

# To study the clinical efficacy and nephrotoxicity along with the risk factors for acute kidney injury associated with parenteral polymyxin B

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## Abstract

**Aim:** The aim of this study was to evaluate the clinical efficacy and nephrotoxicity along with the risk factors for acute kidney injury (AKI) associated with the parenteral polymyxin B in patients with the multidrug resistance (MDR) gram –ve infections in a tertiary Intensive care unit (ICU). **Materials and Methods:** A retrospective cohort study (March 2010-October 2011) was conducted in Medical ICU of a 23 bedded tertiary care hospital in Northern India. **Results:** Out of 71 ICU patients who were administered polymyxin B, only 32 (M:F = 1:0.8) met the inclusion criteria. Patients with concurrent administration of nephrotoxic drugs were excluded from the study. Mean age of patients was  $48.53 \pm 13.90$  years ranging from 16 years to 68 years. 6 out of 32 (18.7%) patients progressed to AKI, whereas renal functions remained normal in 26 (81.2%) patients. No statistically significant difference was observed in mortality between AKI and non AKI patients at the end of therapy (33.3% vs. 26.9%, *P* value 0.756). Older age ( $62.33 \pm 11.90$  vs.  $45.34 \pm 2.45$ , *P* value 0.005) was found to be an independent risk factor for causing nephrotoxicity. **Conclusion:** In the present scenario of rising infections with MDR gram –ve micro-organisms, this pilot study suggests that polymyxin B can be used effectively and safely in patients not receiving other nephrotoxic drugs, with cautious administration in older patients as they are more vulnerable to nephrotoxicity caused by polymyxin B.

**Keywords:** *Acinetobacter baumannii*, acute kidney injury, multidrug resistance gram –ve septicemia, nephrotoxicity, polymyxin B

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**Website:** [www.ijccm.org](http://www.ijccm.org)

**DOI:** 10.4103/0972-5229.120319

**Quick Response Code:**



## Introduction

Multidrug resistance (MDR) is a pandemic emerging globally due to rapidly increasing microbial pathogens resistant to a wide range of antimicrobial agents.<sup>[1-3]</sup> MDR has been identified as the third most important problem of human health by World Health Organization.<sup>[2]</sup> Gram negative pathogens are of major concern with regards to global diffusion of antibiotic resistance, emergence of complex MDR

and pan-resistant phenotypes.<sup>[4]</sup> Gram-negative organisms account for most of the nosocomial infections, including pneumonia, skin infections, intra-abdominal sepsis, urosepsis, and bloodstream infections.<sup>[5]</sup> The implicated gram –ve MDR organisms are presented by a acronym - ESKAPE- *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter*.<sup>[6]</sup>

Gram-negative bacterial resistance increases the burden in the Intensive care unit (ICU) having severe impact in terms of morbidity, mortality and health-care associate costs.<sup>[7]</sup> Treating MDR gram –ve infections especially when it involves critically ill patients is a big clinical challenge. An appropriate use of older antimicrobials agents is the only therapeutic option in the face of the fact that in spite of rapid emergence of gram –ve resistance, no new antimicrobials are in the pipeline to be developed

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during the next decade as noted by the Infectious Diseases Society of America's "Bad Bugs, No Drugs" campaign.<sup>[8]</sup> Intravenous polymyxins (polymyxin B and colistin), an antibiotic class discovered more than 60 years ago has been reintroduced for the treatment of such infections.<sup>[9]</sup> Polymyxins have been considered as an efficacious treatment option for serious infections caused by MDR *P. aeruginosa*, *Acinetobacter* spp., *K. pneumonia* and *Enterobacter* spp. isolates. In addition, considerable activity exists against *Salmonella*, *Shigella*, *Pasteurella* and *Haemophilus* spp.<sup>[10,11]</sup> Questions about its safety has always been a matter of concern to the clinicians because of its proven nephrotoxicity and neurotoxicity, which are attributed to its high binding to brain and renal tissues.<sup>[11]</sup> Recent studies of polymyxin B use in MDR gram -ve infections demonstrate acceptable effectiveness and safety as compared to earlier studies that showed an estimated incidence of nephrotoxicity to be 4-22%.<sup>[12-16]</sup>

### What are Polymyxins?

Polymyxins (polymyxin A-E) known since 1947, are a group of cationic polypeptide antibiotics. Only polymyxin B and E (colistin) have been used in clinical practice due to high toxicity of the remaining agents.<sup>[17]</sup> Polymyxin B is a lipopeptide antibiotic isolated from bacillus polymyxa it differs from colistin in having D-phenylalanine in place of D-leucine.<sup>[18]</sup> Polymyxin B is available for parenteral use as sulphate salt, colistin is available in two commercial forms-colistin sulphate for oral and topical use and sodium salt of colistin methanesulphonate (an inactive prodrug that undergoes hydrolysis *in vivo* and *in vitro* to form the active entity colistin) for parenteral/inhalational use.<sup>[17]</sup>

### Mechanism of action

Polymyxins act by disrupting cytoplasmic membrane causing leakage of gram -ve organism.<sup>[12,19]</sup> Polymyxins exhibits bactericidal action by binding to the lipopolysaccharide cell membrane of gram -ve bacteria displacing the calcium and magnesium bridges that stabilize it.<sup>[20,21]</sup> Major adverse effects associated with the use of polymyxins are nephrotoxicity, neurotoxicity and neuromuscular blockade. The proposed mechanism for nephrotoxicity is increased influx of cations, anions and water leading to cell swelling and lysis. Nephrotoxicity with polymyxins results in acute tubular necrosis and renal insufficiency or failure, manifested by increase in serum urea and creatinine levels associated with decrease in creatinine clearance. Nephrotoxicity caused by polymyxins in the past limited their clinical use. Nephrotoxicity of colistin seems to be less compared to that associated with polymyxin B.<sup>[18]</sup>

Limited studies have been carried out to elucidate the effectiveness and safety of polymyxin B in MDR gram -ve infection though adequate data on colistin are available. We reviewed our recent experience in the use of intravenous polymyxin B against MDR gram -ve organisms with particular attention to its nephrotoxicity and associated factors in the critical care unit.

### Materials and Methods

Our study (March 2009-October 2010) was a retrospective cohort study conducted at the 23 bedded medical ICU of tertiary care hospital in Northern India. Study was approved by Institutional Ethics committee, which omitted the need for informed consent due to its retrospective nature. Medical records of all the critically ill patients with ICU - acquired infections caused by MDR gram -ve bacteria were reviewed to identify the patients who received polymyxin B between this period irrespective of the age, gender or underlying disease.

### Inclusion criteria

- Patients who received polymyxin B for gram -ve sepsis (either suspected or confirmed cases) for at least three consecutive days
- Patients with serum creatinine less than 4 mg/dl
- Patients with serum creatinine measurements available atleast one before the start of antibiotic and one during the therapy.

### Exclusion criteria

- Patients undergoing dialysis at the start of the therapy
- Patients with obstructive renal failure
- Concomitant nephrotoxic drugs (AmphotericinB, aminoglycosides, vancomycin, cyclosporine, cephalothin, Nonsteroidal Antiinflammatory Drugs (NSAIDs) tacrolimus) being administered
- Patients who underwent contrast enhanced computed tomography scan.

Out of 71 patients who were administered polymyxin B for the treatment of ICU acquired MDR gram -ve infections, only 32 patients met the inclusion criteria. For 32 eligible patients, medical records were reviewed retrospectively for demographics, days of hospitalization, underlying disease, medical history, previous surgery, infection on ICU admission, source of infection, organism isolated and their antibiotic sensitivity, dosing frequency and duration of therapy, serum creatinine (baseline and highest during treatment) and outcome (recovery or death) to assess the therapeutic efficacy and

nephrotoxicity of polymyxin B. Baseline serum creatinine was defined as the creatinine level on the day when initial polymyxin dose was administered. Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system was used to assess patients' severity of illness at the time of admission.<sup>[22]</sup>

**Administration of polymyxin B**

All patients (n = 32) in the study received intravenous polymyxin B for MDR gram -ve sepsis resistant to carbapenems. Starting dose of polymyxin B was given as per manufacturer's recommendations that is 5 lac units intravenously 8 h (15,000-25,000 IU/kg/day).<sup>[23]</sup> Dosage adjustment was carried out according to creatinine clearance in patients progressing to renal dysfunction. Creatinine clearance was calculated using the Cockcroft and Gault formula.<sup>[24]</sup>

Primary efficacy end points were resolution of sepsis and survival. Nephrotoxicity after drug therapy was assessed by Risk (R), Injury (I), and Failure (F) and two outcome classes, Loss (L) and End stage kidney disease (E) according to RIFLE criteria for acute kidney injury (AKI) [Table 1].<sup>[25]</sup>

Factors associated with nephrotoxicity like age, polymyxin dose, duration of treatment, baseline creatinine, and days of hospitalization were also studied.

**Statistical analysis**

Statistical analysis of data were carried out using unpaired student t-test, one-way ANOVA, bonferroni's post-hoc, and Fisher test. P value less than 0.05 was considered significant. Data were presented as % or mean ± SD.

**Results**

Present study has been conducted on all patients who received polymyxin B intravenously for treatment of an ICU-acquired MDR gram -ve infection. Patients undergoing dialysis at the start of the therapy, with pre existing obstructive renal failure and having concomitant nephrotoxic drugs were not included in the study. Mean age of patients was 48.53 ± 13.90 years ranging from 16 years to 68 years [Table 2].

*A. baumannii* was the most frequent infecting organism in 26 (81.2%) patients. One patient each was infected with *E. coli*, *P. aeruginosa* and *staphylococcus epidermidis*. Polymicrobial infection was seen in 3 (9.30%) patients. Major bacterial isolation sites were blood (37.5%), abdomen (28.2%), lungs (18.8%), skin and soft tissue (12.5%), and urinary tract (3.12%).

6 out of 32 (18.7%) patients progressed to whereas renal functions remained normal in 26 (81.2%) patients. Out of six patients with the renal dysfunction after polymyxin B administration, five patients developed "risk", whereas only one patient developed "renal injury" as per RIFLE scores. Older age (62.33 ± 11.90 vs. 45.34 ± 2.45, P value 0.005) was found to be an independent factor for causing nephrotoxicity [Table 3]. No significant association was observed between polymyxin dose, duration of treatment, baseline creatinine, and days of hospitalization with nephrotoxicity.

9 out of 32 (28.1%) patients died, whereas 23 (71.9%) patients survived at the end of the therapy. Two out of 6 (33.3%) AKI and 7 out of 26 (26.9%) non AKI patients died, at the end of the treatment with no statistically significant difference (P value 0.756) [Table 3].

**Table 1: RIFLE criteria for AKI grading**

Grades of AKI	Creatinine increase	GFR decrease %	Urine output
Risk	1.5 times	>25	<0.5 ml/kg/h×6 h
Injury	2 times	>50	<0.5 ml/kg/h×12 h
Failure	3 times	>75	<0.5 ml/kg/h×24 h or anuria×12 h
Loss	Persistent ARF (complete loss of renal function for>4 weeks)		
ESRD	End stage renal disease		

AKI: Acute kidney injury; RIFLE: Risk (R), Injury (I), and Failure (F) and two outcome classes, Loss (L) and End stage kidney disease (E); ARF: Acute renal failure

**Table 2: Description of study population**

Variable	Mean±SD	Minimum value	Maximum value
Age (years)	48.53±13.90	16	68
Duration of treatment (days)	7.44±4.94	2	25
Mean dose (lakh units)			
Daily dose	11.09±4.01	5	15
Cumulative dose	79.53±51.67	15	210
Days of hospitalization (days)	23.91±13.34	7	70
APACHE II	11.84±4.29	4	22
Adjusted mortality rate	16.13±10.75	0.8	47.6
Mortality (%)	28.1		

APACHE II: Acute physiology and chronic health evaluation II

**Table 3: Univariate analysis of parameters comparing patients with and without AKI after therapy**

Parameter	AKI (n=6)	Non AKI (n=26)	P value
Female:Male	12:14	3:3	
Age (mean±SD) in years	62.33±11.90	45.34±2.45	0.005
Baseline creatinine (mg/dl)	1.54±0.98	1.08±0.54	0.310
Mean daily dose (lakh units)	10.67±3.71	12.92±5.1	0.421
Mean cumulative dose (lakh units)	79.71±53.59	78.75±46.84	0.809
Duration of therapy in days	7.69±5.27	6.33±3.26	0.733
Days of hospitalization	23.85±13.86	24.17±11.99	0.772
APACHE II	11.34±4.24	14±4.47	0.320
Adjusted mortality rate (%)	15.46±9.68	19.03±15.32	0.790
Mortality (%)	33.3	26.9	0.756

AKI: Acute kidney injury; APACHE II: Acute physiology and chronic health evaluation II

**Table 4: Comparison of studies demonstrating mortality and nephrotoxicity with polymyxin B**

Study	Study details	Mortality (%)	Nephrotoxicity (%)
Ouderkirk <i>et al.</i> , 2003 <sup>[13]</sup>	N=60 retrospective October 1999-May 2005	20	14
Sobieszczyk <i>et al.</i> , 2004 <sup>[14]</sup>	N=25 retrospective January 2000-June 2003	48	10
Holloway <i>et al.</i> , 2006 <sup>[15]</sup>	N=37 retrospective March 2002-May 2005	27	21
Ramasubbun <i>et al.</i> , 2008 <sup>[16]</sup>	N=45 retrospective March 2006-June 2007	52	4
Mendes <i>et al.</i> , 2009 <sup>[12]</sup>	N=114 retrospective March 2000-June 2004	32.4	22
Present study	N=32 retrospective March 2009 to October 2010	28.1	18.7

## Discussion

Recent data on polymyxin B in critically ill patients for the treatment of serious MDR gram -ve infections is limited, but demonstrate acceptable effectiveness and considerably less toxicity than was reported in older studies. Hence, our study is an addition to the meager data about polymyxin B use in MDR gram -ve infections.

To our knowledge, our study is the only study carried out on critically ill patients who were not on nephrotoxic drugs. As nephrotoxic drugs had been a major confounding factor and it was eliminated in our study by strictly excluding patients taking nephrotoxic drugs.

Our study results demonstrated 18.7% incidence of nephrotoxicity with the use of polymyxin B, which is comparable to observed nephrotoxicity in earlier studies ranging from 4% to 22%. In concordance with the other studies showing mortality rate of 20-52%, our study reported overall 28.1% mortality [Tables 3 and 4].

Our study results demonstrated older age as an independent factor, as observed in past studies [Table 3]. No significant association was observed between polymyxin dose, duration of treatment, baseline creatinine, and days of hospitalization with nephrotoxicity in Sobieszczyk and Ouderkirk studies.<sup>[13,14]</sup> In contrast, a study carried out by Mendes *et al.* showed that higher baseline creatinine along with age is a contributing factor for development of nephrotoxicity due to polymyxin B.<sup>[12]</sup>

Mortality was observed in 26.9% non-AKI and 33.3% AKI patients with no statistically significant difference [Table 3], other studies demonstrated association of nephrotoxicity with mortality. This can be explained by the fact that high severity of renal dysfunction, which could contribute to mortality was avoided by early preventive measures being taken in the setting where present study was undertaken. Only one patient developed renal injury whereas failure was not observed in any patient. Polymyxin B had been used judiciously in appropriate dose and duration according to ideal body weight. Further, dose was adjusted daily based on daily monitoring of renal functions

such as creatinine clearance and blood urea nitrogen. Intravenous fluid resuscitation was adequately carried out according to central venous pressure monitoring.

Major draw backs of our study are the small sample size, retrospective nature and lack of comparators. Reason for the small number in our study can be attributed to the restricted use of polymyxin B in critically ill patients and strict exclusion criteria. This study is a pilot study to assess the impact of polymyxin B on disease outcome and prevalence of nephrotoxicity. More exploratory prospective controlled trials are necessary to provide sufficient evidence about efficacy and safety of polymyxin B for their use in clinical practice.

In conclusion, in the present scenario of rising infections with MDR gram -ve bacteria, this pilot study suggests that polymyxin B can be effectively and safely used in patients not receiving other nephrotoxic drugs, with cautious administration in older patients as they appear to be more vulnerable to nephrotoxicity caused by the drug.

## Acknowledgment

We are grateful to Medical ICU team of Fortis Hospital, Mohali with special thanks to Dr. Deepak Bhasin and Dr. Harpal Singh for their continuous and intense co-operation to conduct the study.

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**How to cite this article:** 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.

**Source of Support:** Nil, **Conflict of Interest:** None declared.

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