Research Article

Colistin Nephrotoxicity in Adults: Single Centre Large Series from India

Abdul Ghafur, Swati Gohel, Vidyalakshmi Devarajan, T. Raja[1], Jose Easow[1], M. A. Raja[1], Sankar Sreenivas[1], Balasubramaniam Ramakrishnan[2], T. Ramakrishnan[2], S. G. Raman[1], Dedeepiya Devaprasad[3], Balaji Venkatachalam[3], Ramesh Nimmagadda[1]

Departments of Infectious Diseases, [1]Oncology, [2]Statistics and [3]Intensive Care, Apollo Cancer Institute, Chennai, Tamil Nadu, India

Abstract

Context: Limited Indian data are available on the rate of colistin nephrotoxicity and other risk factors contributing to the development of this important side effect. **Aim:** This study aims to generate data on colistin nephrotoxicity from a large cohort of Indian patients. **Design:** Retrospective cohort study. **Materials and Methods:** Case record analysis of patients who received colistin, in an oncology center in India, between January 2011 and December 2015. Nephrotoxicity was assessed using risk, injury, failure, loss, and end-stage (RIFLE) criteria. **Statistical Analysis:** $P < 0.05$ was considered as statistically significant. **Results:** Out of the 229 patients, 13.1% (30/229) developed abnormal RIFLE. Abnormal RIFLE group ($n = 30$), in comparison to the normal renal function group ($n = 199$), had higher number of patients in intensive care unit (ICU) (96% vs. 79%, $P = 0.02$), higher Acute Physiology and Chronic Health Evaluation (APACHE II) score (23 vs. 19 $P = 0.0001$), Charlson score (5.9 vs. 4.3, $P = 0.001$), mechanical ventilation (90% vs. 67%, $P = 0.016$), 28 days mortality (63% vs. 25%, $P = 0.0001$), and abnormal baseline creatinine (36% vs. 8%, $P = 0.001$). Coadministration of vancomycin had higher rates of nephrotoxicity ($P = 0.039$). There was no significant difference in nephrotoxicity between 6 and 9 MU/day dosing pattern (8.8% vs. 13.8%, $P = 0.058$). **Conclusion:** Nephrotoxicity rate in our retrospective single center large series of patients receiving colistin was 13.1%. Patients with abnormal baseline creatinine, ICU stay, and higher disease severity are at higher risk of nephrotoxicity while on colistin. A daily dose of 9 million does not significantly increase nephrotoxicity compared to the 6 million. Concomitant administration of vancomycin with colistin increases the risk of nephrotoxicity.

Keywords: Carbapenem resistance, colistin, nephrotoxicity, risk, injury, failure, loss, and end-stage

Introduction

High prevalence of carbapenem-resistant Gram-negative bacterial (CRGNB) infections has resulted in extensive usage of colistin (colistimethate sodium) in the day-to-day clinical practice in Indian hospitals.[1] Unfortunately, limited data are available on the rate of colistin nephrotoxicity and risk factors contributing to the development of this important side effect in Indian patients. The available publications from the country included small cohorts of patients.[2-4] Overt fear on the high risk of nephrotoxicity, still prevailing among prescribers; may result in colistin underdosing, treatment failure and development of colistin resistance. The scenario may be more complex among intensive care unit (ICU) patients, especially cancer patients; where the concomitant use of other nephrotoxic agents, is common.[2]

The aim of our study was to ascertain the rate of nephrotoxicity and contributing factors in a large cohort of Indian patients treated with colistin.

Access this article online

Quick Response Code:

Website: www.ijccm.org

DOI: 10.4103/ijccm.IJCCM_140_17

Materials and Methods

This is a retrospective analysis from a single tertiary care onco-hematology center in India. We analyzed medical records of adult patients with CRGNB infections treated with colistin, between January 2011 and December 2015.

Only those patients of age >18, who received colistin for >72 h were included in the study. Those patients with preexisting renal failure and those who received colistin for <72 h were excluded. Demographic details, underlying diagnosis, concomitant use of other nephrotoxic agents (amphotericin B, aminoglycosides, cyclosporine, acyclovir,

Address for correspondence: Dr. Abdul Ghafur, Apollo Cancer Institute, Padma Complex, 320 Anna Salai, Chennai - 600 035, Tamil Nadu, India. E-mail: drghafur@hotmail.com

How to cite this article: Ghafur A, Gohel S, Devarajan V, Raja T, Easow J, Raja MA, *et al*. Colistin nephrotoxicity in adults: Single centre large series from India. Indian J Crit Care Med 2017;21:350-4.

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 risk, injury, failure, loss, and end-stage kidney disease (RIFLE) criteria [Table 1]. Statistical analysis was performed using SPSS 16.0. All $P < 0.05$ was considered as statistically significant.

Results

Details of 250 patients were analyzed. Twenty-one patients out of the 250 had a preexisting renal failure, so were excluded from the study. Out of the 229 patients who satisfied the study criteria, 79 (34.5%) were treated for bacteremia, pneumonia (42%), urinary tract infection (7.4%), soft tissue infection (7.9%), central nervous system infection (1%), and other entities (8%). The patients' demographic and clinical characteristics are listed in Table 2.

Out of 229 patients, 13.1% (30/229) developed abnormal RIFLE during colistin therapy. Out of the 30 patients, 15 developed risk (R), 5 - injury (I), and 10 - failure (F). None of the patients developed loss of function (L) or end-stage disease. Abnormal RIFLE group ($n = 30$), in comparison to the normal renal function group ($n = 199$), had higher number of patients in ICU (96% vs. 79%, $P = 0.02$), higher Acute Physiology and Chronic Health Evaluation (APACHE II) score (23 vs. 19, $P = 0.0001$), Charlson score (5.9 vs. 4.3, $P = 0.001$), mechanical ventilation (90% vs. 67%, $P = 0.016$), 28 days mortality (63% vs. 25%, $P = 0.0001$), and abnormal baseline creatinine (36% vs. 8%, $P = 0.001$). Other baseline parameters were similar in both groups, including daily colistin dose (8.7 vs. 8.5 MU/day, $P = 0.42$), duration (9.1 days vs. 9.3 days, $P = 0.47$), and cumulative colistin dose (79 vs. 78, $P = 0.58$). There was no statistically significant difference in the rate of coadministration of lipo-amphotericin B, aminoglycosides, inotropes, and intravenous contrast between the two groups. There was no statistically significant difference in nephrotoxicity between patients who received colistin alone or with one other nephrotoxic agent (26 out of 183 [14.2%] in the colistin alone group and 4 out of 46 [8.7%] in the colistin plus other nephrotoxic agent group had abnormal RIFLE, $P = 0.464$). However, coadministration of vancomycin had higher rates of nephrotoxicity (26 out of 173 with colistin alone [14.2%] had abnormal RIFLE compared to 3 out of 7 [42%] who received colistin and vancomycin $P = 0.039$). There was no difference between 6 and 9 MU/day dosing pattern (with 3/34 [8.8%] in 6 MU group and 27/195 [13.8%] in 9 MU/day group developing nephrotoxicity $P = 0.058$). The 6 million and 9 million groups were comparable in term of ICU stay (88.2%, 80.5%, $P = 0.345$), APACHE score (19.83 ± 5.4, 19.9 ± 6.3, $P = 0.942$), and Charlson scores (4.2 ± 3, 4.6 ± 2.7, $P = 0.516$). In patients with abnormal RIFLE ($n = 30$) developed on colistin therapy, but normal baseline creatinine to start with; the mean number of days taken for the first abnormal RIFLE value was 9 (9 ± 6, median 8 [5–12]) and in those with abnormal baseline creatinine to start with, mean duration was 7 days (7 ± 10, median 3 [2–4]), revealing earlier nephrotoxicity in those patients with abnormal baseline creatinine (but not statistically significant $P = 0.057$). Mean number of days taken for the abnormal RIFLE to normalize from peak value was 14.7 (± 12.2), median 11 (5–27) in the abnormal baseline group and 9.4 (± 7.5, median 7 [3–14]) in the normal baseline group, denoting numerically longer time for creatinine normalization from peak creatinine value, in the abnormal baseline group compared to normal baseline group (but not statistically significant $P = 0.412$). Mortality was significantly higher in the abnormal RIFLE group, compared to patients with normal renal function (63.3%, 25.5%, $P = 0.0001$).

Table 1: Risk, injury, failure, loss, and end-stage kidney disease (RIFLE) criteria for diagnosis of nephrotoxicity

Category	Criteria
Risk (R)	GFR decreased by 25% or increased creatinine level × 1.5
Injury (I)	GFR decreased by 50% or increased creatinine level × 2
Failure (F)	GFR decreased by 75% or increased creatinine level × 3, or creatinine level >4 mg/dL
Loss of function (L)	Complete loss of renal function for >4 weeks
End stage (E)	Complete loss of renal function >3 months

GFR: Glomerular filtration rate

Discussion

Colistin is the most reliable and most frequently used antibiotic to treat CRGNB infections. Increasing rates of these infections and the familiarity and confidence in using colistin, a drug otherwise known to be nephrotoxic, have indeed made this molecule a day to day option in health-care institutions across the world, especially in countries like India with a high prevalence of CRGNB infections.[2] Renewed interest and research on this old molecule have led to better understanding on the pharmacokinetics-pharmacodynamic and optimal dosing. Rates of nephrotoxicity vary widely among studies, with values of <10% to high rates of 60%.[5-11] Such a wide variation could be due to variability in the criteria used to define nephrotoxicity and various dosing regimens of colistin used.[6] Compared to older studies, the more recent ones report lower rates of nephrotoxicity. This could be due to the availability of more purified forms of colistin and clinicians handling this molecule in a better way with proper renal dose adjustment, avoiding concurrent nephrotoxic drugs and the overall improvement in intensive care management.[5,6]

The largest published single-center cohort study to date on colistin nephrotoxicity, by Falagas *et al*. that retrospectively investigated 258 patients with microbiologically documented infection reported 10% nephrotoxicity.[6] Limited data are available on the rate of colistin nephrotoxicity in Indian population. A recent publication from Mumbai Desai *et al*.[4]

Table 2: Patient demographics

Categories	Abnormal RIFLE *n*=30(%)	Normal RIFLE *n*=199(%)	*P*
Age	53.40±13.28	47.71±15.9	0.067
Group			
Bacteremia	11 (36.7)	68 (34.2)	0.789
Non-Bacteremia	19 (63.3)	131 (65.8)	
Sex			
Male	22 (73.3)	139 (69.8)	0.697
Female	8 (26.7)	60 (30.2)	
Underlying condition			
Haemato-oncology	5 (16.7)	36 (18.1)	0.574
Neurosurgery	12 (40.0)	77 (38.7)	
Solid tumours	8 (26.7)	68 (34.2)	
Others	5 (16.7)	18 (9.0)	
Clinical diagnosis			
Bacteremia	11 (36.7)	68 (34.2)	0.947
Pneumonia	14 (46.7)	82 (41.2)	
UTI	1 (3.3)	16 (8.0)	
Soft Tissue Infection	2 (6.7)	16 (8.0)	
Tracheitis	2 (6.7)	13 (6.5)	
Menigitis	0 (0.0)	2 (1.0)	
Intra-Abdo Infection	0 (0.0)	2 (1.0)	
Abnormal baseline creatinine			
Yes	11 (36.7)	16 (8.0)	0.001
ICU stay			
Yes	29 (96.7)	158 (79.5)	0.02
Surgery			
Yes	15 (50.0)	114 (57.3)	0.55
Mechanical ventilation			
Yes	27 (90.0)	135 (67.8)	0.016
Corticosteroid			
Yes	13 (43.3)	86 (43.2%)	0.99
Chemotherapy			
Yes	6 (20.0)	39 (19.6)	0.959
Period of Neutropenia (Days)			
N <5	2 (6.7)	9 (4.5)	0.641
N 5-10	0 (0.0)	2 (1.0)	1.000
N >10	6 (20.0)	24 (12.1)	0.230
Mucositis			
Yes	5 (16.7)	18 (9.0)	0.195
Lines			
Yes	15 (50.0)	97 (48.7)	0.898
Foleys			
Yes	17 (56.7)	112 (56.3)	0.968
Outcome 28 Days			
Death	19 (63.3)	50 (25.1)	0.0001
Alive	11 (36.7)	11 (74.9)	
AB (lipo- ampho B)			
Yes	5 (16.7)	23 (11.6)	0.426
AG (aminoglycosides)			
Yes	3 (10.0)	17 (8.5)	0.732
Inotropes			
Yes	12 (40.0)	57 (28.6)	0.206
IV contrast			
Yes	3 (10.0)	33 (16.6)	0.433

Contd...

Table 2: Contd...

Categories	Abnormal RIFLE *n*=30(%)	Normal RIFLE *n*=199(%)	*P*
Colistin alone	26 (14.2)	183	0.039
Colistin + Vancomycin	3 (42.7)	7	
Colistin alone	26 (14.2)	183 (90.6)	*P*=0.479
Colistin + L-Amphotericin B	1 (5.3)	19 (9.4)	
Colistin alone	26 (14.2)	183	
Colistin + Aminoglycosides	0 (0)	9	*P*=0.612
Colistin Dose (MU/day)	8.7±0.92	8.51±1.2	0.42

RIFLE: Risk, injury, failure, loss, and end-stage kidney disease; APACHE: Acute Physiology and Chronic Health Evaluation; IV: Intravenous; ICU: Intensive Care Unit; UTI: urinary tract infection

reported 35.89% incidence of nephrotoxicity as per RIFLE criteria, whereas the other available publication Dewan and Shoukat 2014 quoted a rate of 16.12%.[3] We could track only two other publications from India, and both were on polymyxin B nephrotoxicity; (18.7%) by Nandha *et al*. 2013 and (4%) by Ramasubban *et al*. 2008.[12,13]

To the best of our knowledge, the current paper represents the largest Indian and the second largest global data on the rate of nephrotoxicity in patients receiving colistin. The nephrotoxicity rate in our study of 229 patients on colistin therapy was 13.1%. Patients with renal impairment belonged to the category of risk, injury or failure and none developed loss of function or end stage renal disease. Patients in the abnormal RIFLE group had significantly higher number of patients with abnormal baseline creatinine (36.7%) to start with compared to normal RIFLE group (8%) ($P = 0.001$). This finding is in tune with other studies where the incidence of nephrotoxicity was 2.5–7-fold higher in patients with baseline renal dysfunction.[5-7]

In patients who developed abnormal RIFLE on colistin therapy; mean number of days taken for the development of the first abnormal RIFLE value was 7 in patients with abnormal baseline to start with, in contrast to 9 days in patients with normal baseline creatinine; revealing earlier nephrotoxicity in those patients with abnormal baseline creatinine (but not statistically significant $P = 0.057$). The time taken for the abnormal RIFLE to normalize from the peak creatinine value was also numerically longer in abnormal baseline group (mean 14.7 compared to 11 in the normal baseline group, $P = 0.412$). Abnormal RIFLE group, in comparison to the normal renal function group, had higher number of patients in Intensive care, on mechanical ventilation, higher APACHE II score, Charlson score and 28 days mortality. Other baseline parameters were similar in both groups, including daily colistin dose (8.7 vs. 8.5 MU/day, $P = 0.42$), duration (9.1 days vs. 9.3 days, $P = 0.47$), and cumulative colistin dose. The nephrotoxicity rate of 13.1% may not necessarily be due to colistin alone but contributed by other factors. The exact contribution of colistin toward the nephrotoxicity can be ascertained only if we have a comparable control group who did not receive colistin.

In the present study, there was no statistically significant difference in the rate of nephrotoxicity between patients who received colistin and those who received one of the other nephrotoxic agents such as lipo-amphotericin B, aminoglycosides, inotropes or intravenous contrast as well. However, coadministration of colistin with vancomycin resulted in higher rate of nephrotoxicity ($P = 0.039$).

Conclusion

Nephrotoxicity rate in our large single-center retrospective series of patients was 13.1%. Patients with abnormal baseline creatinine, ICU stay and higher disease severity are at higher risk of nephrotoxicity while on colistin. Daily dose of 9 million does not significantly increase nephrotoxicity compared to the 6 million dosing pattern. Concomitant administration of vancomycin with colistin increases the risk of nephrotoxicity.

Financial support and sponsorship

The study was carried out with the research grant from Glenmark Pharmaceuticals, as an investigator-initiated study. The design or data collection of the study and the content of the paper are in no way influenced by the grant provider.

Conflicts of interest

There are no conflicts of interest.

References

1. Ghafur A, Gohel S, Vidyalakshmi PR, Raj R. A retrospective study on colistin nephrotoxicityin pediatric onco-hematology patients. J Pediatr Infect Dis 2015;10:103-7.
2. Ghafur A, Vidyalakshmi PR, Murali A, Priyadarshini K, Thirunarayan MA. Emergence of pan-drug resistance amongst gram negative bacteria! The first case series from India. JMID 2014;4:86-91.
3. Dewan A, Shoukat M. Evaluation of risk of nephrotoxicity with high dose, extended-interval colistin administration. Indian J Crit Care Med 2014;18:427-30.
4. Desai K, Kazi M, Ajbani K, Munshi M, Rodrigues C, Soman R, *et al*. Clinical outcomes and safety of colistin in treatment of gram negative infections: A prospective observational study. Egypt J Crit Care Med 2016;4:67-72.
5. Falagas ME, Kasiakou SK. Toxicity of polymyxins: A systematic review of the evidence from old and recent studies. Crit Care 2006;10:R27.
6. Falagas ME, Rafailidis PI, Ioannidou E, Alexiou VG, Matthaiou DK, Karageorgopoulos DE, *et al*. Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: A retrospective cohort study of 258 patients. Int J Antimicrob Agents 2010;35:194-9.

7. Levin AS, Barone AA, Penço J, Santos MV, Marinho IS, Arruda EA, *et al.* Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Clin Infect Dis 1999;28:1008-11.
8. Michaloupoulos AS, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas ME. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: The renaissance of an old antibiotic. Clin Microbiol Infect 2005;11:115-21.
9. Kasiakou SK, Michalopoulos A, Soteriades ES, Samonis G, Sermaides GJ, Falagas ME. Combination therapy with intravenous colistin for management of infections due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. Antimicrob Agents Chemother 2005;49:3136-46.
10. Koomanachai P, Tiengrim S, Kiratisin P, Thamlikitkul V. Efficacy and safety of colistin (colistimethate sodium) for therapy of infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in Siriraj Hospital, Bangkok, Thailand. Int J Infect Dis 2007;11:402-6.
11. Doshi NM, Mount KL, Murphy CV. Nephrotoxicity associated with intravenous colistin in critically ill patients. Pharmacotherapy 2011;31:1257-64.
12. Nandha R, Sekhri K, Mandal AK. To study the clinical efficacy and nephrotoxicity along with the risk factors for acute kidney injury associated with parenteral polymyxin B. Indian J Crit Care Med 2013;17:283-7.
13. Ramasubban S, Majumdar A, Das PS. Safety and efficacy of polymyxin B in multidrug resistant Gram-negative severe sepsis and septic shock. Indian J Crit Care Med 2008;12:153-7.