

## Treatment of multi drug resistant gram negative bacilli with inhaled polymyxin-b

Suresh Kumar Konkyana<sup>1</sup>. Anil Kumar Akkenapalli<sup>2</sup>

Assistant Professor, Department of Anesthesiology, Osmania Medical College/MGMH, Hyderabad, India

### ABSTRACT

**Introduction:** A major challenge has arisen regarding the treatment of infections caused by Gram-negative bacilli, particularly those with high level intrinsic resistance to many antibiotic classes and extreme ability to acquire resistance. **Aim:** The present study was conducted to assess the safety and efficacy of aerosolized polymyxin-B in comparison to intravenous polymyxin-B therapy for treatment of MDR GNB. **Materials and methods:** Study was performed over a period of 18 months. A Comparative two group randomized clinical study with 50 patients with 25 patients in Group A and 25 patients in Group-B is undertaken to study the outcome of therapy, fever response to therapy and side effects. **Results:** Mean duration of ICU stay was 28.68±9.15 days in Group-A while it was 31.64±9.16 days in Group-B. This was not statistically significant with p-value 0.258786. Pseudomonas aeruginosa is the most common organism isolated. In this study improvement, cure and failure rates were 44%, 44% and 12% respectively in Group-A (inhaled polymyxin b). while improvement, cure and failure rates were 40%, 20% and 40% in Group-B (iv Polymyxin B) which was statistically significant. fever response to study was better in Group-A (inhaled polymyxin B) which was statistically significant. Adverse events to polymyxin B Inhalation (bronchospasm) occurred in 16% of the patients in group-A, Nephrotoxicity in 28% of patients in group -B. but did not lead to suspension of treatment. **Conclusion:** Inhaled polymyxin-B was useful in treatment of nosocomial pneumonia caused by MDR-GNB in mechanically ventilated patients. As the drug is given by inhalational route systemic side effects can be minimized

**Keywords:** Polymyxin-B, Bronchospasm, Nephrotoxicity.

### Introduction

Emergence of nosocomial bacterial pathogens with acquired resistance to almost all available antimicrobial agents, namely 'superbugs', has severely threatened therapeutic choices in the last decade [1]. A major challenge has arisen regarding the treatment of infections caused by Gram-negative bacilli, particularly those with high level intrinsic resistance to many antibiotic classes and extreme ability to acquire resistance, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [2]. No new antibiotic is there even in the drug development pipeline for MDR Gram-negative bacteria. The clinical and economic consequences of the emergence of multidrug-resistant Gram negative bacteria in the intensive care unit (ICU)

setting, combined with the high mortality rate among patients with nosocomial pneumonia, have stimulated a search for alternative therapeutic options to treat such infections. This therapeutic void has created a resurgence of interest in polymyxins [3]. Because of nephrotoxicity, neuromuscular blockade, neurotoxicity with systemic use of polymyxins, aerosolized therapy is used as an alternative method for treating MDR GNB [4, 5]. Aerosolized therapy in place of systemic treatment appears promising, but the current published data are too limited to allow determination of the incremental benefit of aerosolized treatment to systemic treatment. The present study was conducted to assess the safety and efficacy of aerosolized polymyxin B in comparison to intravenous polymyxin B therapy for treatment of MDR GNB.

\*Correspondence

**Dr. Suresh Kumar Konkyana**

Assistant Professor, Department of Anesthesiology,  
Osmania Medical College/MGMH, Hyderabad, India

E Mail: [sureshmaximus@yahoo.com](mailto:sureshmaximus@yahoo.com)

### Materials and methods

Study was conducted in the ICU of Osmania General Hospital, Hyderabad which is a tertiary care centre. Study was performed over a period of 18 months. A

Comparative two group randomized clinical study with 50 patients with 25 patients in Group A and 25 patients in Group-B is undertaken to study the outcome of therapy, fever response to therapy and side effects. The study protocol was approved by ethical committee of the institution. Informed consent from the patient's was taken.

**Inclusion Criteria:** Cases of either sex aged between 18 - 70 years, Patients on ventilator for >48 hours.

**Exclusion Criteria:** Patients with pneumonia prior to ICU admission, ARDS, pulmonary edema, raised renal parameters

Inclusion & exclusion criteria were chosen to prevent variables identified to be associated with mortality in mechanically ventilated patients.

The patients were divided randomly into two groups:

**Group – A:** Polymyxin - B inhaled for 14 days 2 mg/kg/day in two divided doses in a solution of 5 mL of distilled water through a conventional nebulizer. Approximately 20 min before the polymyxin B inhalation, an aerosolized beta2-agonist was administered.

**Group – B:** Polymyxin – B i.v for 14 days 2 mg/kg/day in two divided doses administered over one hour

A total of 25 patients over one year period (August 2011 through July 2012) with pneumonia caused by MDR-GNB were treated with nebulized Polymyxin – B. Compared with I.V Polymyxin –B in equal number of patients

The following information was obtained for each patient. Basic investigation were done and also X – ray showing new or progressive pulmonary infiltrates Fever > 100.4 ° F, Increased amount and purulence of tracheal secretions, Leucocytosis > 12,000 cells/mm<sup>3</sup>.

If resistant to 4 or more of the following antimicrobial agents: An endotracheal aspirate was obtained immediately following clinical suspicion. Microbiological diagnosis of VAP was established by positive cultures of bronchial secretions with isolation of an MDR gram-negative bacterium with a concentration of  $\geq 10^4$  CFU/ml .

The response to treatment was assessed at the time of discharge from the ICU or at the end of antimicrobial therapy, especially if the patient remained hospitalized for a non VAP-related disease.

The primary end point of the study was the clinical outcome of VAP. In patients with normal renal function, nephrotoxicity was defined as a serum creatinine value >2 mg/dL. Bronchospasm during inhaled polymyxin, defined as the increase of respiratory frequency

associated with wheezing, was evaluated.

The therapeutic response was evaluated by one of the following criteria:

**Improvement.** Defined as the reduction and improvement of the appearance of tracheal secretions, reduction or disappearance of chest X-ray alterations, normalization of leukocyte count, patient becoming afebrile and improvement of the mechanical ventilation parameters (FIO<sub>2</sub> and positive end expiratory pressure [PEEP]).

**Cure.** Criteria for improvement plus disappearance of fever, return of spontaneous ventilation, and discharge from the ICU or the hospital.

**Failure** All the situations not classified as improvement or cure.( persistence or worsening of presenting symptoms and/or signs of infection during polymyxin administration)

.Descriptive statistical has been carried out in the present study. Results on continuous measurements are presented on Mean  $\pm$  SD (Min-Max) and results on categorical measurements are presented in Number (%).Statistical analysis was done by applying Chi-square test and P < 0.05 is significant ,P < 0.001 is highly significant

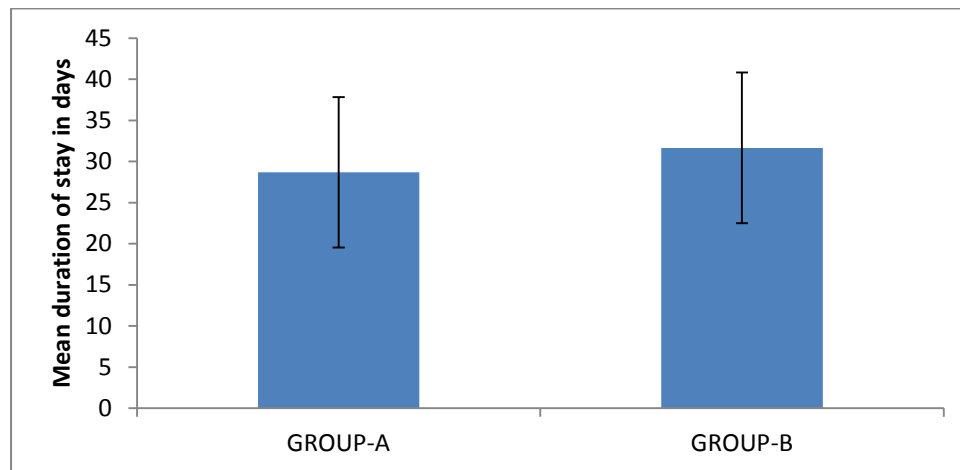
## Results

It is a Comparative two group randomized clinical study with 50 patients with 25 patients in Group A and 25 patients in Group-B is undertaken to study the outcome of therapy , fever response to therapy and side effects. Study was done for period of 18 months .Out of 25 patients 17 are male and 8 are female patients.

**Table1: Age distribution of patients studied**

Age in yrs	GROUP-A	%	GROUP-B	%
18-30	7	28	6	24
31-50	12	48	13	52
51-70	6	24	6	24
Mean age in years ( $\pm$ SD)	41.4 $\pm$ 13.10		41.36 $\pm$ 13.06	

The T-value is 0. The P-Value is 1. The result is not significant at  $p < 0.05$ . The patients who took part in this study were in the age group of 18 to 70 years. On statistical comparison the two groups were comparable.



**Figure 1: Duration of ICU Stay**

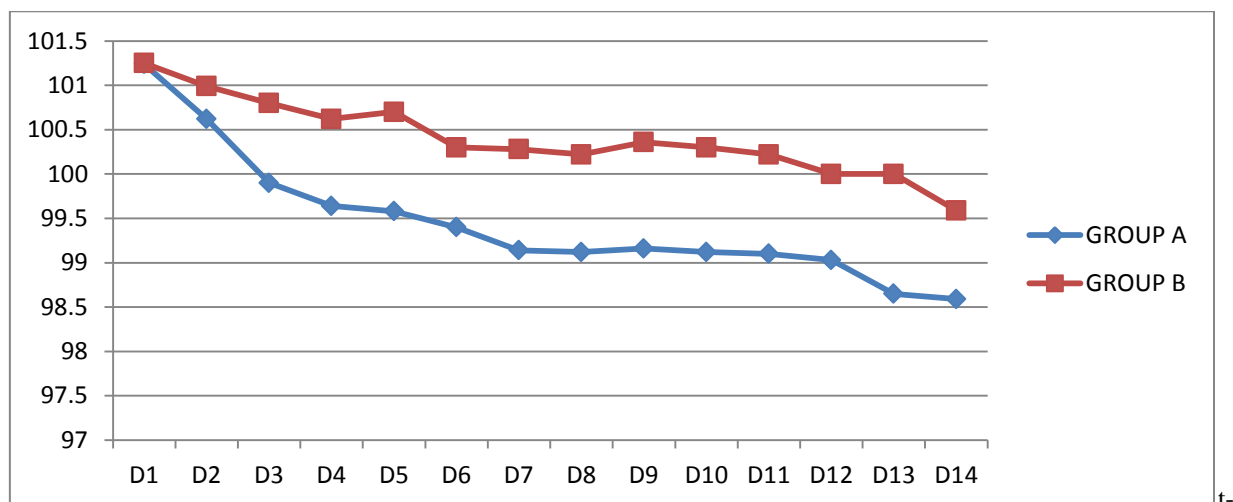
The T-value is 1.142809. The P-Value is 0.258786. The result is not significant at  $p < 0.05$ .

**Table 2: Microorganism Isolated**

Microorganism	GROUP-A		GROUP-B	
<b>Pseudomonas aeruginosa</b>	15	60%	14	56%
<b>Acinetobacter baumannii</b>	5	20%	4	16%
<b>Klebsiella pneumonia</b>	5	20%	7	28%

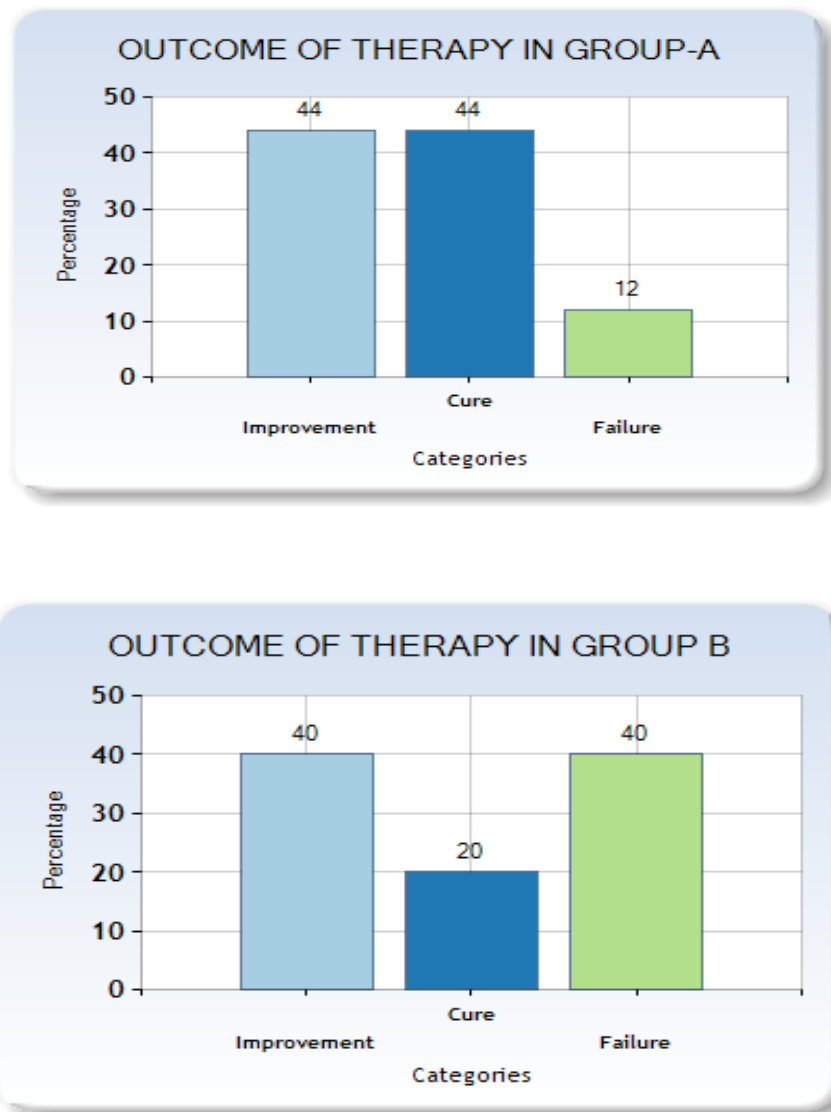
Pseudomonas aeruginosa is the most common organism isolated.

The chi-square statistic is 0.4789. The P-Value is 0.78705. The result is not significant at  $p < 0.05$ .



Value: 4.217922, p-value:0.000264. The result is significant at  $p < 0.05$ .

**Figure 2: Fever response to therapy**



**Figure 3: Outcome of therapy**

The chi-square statistic is 6.0668. The P-Value is 0.04815. The result is significant at  $p < 0.05$

**Table 3: Side effects of patients in two groups studied**

Side Effect	Group-A	Group-B
Bronchospasm	4(16%)	0
Nephrotoxicity	0	7(28%)

**Discussion**

Inhaled antibiotics have been used based on the rationale that the drug would concentrate at the

infection site minimizing toxicity of systemic administration, and this strategy has gained strength.

Gram-negative bacilli and especially *P. aeruginosa* are among the important causes of nosocomial infections worldwide. In this setting, treatment with inhaled polymyxin B may prove to be an interesting alternative because the systemic use of polymyxins seems to yield poor results. There are no other studies which compare inhaled polymyxin B alone with IV polymyxin B alone. The present study was performed to evaluate the effectiveness and safety of inhaled polymyxin B in MDR Pneumonia patients. In this study the inhalational and intravenous dosing regimen was selected based on previous animal studies and ICU practices in this institution. In this study Group-A received 2mg/kg (20000U/kg) polymyxin B via inhalation and Group-B received 2 mg/kg polymyxin B intravenously. These doses were given in two divided doses as preferential accumulation of polymyxin B in the kidneys is a nonpassive process and q12h dosing was less nephrotoxic than q6h dosing[6]. The baseline information was obtained for each patient. Defined as the reduction and improvement of the appearance of tracheal secretions, reduction or disappearance of chest X-ray alterations, normalization of leukocyte count, patient becoming afebrile and improvement of the mechanical ventilation parameters (FIO<sub>2</sub> and positive end expiratory pressure [PEEP]). Criteria for improvement plus disappearance of fever, return of spontaneous ventilation, and discharge from the ICU or the hospital. All the situations not classified as improvement or cure. (persistence or worsening of presenting symptoms and/or signs of infection during polymyxin administration) In this study improvement, cure and failure rates were 44%, 44% and 12% respectively in Group-A (inhaled polymyxin B). While improvement, cure and failure rates were 40%, 20% and 40% in Group-B (iv Polymyxin B) which was statistically significant. Graziella H. Pereira et al study showed that the outcome of treatment with inhaled polymyxin B was cure in 53%, improvement in 42% and failure in 5%. In our study fever response to study was better in Group-A (inhaled polymyxin B) which was statistically significant. There are no studies which compared this factor. In our study adverse events to polymyxin B Inhalation (bronchospasm) occurred in 16% of the patients in group-A but did not lead to suspension of treatment. Pereira et al [7] in their study showed that adverse events during polymyxin B inhalation occurred in 21%. Nephrotoxicity occurred in 28% of Group-B patients while there was no nephrotoxicity in Group-A patients. Neurotoxicity, while difficult to assess in severely ill ICU patients, appeared minimal. In the ICU setting, sepsis, hypotension and the use of other nephrotoxic drugs contribute to impairment of renal function. Our study

was not able to exclude the confounding impact of these variables because of our reliance on sometimes incomplete medical records and the complex nature of treating patients in ICU. Mean duration of ICU stay was 28.68±9.15 days in Group-A while it was 31.64±9.16 days in Group-B. This was not statistically significant with p-value 0.258786. Kofteridis et al [8] in their study also showed that ICU stay in two groups was not statistically significant.

In a recent clinical study on polymyxin B [6], 60 patients with nosocomial infections, mostly due to *A. baumannii*, were investigated. The majority of the patients were mechanically ventilated and had pulmonary infections. The iv polymyxin B dose was adjusted according to the estimated creatinine clearance: 20–50 mL/min, 75% of the total daily dose of 2.5 mg/kg; <20 mL/min, 33% of the total daily dose. The overall mortality of these patients was 20%. Bacteria were cleared in 88% of the patients; however, susceptibility testing revealed that the bacteria persisting in other patients remained susceptible to polymyxin B. A major drawback in both clinical efficacy and microbiological endpoint analyses is that up to 90% of patients received combination therapy with another agent active against *P. aeruginosa* and *A. baumannii* [9]. In another study, only patients who received combination therapy were included. Twenty-nine treatments from 25 patients were analysed. Ninety-two per cent of the patients were from intensive care units and 88% were mechanically ventilated. All patients had respiratory tract infections caused by *A. baumannii* (55%), *P. aeruginosa* (41%) and *Alcaligenes xylosoxidans* (3%). Only seven *A. baumannii* and five *P. aeruginosa* isolates were resistant to all available antibiotics except polymyxin B. Since all patients were treated with another antibiotic, efficacy analysis of polymyxin B was compromised. [9]. The overall discharge mortality was 48%. Follow-up cultures were available in 22 cases, of which 9 achieved microbiological clearance but were associated with a longer duration of therapy. Resistance to polymyxin B was not observed during the therapy [9]. Holloway et al [10] recently published their experience with the treatment of 37 patients with infections due to polymyxin-only-susceptible *A. baumannii*, of whom 33 received polymyxin B therapy. Monotherapy with polymyxin B was used in 27 patients. Most infections were ventilator-associated pneumonia. Nine (27%) patients died after treatment with polymyxin B. Microbiological cure was achieved in 17 (81%) of 21 patients evaluated for this outcome [11]. In our recent study on the treatment of 13 patients with iv polymyxin B against infections caused by MDR metallo-β-lactamase-

producing *P.aeruginosa*, 65.8 patients had pneumonia, of whom 4 were ventilator-associated. Overall in-hospital mortality was 54%. 65 Of six patients with ventilator-associated pneumonia treated with polymyxin B, four (67%) died within 30 days after initial treatment with polymyxin B [12]. Mortality rates (VAP mortality and all cause mortality rates) were not compared in our study because we excluded patients with raised renal parameters, ARDS and pulmonary edema. This would have been confounding factor in evaluation of mortality rates. Duration of mechanical ventilation was also not evaluated as the patients were being ventilated mechanically for reasons other than MDR VAP. Though there are limitations in our study outcome of inhaled polymyxin B therapy is significant. The response was good and might be explained by the possible high concentration of the inhaled drug in the pulmonary compartment. In our study the isolates were not tested for polymyxin B resistance because microdilution was not available and disk diffusion is not a reliable method. This could have acted as a confounding factor in failure cases. The pharmacokinetic properties and dosing strategies of aerosolized polymyxin are not well defined. Whether the various forms of polymyxin used for inhalation therapy or the different types of nebulizing systems influence the effectiveness and safety of colistin remains to be determined [13-16]. Further pharmacokinetic-pharmacodynamic studies in which serum concentrations achieved by varying doses of polymyxin are compared to the MIC of the infecting organisms are required so that the optimal dose of polymyxin can be determined. This is important not only for optimal effectiveness of the drug but also to prevent polymyxin resistance.

### Conclusions

Aerosolized administration of Polymyxin B is a promising therapy for management of patients with pneumonia due to multi drug resistant Gram-negative bacteria. Aerosolized polymyxin B was safe in this group of patients. Inhaled Polymyxin-B deposits the drug at the site of infection and facilitates better antimicrobial action. In summary, despite the limitations of this study, we considered that inhaled polymyxin-B was useful in treatment of nosocomial pneumonia caused by MDR-GNB in mechanically ventilated patients. As the drug is given by inhalational route systemic side effects can be minimized. The results of this study should lead to randomized controlled studies to establish the role of this form of treatment.

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