Retrospective Study of Nephrotoxicity Rate among Adult Patients Receiving Colistin Compared to β-lactam Antibiotics

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ABSTRACT

Purpose: Patients receiving colistin for carbapenem-resistant gram-negative bacteria (CR-GNB) infections generally have multiple risk factors for nephrotoxicity, so it might be possible that colistin may be erroneously blamed for the nephrotoxicity.

Materials and methods: We retrospectively analyzed case records of patients who received colistin and those who received antibiotics other than colistin [carbapenem or β-lactam–β-lactamases inhibitors (βL–βLI)] for gram-negative bacteremia. Those patients with preexisting renal failure and those who received antibiotics for <72 hours were excluded from the study. Nephrotoxicity was assessed using the risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, end-stage kidney disease (RIFLE) criteria.

Results: Out of the 222 patients, the colistin arm had 118 and the noncolistin arm had 104 patients. Even though the colistin arm had significantly higher number of sicker patients with neutropenia (40.7% vs 14.4%, $p = 0.0001$), mechanical ventilation (0.0001), having lines (0.0001), on inotropes (0.003), receiving other nephrotoxic drugs (0.0001), and higher Pitt score ($p = 0.0001$), there was no significant difference in the nephrotoxicity between the two arms (10.2% vs 9.6%, $p = 0.89$). Logistical regression showed a higher Pitt bacteremia score ($p = 0.03$) and a higher Charlson comorbidity index ($p = 0.02$), but not colistin administration ($p = 0.32$), were independently associated with nephrotoxicity.

Conclusion: Administration of colistin was not associated with higher rates of nephrotoxicity than carbapenems or βL–βLI agents.

Keywords: Carbapenem resistance, Colistin nephrotoxicity, Risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, end-stage kidney disease score.

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INTRODUCTION

Global dissemination of CR-GNB has resulted in a significant increase in the usage of colistin and the situation is no different in India.[1,2] Nephrotoxicity has always been a concern with use of colistin. Traditionally, colistin *per se* is considered to be the culprit for nephrotoxicity. Unfortunately, contribution of colistin toward the nephrotoxicity has not been studied in well-controlled properly matched trials. Colistin is generally used in patients who are critically ill with various stages of sepsis, including septic shock. Patients receiving colistin are generally sicker, with multiple other risk factors for nephrotoxicity such as severe sepsis and coadministration of other nephrotoxic drugs. Acute kidney injury (AKI) is common in sepsis and is independent of the drugs used to treat sepsis.[3] So, it is possible that the nephrotoxicity rate of colistin is overestimated. There is a remarkable variation in the reported rates of nephrotoxicity associated with colistin use (0–53%), due to lack of proper definition of nephrotoxicity, proper control group, and unmatched risk factors.[4] The concern of nephrotoxicity leads to underdosing of colistin that in turn leads to poor outcomes and colistin resistance. So, it is need of the hour to delineate the nephrotoxicity risk due to colistin usage *per se*, in critically ill patients where other contributing factors including concomitant nephrotoxic drugs are used. With this aim, we designed our study to assess the risk of nephrotoxicity, as defined by the RIFLE classification system,[5] in patients receiving colistin while compared to those not receiving colistin.

MATERIALS AND METHODS

This was a retrospective study done in an oncology center in South India. We analyzed medical records of patients with GNB bacteremia

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who received colistin or antibiotics other than colistin (carbapenem or βL–βLI) during period of January 2014–July 2017.

Only those patients of age ≥18 years who received antibiotics for ≥72 hours were included in the study. Patients with preexisting renal failure or chronic kidney disease and those who received antibiotics for <72 hours were excluded. Demographic details, underlying diagnosis, concomitant use of other nephrotoxic agents (amphotericin B, aminoglycosides, cyclosporine, acyclovir, vancomycin, cyclophosphamide, methotrexate, cisplatin, nonsteroidal anti-inflammatory medications, diuretics, and intravenous contrast), and dose and duration of colistin were collected. Creatinine values before initiation of colistin, during, and at the end of treatment were tracked. Nephrotoxicity was assessed using the RIFLE criteria.

Patients were divided into colistin and noncolistin groups. Patients who received colistin alone or in combination with other antibiotic were included in the colistin arm, whereas, those patients who received antibiotics other than colistin (carbapenem or βL–βLI) were included in the noncolistin arm. Comparative analyses of various parameters, univariate and multivariate logistic regression analysis, using abnormal RIFLE as the dependent variable were performed using SPSS 25.0. All p values <0.05 were considered as statistically significant.

RESULTS

A total of 222 patients met the inclusion criteria and their records were analyzed. The colistin arm had 118 patients and the non-colistin arm had 104 patients (Table 1). In the noncolistin arm, 80 patients received cefoperazone–sulbactam and 24 patients received meropenem. Patients in the colistin arm were significantly younger than in noncolistin arm (44.6 ± 18.2 vs 51.6 ± 18.9 years; $p = 0$–005). There was no significant difference in distribution of gender between the two arms. Patients belonging to the colistin arm were more likely to have hematological (49/118 vs 23/104; $p < 0.05$) and neurosurgical (29/118 vs 2/104; $p < 0.05$) conditions as their basic disease compared to patients in the noncolistin arm; whereas solid organ malignancies were more common in the non-colistin arm (33/118 vs 65/104; $p < 0.05$).

Pneumonia (21/118 vs 10/104; $p < 0.05$), meningitis (4/118 vs 0/104; $p < 0.05$), skin/soft tissue infection (3/118 vs 2/104; $p < 0.05$), line-related bacteremia (17/118 vs 7/104; $p < 0.05$), and gut translocation (36/118 vs 21/104; $p < 0.05$) as the source of bacteremia were significantly higher in the colistin arm as compared to the non-colistin arm. Intra-abdominal infection (9/118 vs 32/104; $p < 0.05$), urinary tract infection (16/118 vs 32/104; $p < 0.05$), and unknown focus (10/118 vs 10/104; $p < 0.05$) as the source of bacteremia were significantly higher in the noncolistin arm.

Distribution of comorbidities like diabetes mellitus, hypertension, chronic liver disease, and heart failure was comparable between the two arms. Presence of an immunocompromised state (60/118 vs 13/104; $p < 0.05$), mechanical ventilation (61/118 vs 19/104; $p < 0.05$), neutropenia (48/118 vs 15/104; $p < 0.05$), central lines (59/118 vs 20/104; $p < 0.05$), urinary catheter (40/118 vs 11/104; $p < 0.05$), surgery (48/118 vs 11/104; $p < 0.05$), admission in critical care unit at the time of bacteremia (71/118 vs 16/104; $p < 0.05$), and inotropic requirement (40/118 vs 17/104; $p < 0.05$) was significantly higher in the colistin arm as compared to the noncolistin arm. Use of chemotherapeutic agents and diuretics was comparable in both arms. Significantly more number of patients in the colistin arm

Table 1: Distribution of various variables of the two study groups

Categories	Colistin arm (n = 118)	Noncolistin arm (n = 108)	p value
Age (mean ± 2SD) in years	44.6 + 18.2	51.6 + 18.9	0.005
Male *n* (%)	72 (61)	52 (50)	0.099
Basic diagnosis			
Hematological *n* (%)	49 (41.5)	23 (22.1)	0.0001
Neurosurgical *n* (%)	29 (24.6)	2 (1.9)	
Solid tumors *n* (%)	33 (28)	65 (62.5)	
Others *n* (%)	7 (5.9)	14 (13.5)	
Source of bacteremia			
Meningitis *n* (%)	4 (3.4)	0	0.0001
Pneumonia *n* (%)	21 (17.8)	10 (9.6)	
Intra-abdominal infection *n* (%)	9 (7.6)	32 (30.8)	
Urinary tract infection *n* (%)	16 (13.6)	22 (21.2)	
Soft tissue infection *n* (%)	3 (2.5)	2 (1.9)	
Gut translocation *n* (%)	36 (30.5)	21 (20.2)	
Central line *n* (%)	17 (14.4)	7 (6.7)	
Unknown source *n* (%)	10 (8.5)	10 (9.6)	
Risk factors			
DM *n* (%)	33 (28)	38 (36.5)	0.172
HTN *n* (%)	34 (28.8)	29 (27.9)	0.878
CLD *n* (%)	2 (1.7)	0	0.5
CHD *n* (%)	8 (6.8)	7 (6.7)	0.988
IMC *n* (%)	60 (50.8)	13 (12.5)	0.0001
Neutropenia *n* (%)	40 (40.7)	15 (14.4)	0.0001
Mechanical ventilation *n* (%)	61 (51.7)	19 (18.3)	0.0001
Central line *n* (%)	59 (50)	22 (21.2)	0.0001
Urinary catheter *n* (%)	40 (33.9)	11 (10.6)	0.0001
ICU admission during bacteremia *n* (%)	71 (61.2)	16 (15.4)	0.0001
Chemotherapy *n* (%)	44 (37.3)	33 (31.7)	0.385
Surgery *n* (%)	48 (40.7)	11 (10.6)	0.0001
Diuretics *n* (%)	31 (26.3)	20 (19.2)	0.213
Inotropes *n* (%)	40 (33.9)	17 (16.3)	0.003
Nephrotoxic drugs (%)	31 (26.3)	8 (7.7)	0.0001
APACHE score (mean ± 2SD)	20.2 + 7.3	17 ± 7.6	0.044
Charlson comorbidity index (mean ± 2SD)	4.7 + 2.9	4.6 + 2.7	0.721
Pitt bacteremia score (mean ± 2SD)	3.2 + 2.2	1.9 + 1.9	0.0001
Outcomes			
All-cause mortality at 30 days *n* (%)	39 (33.1)	20 (19.2)	0.02
Abnormal RIFLE *n* (%)	12 (10.2)	10 (9.6)	0.89

received other nephrotoxic agents as compared to the non-colistin arm (31/118 vs 8/104; $p < 0.05$).

The mean dose, mean duration, and cumulative dose of colistin used were 8.54 ± 1.08 million units/day, 8.10 ± 4.63 days, and 69.02 million units, respectively. Patients in the colistin arm had significantly higher acute physiology, age, chronic health evaluation (APACHE) (20.7 ± 7.3 vs 17 ± 7.6, $p = 0.04$) and Pitt bacteremia (3.2 ± 2.2 vs 1.9 ± 1.9; $p < 0.05$) scores in comparison to those

in the non-colistin arm. The Charlson comorbidity index was not significantly different between the two groups. Distribution of patients with abnormal RIFLE was not significantly different between the two groups (12/118 vs 10/104; $p = 0.89$). At 30 days, significantly higher number of patients died in the colistin arm as compared to the noncolistin arm (39/118 vs 20/104; $p = 0.02$).

On univariate logistic regression analysis, male sex (OR = 3.5; 95% CI = 1.05–11.65, $p = 0.04$), and the higher Charlson comorbidity index of ≥ 4 (OR = 8.64; 95% CI = 1.63–45.57; $p = 0.01$) were associated with abnormal RIFLE. On multivariate logistic regression analysis, higher Pitt bacteremia score of ≥ 3 (OR = 3.35; 95% CI = 1.11–9.91; $p = 0.03$) and higher Charlson comorbidity index of ≥ 4 (OR = 5.52; 95% CI = 1.11–9.91; $p = 0.02$) were the only variables independently associated with nephrotoxicity (Table 2). Other parameters like diabetes, age, hypertension, and use of nephrotoxic drugs were not independent risk factors for the development of abnormal RIFLE. Colistin administration *per se* was not an independent risk factor for nephrotoxicity ($p = 0.32$).

DISCUSSION

Though the conundrum of monotherapy vs combination therapy is not yet resolved, colistin is undoubtedly the backbone of the therapeutic approach against CR-GNB infections.[6] Colistin, a drug introduced in 1960s, later went out of use in 1970s due to its high rate of nephrotoxicity and due to the availability of newer and less nephrotoxic drugs.[7] Global dissemination of CR-GNB has helped colistin to attain the status of an indispensable agent in critical care units. Reported rates of nephrotoxicity vary widely (0–60%) among studies.[8,9] Variability in the criteria used to define nephrotoxicity could be one of the reasons behind this. Compared to older studies, more recent ones report lower rates of nephrotoxicity. This could be due to less impurities present in the newer colistin preparations and better understanding of fluid management strategies in septic patients in modern intensive care units.[4,10–12] The nephrotoxicity rate in a recently published study from our own center was 13.3%.[12]

Concomitant use of vancomycin, abnormal baseline creatinine, ICU stay, and higher disease severity were associated with higher rates of nephrotoxicity in patients on colistin.[12]

Sepsis *per se* is a well-defined independent risk factor for the development of AKI.[3] Acute kidney injury develops in 51% of patients having septic shock with blood culture positivity.[3] Gram-negative sepsis has been proven to be an independent risk factor of AKI in ICUs.[13] Proinflammatory cytokines are released on exposure to lipopolysaccharide, leading to intrarenal vasoconstriction and a reduction in the glomerular filtration rate.[14] Sepsis and gram-negative bacteremia, two factors independently associated with the development of AKI, are present in most patients receiving colistin.

Exact mechanism of nephrotoxicity is not known but polymyxins cause damage to kidneys at the level of proximal tubules and can be directly toxic to mammalian urothelium.[15] One of the main reasons for the wide variability in the rates of nephrotoxicity is the difference in definition of renal failure used in various studies. The RIFLE criteria detect AKI with high sensitivity and high specificity and also predict prognosis of the patients.[5] Most studies reporting high colistin nephrotoxicity rates had methodological defects such as absence of control groups and not considering sepsis and its severity as potential confounding factors.[16–19] Acute kidney injury is common in septic shock and it may potentiate or lead to overestimation of nephrotoxicity rates of any drug.[20] A study done by Rocco et al. reported that the onset of AKI was two times more likely with SAPS II scores ≥ 44 and six times more likely with presence of septic shock at infection onset and was independent of colistin use.[21] A meta-analysis on six controlled studies comparing colistin vs other antibiotics for treatment of ventilator associated pneumonia (VAP) suggested that the nephrotoxicity rate for colistin was similar to that in the control group.[22] As per the NEFROINT multicenter study from Italy, 40% of the patients admitted to ICU with a normal renal function at the time of admission developed AKI regardless of whether or not nephrotoxic drugs were administered.[23] However, a large single-center prospective cohort study from Israel reported

Table 2: Univariate and multivariate regression analysis between normal and abnormal RIFLE

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	p value	Odds ratio	95% confidence interval	p value
Sex	3.50	1.05–11.65	0.04	2.75	0.93–8.10	0.066
ICU admission during bacteremia	1.43	0.37–5.47	0.60			
DM	1.93	0.56–6.64	0.29			
HTN	0.38	0.10–1.39	0.14	0.41	0.13–1.27	0.12
IMC	1.49	0.39–5.69	0.55			
Chemotherapy	0.51	0.14–1.86	0.31			
Surgery	2.05	0.44–9.47	0.35			
Neutropenia	0.90	0.23–3.51	0.88			
Diuretics	2.24	0.59–8.49	0.23	2.62	0.67–7.59	0.18
Nephrotoxic drugs	1.61	0.33–7.83	0.55			
Inotropes	0.46	0.11–1.83	0.27			
Central line	0.64	0.21–1.98	0.44			
Urinary catheter	1.50	0.37–6.38	0.56			
Colistin/noncolistin	1.22	0.32–4.57	0.76	0.59	0.20–1.69	0.32
Charlson comorbidity index	8.64	1.6–45.57	0.01	5.52	1.26–24.09	0.02
Pitt bacteremia score	2.35	0.53–10.27	0.25	3.32	1.11–9.91	0.03
Age	0.41	0.10–1.70	0.22	0.41	0.11–1.41	0.17

higher nephrotoxicity in the colistin arm compared to patients receiving β-lactam antibiotics.[24]

In our study, the rate of kidney injury in the colistin arm was 10.2%, marginally lower than an earlier report (13.3%) from our own center and rather lower in comparison to the 16–35% reported in other Indian studies.[8,12,25,26] None of these studies, including our own earlier one, had a comparative arm with patients not receiving colistin. To the best of our knowledge, this is the first study from India comparing the nephrotoxicity in patients receiving colistin to those not receiving colistin. Even though patients in the colistin arm were sicker, with higher APACHE and Pitt bacteremia scores, greater number of patients with neutropenia, and on mechanical ventilation, nephrotoxicity was not significantly different in both arms (10.2% vs 9.6%, $p = 0.89$) indicating that colistin administration doesn't increase the nephrotoxicity risk compared to carbapenem or βL–βLI agents. On logistic regression analysis, higher Charlson comorbidity index and Pitt bacteremia score were the only independent variables for abnormal RIFLE. Colistin administration was not independently associated with the development of abnormal RIFLE, despite receiving the current dosing recommendation of 9 million a day. The result of our study should encourage clinicians to administer the recommended colistin dose, without any fear of nephrotoxicity. Major limitation of our study is its retrospective single-center design. Inclusion of a comparator arm and a large cohort of patients should be considered strengths of this study. Prospective randomized controlled trials are need of the hour.

Conclusion

In our single-center retrospective comparative cohort study, there was no statistically significant difference in nephrotoxicity in patients receiving colistin compared to those who received a β-lactam antibiotic such as a βL–βLI agent or carbapenem. Higher Pitt bacteremia score and Charlson comorbidity index were independent risk factors for the development of abnormal RIFLE. Colistin administration was not independently associated with nephrotoxicity.

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