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Polymyxin B- Compared to Beta-Lactam- Based Regimens for the Treatment of Carbapenem-Resistant Gram Negative Bacterial Pneumonia

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Abstract

Background: Infections caused by multidrug resistant (MDR) gram-negative bacteria (GNB) are an increasingly common problem in hospitalized patients. As conventional antimicrobials prove to be ineffective, this therapeutic challenge may be met by polymyxin B (PB). The use of PB for treatment of pneumonia (PNA) is controversial as previous studies have reported reduced efficacy of PB, possibly due to limited lung penetration. Nonetheless, PB is frequently used with variable success. We aim to characterize the clinical effectiveness of PB for the treatment of MDR GNB PNA.

Methods: This is a retrospective cohort study of patients from Columbia University Medical Center from 2013-2014 who had PNA with a respiratory culture positive for a carbapenem resistant GNB. Subjects met National Healthcare Safety Network criteria for PNA and received at least 48 hours of active antibiotic treatment. We compared subjects who received a PB based regimen to those who received a beta lactam (BL) based regimen (without PB). The primary outcome was clinical response after antibiotic therapy ; additional outcomes were 30-day all-cause mortality and nephrotoxicity.

Results: 95 patients met inclusion criteria; mean age was 65 years and 68% were male. Cultures were comprised of *Pseudomonas aeruginosa* (49%), *Acinetobacter baumannii* (22%), and *Klebsiella pneumoniae* (25%). 49 patients (52%) received a PB containing regimen. The PB group were younger, more likely to be in an intensive care unit (ICU) and more likely to have an indwelling tracheostomy compared to the BL group (all p values < .05). Clinical response to therapy was 47% in PB group and 78% in the BL group (p=0.003). 30-day mortality was 49% and 24% in the PB and BL groups respectively (p=0.038). In a multivariable model adjusting for age, BMI, organism, WBC, AKI, receiving an aminoglycoside, and ICU stay, the odds ratio of clinical success was 0.335 (95% confidence interval 0.105-1.067, p=0.064) for those with a PB vs. BL regimen. Of 63 patients evaluable for nephrotoxicity, 24 (75%) in the PB group developed acute kidney injury (AKI) on treatment compared to 7 (23%) in the BL group.

Conclusion: A PB based regimen for the treatment of MDR GNB PNA resulted in significantly higher mortality and lower odds of clinical success compared to those who received a BL regimen, though those who received PB were more critically ill. These data highlight the need for better therapeutic options for MDR GNB PNA.

Introduction

- Infections caused by multidrug resistant (MDR) gram-negative bacteria (GNB) are an increasingly common problem in hospitalized patients .
- As infections caused by MDR GNB increase in frequency and severity, the use of polymyxin-B (PB) to treat these infections also increases.[1]
- However, the use of PB for treatment of pneumonia (PNA) is controversial, as previous studies have reported reduced efficacy of PB for treating PNAs. This may be due to suboptimal dosing of PB in previous years or perhaps due to limited lung penetration of the drug.[2] Nonetheless, PB is often used in these situations as limited options are available.
- We aim to characterize the clinical effectiveness of PB for the treatment of MDR GNB PNA.

Methods

- This is a retrospective cohort study of patients from Columbia University Medical Center who had PNA with a respiratory culture positive for a carbapenem resistant GNB in 2013- 2014.
- Subjects met National Healthcare Safety Network criteria for PNA and received at least 48 hours of active antibiotic treatment.[3]
- We compared subjects who received a PB based regimen to those who received a beta lactam (BL) based regimen (without PB).
- The primary outcome of interest was clinical success at the end of antibiotic treatment. Clinical Success was defined as clinical improvement at the end of treatment.
- Secondary outcomes included 30-day all cause mortality and development of new AKI during treatment.
- IBM SPSS Statistics Version 23.0 was used for all statistical analyses

Results

Table 1: STUDY POPULATION

Patient Characteristics	PB regimen (N=49)	BL regimen (N=46)	p-value
Age	59 [43-72]	67 [54-81]	**0.031***
Male	39 (80)	29(63)	0.119
Body Mass Index	28.7 [24-33]	24.9 [20-30]	**0.005***
Charlson Comorbidity Index	3 [1.5-5]	2.5[1-4]	0.234
Diabetes	12 (25)	20 (44)	0.082
Chronic Steroids	8(16)	15(33)	0.094
Mechanical Ventilation PTA	15(31)	21 (46)	0.221
Indwelling Tracheostomy PTA	6(12)	18(39)	**0.004***
Long term care facility resident PTA	13 (27)	18 (39)	0.276
In ICU at time of culture	41(84)	25(54)	**0.004***
Ventilator-associated pneumonia	34(69)	35(76)	0.616
WBC at time of pneumonia (x10^9 per liter (L))	14 [9-22]	13[10-13]	0.441
SCr at time of pneumonia (mg/dl)	1.5 [0.9-2.8]	1.3 [.53-2.3]	0.007
Acute Kidney Injury at time of pneumonia	26(53)	19 (41)	0.347
Acinetobacter baumannii	10 (20)	11 (24)	0.870
Klebsiella pneumoniae	22 (45)	2 (4)	**<.001***
Pseudomonas aeruginosa	13 (27)	34 (74)	**<.001***
Other Organisms	6(12)	1 (2)	0.112
Polymicrobial	2 (4)	2(4)	0.500
Duration of Therapy	14 [9-17.5]	10 [7-16]	0.105
Concomitant aminoglycoside use	17 (35)	27(59)	**0.032***
Concomitant inhaled antimicrobials	6(12)	10(22)	0.336
Hospital LOS (days)	43	26.5	**0.007***

*P value <.05 considered significant
All values presented as frequency (%) or medians (interquartile ranges) as appropriate; PTA: prior to admission

Figure 1: Clinical Success, Mortality, and Bacterial Eradication

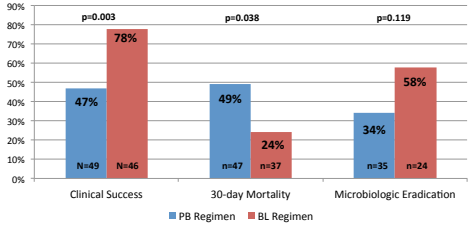

Table 2: Clinical Success by Organism

Table 2: RESULTS	PB regimen (N=49)	BL Regimen (N=46)	p-value
Clinical Success	23 (47)	36 (78)	0.003
Acinetobacter baumannii (n=21)	7/10 (70)	9/11 (82)	0.635
Klebsiella pneumoniae (n=24)	8/22 (36)	1/2 (50)	1.0
Pseudomonas aeruginosa (n=47)	8/13 (62)	27/34 (79)	0.096
Other organisms (n=7)	1/6 (17)	0/1 (0)	1.0

Figure 2: Renal Impairment

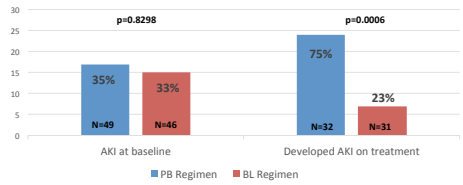

Table 4: Univariate and Multivariate Analysis For Clinical Success after Antibiotic Therapy

	Univariate Analysis		Multivariate Analysis	
Characteristics	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age	1.01 (0.98,1.03)	0.69	1.01 (0.98,1.04)	0.65
Body Mass Index	0.94 (0.88,1.00)	0.06	0.98 (0.902,1.062)	0.61
Charlson Comorbidity Index Score (CCIS)	0.803 (0.680,0.948)	0.010	0.805 (0.668,0.969)	**0.02***
Indwelling tracheostomy	1.302 (0.492,3.446)	0.595	0.349 (0.090,1.350)	0.13
WBC at time of pneumonia	0.948(0.90,0.99)	0.035	0.941 (0.89,0.99)	**0.05***
Acute kidney injury at time of PNA	0.41 (0.17,0.95)	0.04	0.48 (0.17,1.39)	0.17
ICU at time of pneumonia	0.406 (0.152,1.081)	0.071	0.714 (0.198,2.569)	0.60
Pseudomonas isolated	2.917 (1.227,6.934)	0.015	0.712 (0.405,1.251)	0.24
Klebsiella isolated	0.252 (0.095,0.665)	0.005		
Polymyxin B based therapy	0.246 (0.1,0.6)	0.002	0.335 (0.105,1.067)	0.06
Concomitant aminoglycoside	2.370 (1.0,5.61)	0.05	2.002 (0.696,5.765)	0.20

Conclusions

- Patients treated with a polymyxin based regimen for their MDR GNB PNA had higher mortality and lower odds of clinical success compared to those treated with a beta lactam based regimen.
- Clinical response to therapy was 47% in PB group and 78% in the BL group (p=0.003).
- 30-day mortality was 49% and 24% in the PB and BL groups respectively (p=0.038).
- In univariate analysis, patients receiving PB had lower odds of clinical success (OR=0.26, p=0.002), but this was not statistically significant in multivariable model.
- PB was associated with increased risk of nephrotoxicity: Of the 63 patients evaluable for nephrotoxicity, 24 (75%) in the PB group developed acute renal failure on treatment compared to 7 (23%) in the beta lactam group (p=0.0006).
- Some limitations of this data include our small sample size and the heterogeneity of treatment regimens.
- These data highlight the need for better therapeutic options for MDR GNB PNA.

References

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3. Centers for Disease Control. Pneumonia (Ventilator-associated [VAP] and non-ventilator-associated Pneumonia Event. http://www.cdc.gov/nhsn/PDFs/pscManual/6pscVAPcurrent.pdf.January 2016.