ORIGINAL ARTICLE

Incidence and outcomes of Colistin-induced Acute Kidney Injury in Cancer Patients with Multi-Drug Resistant Infections

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Abstract

Background
Developing countries have seen a resurgence in use of colistin in recent years for treatment of multidrug resistant (MDR) gram-negative bacterial infections. Colistin is associated with increased risk of nephrotoxicity and potentially poor outcomes in high-risk patients. We studied cancer patients at our center, to analyze incidence, risk factors, and outcomes of acute kidney injury associated with use of colistin.

Methods
We reviewed patients from January 2015 until December 2018 in this single center retrospective study. Adults with solid organ or hematological malignancies with confirmed or suspected multi drug resistant gram-negative infections and received colistin for at least 48 hours were included. Outcomes of AKI including need for renal replacement therapy (intermitting or continuous), length of stay and mortality were studied. Patients were followed up for 3-6 months following an episode of AKI to review development of CKD. AKI was defined according to Kidney Disease Improving Global Outcomes (KDIGO).

Results
A total of 115 patients who received colistin were included in this study. Mean age was 42.63 ± 15.44 years. Majority (68.7%) were male. In multivariable analysis, three independent variables including weight (adjusted odds ratio [AOR] 1.04; 95% confidence interval [CI] 1.01-1.10) underlying malignancy (solid versus hematological (AOR 3.39; 95% CI (1.15-9.98), 0.02) and need for admission to intensive care unit (ICU) (AOR 2.75; 95% CI (1.00-7.82), 0.05) were identified as significant independent risk factor for nephrotoxicity. In patients who had AKI, mean length of hospital stay was 21.7 ± 13.7 days, 20% required RRT and 10.4% developed residual CKD. Mortality was 60% in these patients.

Conclusion
Increased weight, i.e.; BMI above 25, solid organ malignancy and ICU admission were significantly associated with increased risk of AKI in this cohort. Patients who required RRT had poor outcomes with mortality of 94% in the subgroup of patients who required RRT.

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Background
There has been an over-whelming increase in the incidence of multi-drug resistant gram negative (MDRGN) infections in recent years, particularly in immunocompromised patient population owing to the advances in cancer chemotherapy agents and lack of effective antimicrobial stewardship programs. This poses a challenging situation for physicians in terms of management with limited antibiotic options available which in turn has led to an increase in use of colistin.

According to 2019 CDC report, 2.8 million antibiotic resistant infections occurred in USA per year. Antibiogram at our institute shifted from 94% *E.coli* and 75% *Acinetobacter baumanii* carbapenem susceptibility in 2017 to 79% and 48% susceptibility in 2020, respectively, indicating an increasing trend of antibiotic resistance. Colistin, belonging to polymyxin group of antibiotics, is currently one of the few options available for these drug resistant infections. However, the associated nephrotoxicity, a recognized adverse effect of colistin, though reversible, constitutes a limiting factor. Various studies have revealed variable results of this nephrotoxic potential which could be due to the different doses and duration of colistin and differences in criteria used to establish acute kidney injury (AKI).[7,8,9,10] While there is existing data regarding colistin-induced nephrotoxicity, little has been published about the same in cancer population.[1,2] We conducted this study primarily to determine the incidence of colistin-induced nephrotoxicity in cancer patients with MDRGN infections along with the possible predisposing factors and mortality.

Study Design and Methods
This is a single center, retrospective observational study, conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC), Lahore, between January 2015 and September 2018. The data was retrieved from Hospital Information System (HIS) by reviewing physician notes and the laboratory tests after receiving approval of the institutional

review board (IRB), IRB number EX-25-03-19-01. All patients aged 18 years and above with a solid organ or hematological malignancy admitted with a suspected or culture proven multi-drug resistant gram-negative infection with or without bacteremia, including lower respiratory tract infections (LRTI), wound infections, urinary tract infections (UTI) and intra-abdominal infections, being treated with intravenous colistin for >48 hours were included in the study while those with end-stage renal disease (defined as people who were on maintenance haemodialysis or peritoneal dialysis or patients with a renal transplant) were excluded. All the patients received combination treatment with a carbapenem.

The dose of colistin was weight-based, calculated as 2.5-5 mg/kg/day, and was administered as sodium salt of colistin methanesulfonate (CMS). Serum creatinine was checked at baseline and then repeated periodically while on colistin. Patients were followed at six weeks and three months following discharge from hospital.

Acute kidney injury was defined using the Kidney Disease Improving Global Outcomes (KDIGO) criteria according to which AKI is defined as any of:

- increase in serum creatinine by 0.3mg/dl or more within 48 hours or
- increase in serum creatinine to 1.5 times baseline or more within the last 7 days or
- urine output less than 0.5mL/kg/h for 6 hours.[1]

AKI staging also was defined using KDIGO criteria, whereby:

- Stage 1 consists of serum creatinine 1.5- 1.9 times baseline or >0.3 mg/dl increase and urine output < 0.5 ml/kg/h for 6 h,
- Stage 2 consists of serum creatinine 2- 2.9 times baseline and urine output < 0.5 ml/kg/h for 12h,
- Stage 3 consists of serum creatinine 3 times baseline or increase in serum creatinine to >4 mg/dl or initiation of renal replacement therapy and urine output < 0.3 ml/kg/h for 24 h or anuria for > 12h.[1]

Renal recovery was defined as >50% decline in serum creatinine from the peak value at six weeks following AKI. Residual renal dysfunction was defined as a glomerular filtration rate (GFR) of < 60 ml/min at three months following colistin therapy. Other study variables included age, gender, weight, co-morbid conditions, neutropenia (defined as absolute neutrophil count of < 500 cells), source of infection (including lower respiratory tract infection, urinary tract infection, wound infection, intra-abdominal infection with identification of source done based on symptoms and signs, laboratory results and radiological findings), causative pathogens, bacteremia, dose and duration of colistin, use of concomitant nephrotoxic drugs, ICU admission, length of hospital stay and mortality.

Statistical analysis was performed using the SPSS software version 20. Continuous variables were stated as mean and categorical variables were computed as frequencies and percentages. Categorical variables were compared using chi-square test or fisher's exact test (where necessary). The continuous variables were compared using the independent t-test. Multivariable logistic regression model was used to identify the independent risk factors associated with nephrotoxicity. Statistical significance was defined as a two-tailed p-value 0.05.

Results

A total of 115 patients (table 1) were included in this study out of which 79 (68.7%) were males. The mean age of study population was 42.63 ± 15.44 years with a diagnosis of hematological malignancy in 47 (40.86%) patients while 68 (59.13%) had a solid organ malignancy. Underlying co-morbid conditions were present in 42 (36.5%) patients, most common being diabetes and hypertension, i.e. 9 (21.42%) patients had diabetes alone, 5 (11.9%) with hypertension while 15 (35.71%)

Table 1: Baseline Characteristics of Cancer Patients with Multidrug Resistant Gram-Negative Infections treated with Colistin (N = 115)

Variables Categories	Total = N (%)
Age	
- Mean ± standard deviation	42.63 ± 15.44
Sex	
- Male	79 (68.7%)
- Female	36 (31.3%)
Comorbidity	
- No	73 (63.5%)
- Yes	42 (36.5%)
Diagnosis	
- Solid malignancy	68 (59.1%)
- Hematological malignancy	47 (40.9%)
Acute kidney injury	
- No	40 (34.8%)
- Yes	75 (65.2%)
Indications of Colistin	
- Suspected	31 (27.0%)
- Confirmed	84 (73.0%)
Patient status	
- Alive	61 (53.0%)
- Death	54 (47.0%)
Need for renal replacement therapy	
- No	100 (87.0%)
- Yes	15 (13.0%)
Residual chronic kidney disease	
- No	16 (13.9%)
- Yes	12 (10.4%)
- No data	20 (17.4%)
- N/A	67 (58.3%)

***standard deviation**

(N/A: Not applicable, for those patients who did not develop AKI)

had concomitant diabetes and hypertension. All 115 patients were treated for multi drug resistant gram negative (MDRGN) infection, out of which 84 (73%) patients had a confirmed MDR infection based on cultures of sputum and urine in 25% each, wound swab in 16.7% and gastrointestinal tract was identified as the possible source (based on symptoms, clinical exam and radiological findings) in 15.5% of the cases while in 13.1% cases, source remained unidentified. Bacteremia was present in 38 (45.23% cases). Most commonly isolated organisms included *Escherichia coli* (40.47%), *Acinetobacter baumanni* (27.38%) and *Klebsiella pneumoniae* (15.47%). All patients were treated with intravenous colistin in combination with a carbepenem, majority (84%) treated for a duration longer than 72 hours while those who received for less than 48 hours were not included. Colistin was continued in those patients who had AKI at renal adjusted dose.

Seventy five (65.2%) patients (males 67.1%, females 61.1%, p= 0.42) developed acute kidney injury (AKI) with no statistically significant difference between the two genders. The mean weight of individuals who developed AKI was 62.75 kg. Majority (84%) of the patients with AKI received colistin for a duration longer than 72 hrs at a dose of 9miu/day. Seventy two percent of the neutropenic patients had AKI. A total of 27 (23.5%) patients developed stage 1 AKI, 11 (9.6%) stage 2 and 37 (32.2%) developed stage 3 AKI. Mean time from start of colistin therapy to AKI was 2.63 ± 1.53 days with peak creatinine of 2.31 ± 1.47, p=0.001 and creatinine at discharge of 1.27 ± 1.04, p-value 0.07. Fifteen patients required renal replacement therapy, p= 0.002, with 87% undergoing continuous renal replacement therapy (CRRT), 6.7% each hemodialysis and sustained low efficiency dialysis (SLED) for a mean duration of 1.5 days. The mean length of hospital stay was 21.57 days. Mortality was found to be higher in the AKI group i.e. 83.3%, p=0.001(table 2). At 6 weeks follow up, mean serum creatinine in those who developed AKI was 1.8. The multivariate analysis showed that solid organ tumor (p-value 0.02), increased weight (0.03) and ICU admission (p-value 0.05) were significantly associated with acute kidney injury. Fifty nine percent had a solid organ malignancy which was found to be significantly associated with a p-value of 0.03 (table 3). Out of 75 with AKI, 12 (16%) patients developed residual CKD on 3 months follow up. Fourteen percent of the patients were lost to follow up before 6 weeks and a total of 26.7% were lost to follow up after 6 weeks.

Discussion

Multi drug resistant gram-negative (MDRGN) infections, broadly defined as resistance to three or more classes of antibiotics,[2] have become a major source of concern in recent years, with a rising incidence owing to various factors while the choice of effective antibiotics against such infections is limited.[3] Colistin is one such antibiotic currently used as the last resort, however, the associated nephrotoxic potential presents physicians with a treatment challenge given the fact that multi resistant infections in most instances are encountered in critically ill patients who already are on other potentially nephrotoxic agents. Because of this, the use of colistin was abandoned in 1970s.[4] However, with the rise in MDRGN infections, a recent resurgence in the use of colistin has been observed, though the

Table 2: Stratification of Demographic Characteristics and Clinical Outcomes in Cancer Patients with Multidrug Resistant Infections Treated with Colistin

Variables Categories	No AKI 40 (34.8%)	AKI 75 (65.2%)	p-value
Age			0.69
- Mean ± standard deviation	41.68 ± 16.30	43.15 ± 15.06	
Sex			
- Male	26 (32.9%)	53 (67.1%)	0.42
- Female	14 (38.9%)	22 (61.1%)	
Comorbidity			
- No	23 (31.5%)	50 (68.5%)	0.33
- Yes	17 (40.5%)	25 (59.5%)	
Diagnosis			0.29
- Solid malignancy	21 (30.9%)	47 (69.1%)	
- Hematological malignancy	19 (40.4%)	28 (59.6%)	
Indication of colistin			
- Suspected	10 (32.3%)	21 (67.7%)	0.73
- Confirmed	30 (35.7%)	54 (64.3%)	
Patient status			
- Alive	31 (50.8%)	30 (49.2%)	0.001
- Death	9 (16.7%)	45 (83.3%)	
Need for renal replacement therapy			
- No	40 (40.0%)	60 (60.0%)	0.002
- Yes	0 (0.0%)	15 (100.0%)	

Table 3: Risk Factors of Colistin-induced Acute Kidney Injury in Cancer Patients with Multidrug Resistant Infections

Variables Categories	Unadjusted OR (CI), p-value	Adjusted OR (CI), p-value
Weight (kg)		
- Mean weight	1.01 (1.01 1.07), 0.01	1.04 (1.01 1.10), 0.03
Diagnosis		
- Hematological	**Ref**	**Ref**
- Solid	1.52 (0.70 3.30), 0.29	3.39 (1.15 9.98), 0.02
ICU admission		
- No	**Ref**	**Ref**
- Yes	3.98 (1.76 9.01), 0.001	2.75 (1.00 7.82), 0.05

associated nephrotoxicity remains a concern. It is believed to exert its nephrotoxic effect by causing acute tubular necrosis.[5] It is excreted in urine via glomerular filtration followed by tubular reabsorption with less than 5% of the daily dose actually being excreted, which leads to accumulation within the proximal tubular epithelial cells.[6] This effect has been studied previously with a wide range of nephrotoxicity being observed, between 10.9% and 69%.[7,8,9,10] This difference could be attributed to different dosage, colistin preparation used and the criteria used to determine incidence of acute kidney injury. In a study conducted in patients with hematological malignancy by Durakovic *et al*, no statistically significant difference was found between the colistin treatment group and the control group in serum creatinine level.[11] This has led to the recent understanding that colistin might not be as nephrotoxic as has previously been reported.[11] So far the most commonly studied risk factors are age,[13] hypoalbuminemia, hyperbilirubinemia, concomitant nephrotoxic agents, cumulative dose and duration of colistin.[14,15,16] Another limiting factor in truly assessing/analyzing colistin-induced nephrotoxicity is the criteria being used, with some studies using RIFLE criteria and others, KDIGO criteria.

In a prospective observational study conducted in non-cancer population by Seroli *et al* in Barcelona, incidence of AKI was found to be 51.9% with renal recovery in 62.3% patients and factors reported to predispose to acute kidney injury included older age, concomitant use of other nephrotoxic drugs (including NSAIDs, loop diuretics) and higher cumulative dose of colistin.[4] In our study, we did not find a significant correlation between colistin related nephrotoxicity and age, gender or simultaneous use of other potentially nephrotoxic agents including antibiotics (most common ones used in our study population were vancomycin, meropenem, amphotericin) and chemotherapeutic agents (including cisplatin and methotrexate). In a retrospective study conducted at Malaysia, no correlation was found between renal injury and age, gender or route of administration.[17] In another multicenter study conducted in non-cancer population, the incidence of colistin induced nephrotoxity, using KDIGO criteria was found to be 34.30% with the significant risk factors being baseline serum creatinine, colistin dose and concomitant use of loop diuretics.[7] While in another prospective study conducted, older age was found to be a risk factor for AKI.[18] There are only a few studies done in cancer population. In one retrospective study conducted in solid organ transplant recipients, low rate of nephrotoxicity was observed while in another it was higher in those given a loading dose of colistin.[19,20] In view of variations in the results, further case control studies are required to validate these results to truly establish colistin-induced nephrotoxicity.

Important limitation of our study is the retrospective design, lack of a control group, and lack of renal histology. The latter was associated with various factors including limited available clinical opportunities to perform a diagnostic kidney biopsy, risk of delay in treatment of sepsis, uncertain benefit of diagnostic kidney biopsy to alter clinical management, cytopenias in patients with haematological malignancies or those had received chemotherapy or cytoreductive treatments in recent weeks.

Conclusion

In conclusion, incidence of AKI was significantly higher in overweight patients with solid organ tumors admitted to ICU and a higher mortality was observed in the patients affected with acute kidney injury.

These observations highlight the nephrotoxic potential of colistin associated with poor patient outcome, requiring a low threshold to identify and address the decline in renal function. It is vital that the clinicians work in close liaison with nephrology and infectious disease specialists to devise an effective management plan including appropriate choice of antibiotics, source control, identification of all the factors contributing to nephrotoxicity

and attempts to foster early arrest of acute kidney injury to ensure favorable clinical outcome.

References

1. Palevsky, Paul M., *et al*. "KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury." *Am J Kidney Dis* 61.5 (2013): 649-672.
2. Hawkey, Peter M., *et al*. "Treatment of infections caused by multidrug resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/healthcare Infection Society/british Infection Association Joint Working Party." *J Antimicro Chemo* 73. suppl_3 (2018): iii2-iii78.
3. Bassetti, Matteo, *et al*. "Treatment of infections due to MDR Gram negative bacteria." *Frontiers in Medicine* 6 (2019).
4. Li, Jian, *et al*. "Evaluation of colistin as an agent against multi-resistant Gram-negative bacteria." *Int'l J Antimicro Agents* 25.1 (2005): 11-25.
5. Gai, Zhibo, *et al*. "Molecular mechanisms of colistin-induced nephrotoxicity." *Molecules* 24.3 (2019): 653.
6. Sandri, Ana M., *et al*. "Population pharmacokinetics of intravenous polymyxin B in critically ill patients: implications for selection of dosage regimens." *Clin. Infec Dis* 57.4 (2013): 524-531.
7. Gul, Serdar, *et al*. "Risk factors for colistin-associated acute kidney injury: a multicenter study from Turkey." *Jap J Infec Dis* 69.2 (2016): 109-112.
8. Justo, Julie Ann, and John A. Bosso. "Adverse reactions associated with systemic polymyxin therapy." *Pharmacotherapy: J Human Pharmacology and Drug Therapy* 35.1 (2015): 28-33.
9. Pintado, Vicente, *et al*. "Intravenous colistin sulphomethate sodium for therapy of infections due to multidrug-resistant gram-negative bacteria." *Journal of Infection* 56.3 (2008): 185-190.
10. Hartzell, Joshua D., *et al*. "Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center." *Clin. Infec Dis* 48.12 (2009): 1724-1728.
11. Durakovic, Nadira, *et al*. "Efficacy and safety of colistin in the treatment of infections caused by multidrug-resistant Pseudomonas aeruginosa in patients with hematologic malignancy: a matched pair analysis." *Internal Medicine* 50.9 (2011): 1009-1013.
12. Kallel, Hatem, *et al*. "Colistin as a salvage therapy for nosocomial infections caused by multidrug-resistant bacteria in the ICU." *Int'l J Antimicro Agents* 28.4 (2006): 366-369.
13. Al-Abdulkarim, Dalal A., *et al*. "Colistin-induced Nephrotoxicity in a Tertiary Teaching Hospital." *Saudi J Kidney Dis and Transp* 31.5 (2020): 1057.
14. Rocco, Monica, *et al*. "Risk factors for acute kidney injury in critically ill patients receiving high intravenous doses of colistin methanesulfonate and/or other nephrotoxic antibiotics: a retrospective cohort study." *Critical care* 17.4 (2013): R174.
15. Pogue, Jason M., *et al*. "Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system." *Clin Infec Dis* 53.9 (2011): 879-884.
16. Kim, Jieun, *et al*. "Clinical characteristics and risk factors of colistin induced nephrotoxicity." *Int'l J Antimicro Agents* 34.5 (2009): 434-438.
17. Rasidin, Rashizal Sazli Mohd, *et al*. "Colistin-associated nephrotoxicity among patients in intensive care units (ICU) of hospitals in Selangor." *Med J Malaysia* 72.2 (2017): 101.
18. Durante-Mangoni, Emanuele, *et al*. "Acute kidney injury during colistin therapy: a prospective study in patients with extensively-drug resistant Acinetobacter baumannii infections." *Clin Micro and Inf* 22.12 (2016): 984-989.
19. Neyra, K., *et al*. "Colistin (COL) in Solid Organ Transplant Recipients (SOTR): Friend or Foe?." *Am J Transp* Vol. 18. 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY, 2018.
20. Katip, Wasan, Suriyon Uitrakul, and Peninnah Oberdorfer. "Clinical outcomes and nephrotoxicity of colistin loading dose for treatment of extensively drug-resistant Acinetobacter baumannii in cancer patients." *Infection and Drug Resistance* 10 (2017): 293.
21. Phe, Kady, *et al*. "Predicting the risk of nephrotoxicity in patients receiving colistimethate sodium: a multicentre, retrospective, cohort study." *J Antimicro Chemo* 71.12 (2016): 3585-3587.