.302 (1.418, 7.686)	0.006	2.620 (0.971, 7.066)	0.057
Colistin dose^	0.417 (0.169, 1.029)	0.058	0.407 (0.124, 1.342)	0.140
Colistin nebs	1.400 (0.645, 3.041)	0.395	-	-
Number of nephrotoxic medicines	1.777 (1.062, 2.974)	0.029	1.453 (0.808, 2.611)	0.212
SOFA score	1.103 (1.016, 1.198)	0.020	1.008 (0.912, 1.114)	0.877
Serum C-reactive protein	1.019 (1.011, 1.028)	<0.001	1.011 (1.000, 1.023)	0.049
Serum lactate	2.811 (1.787, 4.420)	<0.001	1.714 (1.015, 2.895)	0.044
Serum albumin	0.971 (0.895, 1.053)	0.474	-	-

Reference category: [@]Female, ^Low dose

Table-3: Cross tabulation of acute kidney injury and outcomes

	Alive	Death	Total
AKI	37 (47.44%)	41 (52.56%)	78
No AKI	54 (75.00%)	18 (25.00%)	72
Total	91 (60.67%)	59 (39.33%)	150

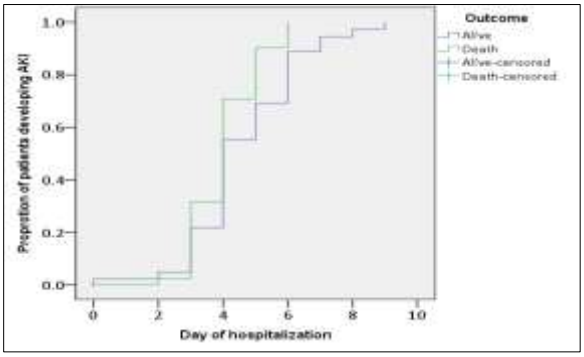

Figure-1: Comparison of timing of onset of acute kidney injury based on mortality status

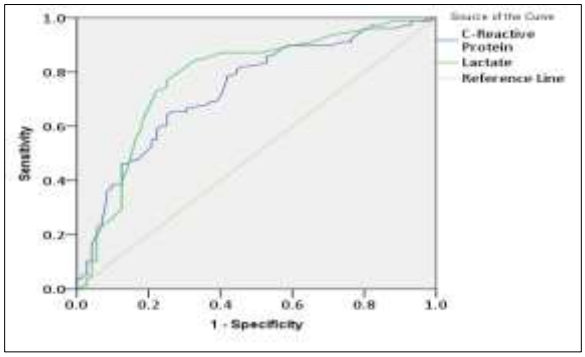

Figure-2: ROC curves for serum C-reactive protein and lactate

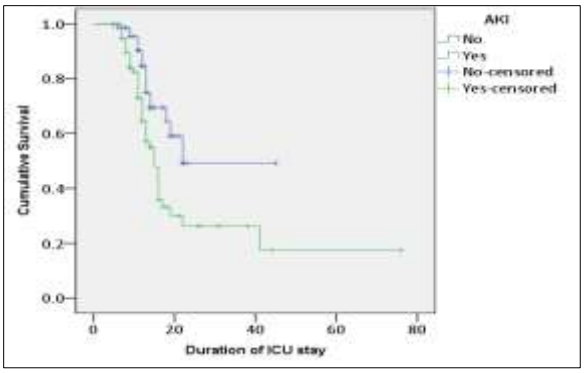

Figure-3: Effect of AKI on survival in ICU

DISCUSSION

Our data has given very insightful results. A little more than one half of the patients developed AKI after being treated with colistin in ICU. Elevated levels of serum CRP and lactate at the time of admission to ICU were predictive of this, whereas many other factors including demographic characteristics, co-morbid conditions or concurrent use of other nephrotoxic medicines did not have any predictive value. The overall predictive accuracy of these two variables is acceptable, even when judged by different statistical cut-offs for interpretation of area under ROC curves.[11] There is a lot of published international literature documenting the incidence of AKI amongst critically ill patients receiving colistin. In a meta-analysis of 6199 adult patients, the pooled incidence of nephrotoxicity with colistin (defined by RIFLE criteria) was 45%.[12] Similarly, another systematic review incorporating 237 studies described an incidence of 39.3% for AKI with colistin, with a 2.23 times higher risk as compared to patients managed with non-polymyxin-based regimens.[13] Local Pakistani data is not that extensive. Amongst 73 patients receiving colistin in a prospective cohort study carried out at Sindh Institute of Urology and Transplant Karachi, 30 (41.10%) had AKI.[14] However, drawing conclusions about a cause-and-effect relationship is impossible as the timing of development of AKI with reference to initiation of polymyxin therapy has not been clearly stated in that paper. In another retrospective review of 153 neonates treated with colistin at Karachi, nephrotoxicity occurred in 5.2% cases only.[15] The authors have acknowledged a lower frequency of nephrotoxicity amongst their patients, putting it down to a shorter duration of treatment.

Serum CRP and lactate were found to be independent predictors for development of AKI amongst our patients. Amongst 100 patients with multidrug resistant gram-negative infections treated in an ICU in Latvia, Aitullina, *et al* showed that the baseline serum CRP levels were almost two times higher amongst patients who later developed AKI with colistin use, as compared to patients who did not develop AKI.[16] On the contrary, Chang, et al did not find serum CRP to be associated with a higher risk of subsequent AKI amongst 251 patients from 14 teaching hospitals in China.[17] In a group of 412 Thai patients, a higher proportion of patients progressing to AKI had hyperlactatemia as compared to those without AKI.[18]

As far as the other variables are concerned, existing literature provides conflicting evidence to support or refute their role as predictors of AKI. Various studies have described different combinations of predictive factors. There was no relationship between age and the risk of nephrotoxicity, presumably because of a relatively young age of patients in this study. The functional renal reserve in such an age group would obviously be better than that in older patients. There is also a lesser chance of having co-morbidities at this stage. We also did not find higher chances of nephrotoxicity with increasing number of other nephrotoxic medications as previously reported by Gul, *et al,* and Min, *et al*.[9, 19] Contradictory results have been described by Liu, et al in a met-analysis of 18 studies.[20] Our results were not consistent with the general belief that colistin nephrotoxicity is dose dependent, similar to the findings presented by Balkan, et al in a multicenter study on 198 patients from Turkey, and Jin, *et al*, in a retrospective cohort study from China.[21, 22]

The higher mortality and prolonged length of ICU stay observed in this study is generally in agreement with results from many other studies. Amongst 298 patients from Lebanon, Moghnieh, *et al* showed that patients with colistin induced AKI had nearly 4 times higher risk of death.[23] Similarly, mortality rates were much higher amongst patients with AKI as compared to those without AKI (47.7 vs 21.8%) amongst 198 patients from a tertiary care hospital in Saudi Arabia.[24]

The strength of this study lies in the prospective design and robust selection criteria, whereby all eligible patients were consecutively recruited for this study, and only a few exclusion criteria were applied. This means that the cohort included in this study would be representative of patients in other similar setups in the real-world, making generalization of results easier.

Acute kidney injury in ICU settings could have multiple diverse etiologies. Patients included in this study had many other risk factors for the development of AKI, including but not limited to sepsis, hypovolemia, hypotensive episodes, use of other nephrotoxic medications and mechanical ventilation. Some of these, such as concomitant nephrotoxic medicines use, were excluded as potential causes on binary logistic regression, whereas others could not be taken care of. We are thus not sure whether AKI amongst our patients was purely related to the use of colistin, or was multifactorial. Most of the parameters recorded in this study were collected at the time of admission or during the first 24 hours only. Many new developments in the subsequent time period, such as hypotensive episodes, could have influenced the development of AKI, but we did not record any such data. Another major limitation of this study is the lack of follow

up after shifting patients out of ICU and the absence of data on recovery of renal functions in patients developing AKI.

CONCLUSION

AKI is frequently seen in patients treated with colistin in ICU. Association with worse outcomes, especially a higher risk of mortality, makes this a significant problem. Higher serum levels of infection markers, particularly CRP and lactate, can be used to predict this. Alternative antibiotics should thus be considered as therapeutic agents in such high-risk patients.

AUTHORS CONTRIBUTION

BA: Acquisition of data, drafting of article, final approval. ARA: Data analysis, drafting of article, final approval. AN: Interpretation of data, critical revision, final approval. AR: Study design, critical revision of manuscript, final approval. ZS: Acquisition of data, drafting article, final approval. SS: Study design, critical revision of article, final approval.

REFERENCES

1. Wang Z, Zhang L, Li S, Xu F, Han D, Wang H, *et al*. The relationship between hematocrit and serum albumin levels difference and mortality in elderly sepsis patients in intensive care units-a retrospective study based on two large database. BMC Infect Dis 2022;22(1):629.
2. Abu-Humaidan AHA, Ahmad FM, Al-Binni MA, Bani Hani A, Abu Abeeleh M. Characteristics of adult sepsis patients in the intensive care units in a tertiary hospital in Jordan: an observational study. Crit Care Res Pract 2021;2021:2741271.
3. Bonnet V, Dupont H, Glorion S, Aupee M, Kipnis E, Gerard JL, *et al*. Influence of bacterial resistance on mortality in intensive care units: a registry study from 2000 to 2013 (IICU Study). J Hosp Infect 2019;102(3):317–24.
4. Ustundag G, Oncel EK, Sahin A, Keles YE, Aksay AK, Ciftdogan DY. Colistin treatment for multidrug-resistant gram-negative infections in children: caution required for nephrotoxicity. Sisli Etfal Hastan Tip Bul 2022;56(3):427–34.
5. Bintang M, Nopparat J, Srichana T. In vivo evaluation of nephrotoxicity and neurotoxicity of colistin formulated with sodium deoxycholate sulfate in a mice model. Naunyn Schmiedebergs Arch Pharmacol 2023;396(11):3243–52.
6. Tabish M, Mahendran M, Ray A, Vikram NK. Colistin-induced acquired Bartter-like syndrome: an unusual cause of meltdown. BMJ Case Rep 2020;13(2):e232630.
7. Ordooei Javan A, Shokouhi S, Sahraei Z. A review on colistin nephrotoxicity. Eur J Clin Pharmacol 2015;71(7):801–10.
8. Al Sulaiman K, Aljuhani O, Alhammad AM, Al Aamer K, Alshehri S, Alhuwahmel A, *et al*. The potential role of adjunctive ascorbic acid in the prevention of colistin-induced nephrotoxicity in critically ill patients: A retrospective study. Saudi Pharm J 2022;30(12):1748–54.
9. Gul H, Arshad AR, Khan HA, Ijaz MM. Impact of acute kidney injury on in-hospital outcomes amongst critically ill patients. J Pak Soc Intern Med 2023;4(1):24–28.
10. Deniz M, Alişik M. Risk factors and prognosis for the development of acute kidney injury in patients using colistin in the intensive care unit: A retrospective cohort study. Medicine (Baltimore) 2024;103(2):e36913.
11. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol 2010;5(9):1315–6.
12. Sisay M, Hagos B, Edessa D, Tadiwos Y, Mekuria AN. Polymyxin-induced nephrotoxicity and its predictors: a systematic review and meta-analysis of studies conducted using RIFLE criteria of acute kidney injury. Pharmacol Res 2021;163:105328.
13. Wagenlehner F, Lucenteforte E, Pea F, Soriano A, Tavoschi L, Steele VR, *et al*. Systematic review on estimated rates of nephrotoxicity and neurotoxicity in patients treated with polymyxins. Clin Microbiol Infect 2021: S1198-743X(20)30764–3.
14. Babar ZU, Dodani SK, Nasim A. Treatment outcome and adverse effects of colistin in adult patients with carbapenem-resistant gram-negative bacteremia from Pakistan. Int J Infect Dis 2021;106:171–5.
15. Ambreen G, Salat MS, Hussain K, Raza SS, Ali U, Azam I, *et al*. Efficacy of colistin in multidrug-resistant neonatal sepsis: experience from a tertiary care center in Karachi, Pakistan. Arch Dis Child 2020;105(9):830–6.
16. Aitullina A, Krumina A, Svirskis S, Purvina S. Colistin use in patients with extreme renal function: from dialysis to augmented clearance. Medicina (Kaunas) 2019;55(2):33.
17. Chang K, Wang H, Zhao J, Yang X, Wu B, Sun W, *et al*. Risk factors for polymyxin B-associated acute kidney injury. Int J Infect Dis 2022;117:37–44.
18. Arrayasillapatorn N, Promsen P, Kritmetapak K, Anunnatsiri S, Chotmongkol W, Anutrakulchai S. Colistin-induced acute kidney injury and the effect on survival in patients with multidrug-resistant gram-negative infections: significance of drug doses adjusted to ideal body weight. Int J Nephrol 2021;2021:7795096.
19. Min KL, Son ES, Kim JS, Kim SH, Jung SM, Chang MJ. Risk factors of colistin safety according to administration routes: Intravenous and aerosolized colistin. PLoS One 2018;13(11):e0207588.
20. Liu J, Shu Y, Zhu F, Feng B, Zhang Z, Liu L, *et al*. Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant Acinetobacter baumannii infections: A systematic review and network meta-analysis. J Glob Antimicrob Resist 2021;24:136–47.
21. Balkan, II, Dogan M, Durdu B, Batirel A, Hakyemez IN, Cetin B, *et al*. Colistin nephrotoxicity increases with age. Scand J Infect Dis 2014;46(10):678–85.
22. Jin J, Zhu J, Zhu Z, Kim WY, O'Rourke J, Lin Z, *et al*. Clinical efficacy and nephrotoxicity of intravenous colistin sulfate in the treatment of carbapenem-resistant gram-negative bacterial infections: a retrospective cohort study. Ann Transl Med 2022;10(20):1137.
23. Moghnieh R, Husni R, Helou M, Abdallah D, Sinno L, Jadayel M, *et al*. The prevalence and risk factors of acute kidney injury during colistin therapy: a retrospective cohort study from Lebanon. Antibiotics (Basel) 2023;12(7):1183.
24. Almutairy R, Aljrarri W, Noor A, Elsamadisi P, Shamas N, Qureshi M, *et al*. Impact of colistin dosing on the incidence of nephrotoxicity in a tertiary care hospital in Saudi Arabia. Antibiotics (Basel) 2020;9(8):485.

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