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Polymyxin B Combination Therapy for the Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections

*Justin Siegfried[1], Marco R Scipione[1], John Papadopoulos[1], Kenneth Inglima[2], Maria Aguero-Rosenfeld[2] and Yanina Dubrovskaya[1]**

[1]Department of Pharmacy, NYU Langone Medical Center, USA

[2]Department of Microbiology, NYU Langone Medical Center, USA

Abstract

Background: Recent studies suggest a mortality benefit in patients with carbapenem-resistant *Klebsiella pneumoniae* (CRKP) who received combination therapy with more than one active *in vitro* agent. CRKP isolates often preserve susceptibility to polymyxins only; therefore, having two active agents may not be an option.

Objective: Evaluate clinical outcomes in CRKP infections who received polymyxin B (PMB) backbone therapy in combination therapy with *in vitro* active *vs.* inactive agent(s).

Methods: This single center retrospective cohort study evaluated adult patients with CRKP infections who had presumed sepsis syndrome and received PMB combination therapy ≥48 h.

Results: Among 170 patients with CRKP infections between 2007 and 2014, 62 patients treated with PMB plus active (n=30) or inactive agent(s) (n=32) were included. Median age was 78 (31-93) years, mAPACHE score was 18 (5-29), 76% of patients required intensive care unit (ICU) stay, 60% had septic shock, and these were comparable between groups. The most common infections were respiratory and bacteremia. Agents most frequently used in combination with PMB were tigecycline (60%) and meropenem (34%). In-hospital mortality was 57%. In patients treated with PMB plus *in vitro* active *vs.* inactive agent(s) mortality was 67% *vs.* 47%, P=0.13; microbiologic failure was 39% *vs.* 52%, P=0.34 and clinical failure was 57% *vs.* 44%, P=0.45. In multivariate analysis, ICU stay was associated with 11-fold increase in mortality (odds ratio [OR] 11.55; 95% confidence interval [CI] 2.15 to 62.01, P=0.004) and urinary tract infection was associated with survival ([OR] 0.09; 95% [CI] 0.009 to 0.863, P=0.037).

Conclusions: In this study mortality, microbiological and clinical failure was comparable between patients with CRKP infections treated with PMB in combination with *in vitro* active *vs.* inactive agent(s).

Keywords: Polymyxin B; *in vitro* susceptibility; Carbapenem-resistant *Klebsiella pneumoniae*; Clinical outcomes

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Correspondence:
Yanina Dubrovskaya, Department of Pharmacy, NYU Langone Medical Center, 545 First Avenue, Greenberg Hall, SC2-097, USA, Tel: 212 263 6436; E-mail: yanina.dubrovskaya@nyumc.org

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Introduction

The emergence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has steadily become a disseminated, global antibiotic resistance threat [1-5]. Infections caused by CRKP are associated with high rates of therapeutic failure and mortality compared to carbapenem-susceptible *K. pneumoniae* infections. An overall mortality rate of 48% was reported in patients with CRKP as compared to 26% in those with carbapenem-susceptible *K. pneumoniae* infections [6,7]. Due to the highly multidrug-resistant profile of CRKP isolates, the patients' management presents a significant clinical challengeas the optimal treatment regimen has yet to be identified.

Polymyxins (PMB or colistin) and tigecycline usually retain *in vitro* and *in vivo* microbiological activity against CRKP and are the last resort drugs utilized for treatment [8]. Two recent large, multicenter retrospective studies demonstrated lower mortality rates in critically ill patients with CRKP bacteremia who received definitive combination therapy [2,8]. Combination therapy was defined as administration of more than one *in vitro* active agent against CRKP isolates [2,8]. In both of these studies, a high percentage of CRKP isolates had preserved susceptibility to both polymyxin and tigecycline. Therefore, more than half of the patients received definitive therapy with more than one active *in vitro* agent, which could have influenced the mortality outcomes.

Though recent studies suggest a mortality benefit in patients who received combination therapy with more than one active *in vitro* agent, applying this to clinical practice continues to present a therapeutic dilemma. CRKP isolates often preserve susceptibility to polymyxins only; therefore, having two active agents against CRKP isolates may not always be an option. In this clinical situation, polymyxins are usually the only remaining active agent and the backbone for definitive therapy. The addition and benefit of other antimicrobial agents with *in vitro* resistance is not yet known. Gentamicin and/or amikacin may preserve susceptibility, however minimal inhibitory concentrations (MIC) usually remain high and these regimens are unlikely to be effective, even with optimal pharmacodynamic dosing [9]. Providers are also reluctant to prescribe concomitant aminoglycoside and polymyxin therapy due to the high risk for nephrotoxicity. Other agents, such as tigecycline have reported *in vitro* synergy with PMB. However, the clinical advantage of utilizing tigecycline when a CRKP isolate is found to be non-susceptible remains unclear [10,11]. Lastly, many clinicians have challenged the necessity of including a carbapenem in combination for CRKP infections because carbapenems are hydrolyzed by KPCs and selective pressure associated with use may contribute to the persistence of CRKP infections in colonized patients [12-14].

The objective of this study was to compare outcomes of patients with infections caused by CRKP isolates susceptible to PMB and treated with PMB as backbone therapy in combination with *in vitro* active *vs.* inactive agent(s).

Methods

Study design

This was a retrospective cohort study in a tertiary care academic medical center in New York City. The study population included adult patients (age ≥18 years) with CRKP infections who had presumed sepsis syndrome and received PMB as backbone therapy in combination with *in vitro* active *vs.* inactive agent(s) for ≥48 h. Only the first treatment course was included.

Microbiology

Cases were identified from a microbiology laboratory report of CRKP isolates from 1 January 2007 to 1 July 2014 and by review of electronic health records (EHR). The Vitek-2 system (bioMérieux®) used by our microbiology laboratory has built-in analysis software (version R05.01) that enables it to identify resistance phenotypes. According to Clinical and Laboratory Standards Institute (CLSI) for antimicrobial susceptibility testing, carbapenemase-producing isolates of *Enterobacteriaceae* usually test intermediate or resistant to one or more carbapenems. Ertapenem nonsusceptibility is the most sensitive indicator of carbapenemase production [15]. Isolates were included if either ertapenem/imipenem MIC was reported as resistant by Vitek-2.Susceptibility to tigecycline or PMB was defined by Kirby-Bauer disk diffusion or by Etest utilizing an MIC of 2 mg/L, according to the Food and Drug Administration (FDA) breakpoints for Enterobacteriaceae.

Data collection

Patients' demographic information, baseline characteristics, clinical data on day of positive culture (type of infection, modified APACHE (mAPACHE) score, intensive care unit (ICU) admission, and presence of septic shock), microbiology and antimicrobial data were collected by retrospective review of EHR.

Definitions

Presumed sepsis syndromes were defined by one of the following criteria: a positive blood culture; the presence of systemic inflammatory response syndrome (SIRS) plus a positive culture from a non-sterile site; a clinical pulmonary infection score (CPIS) of ≥6 for pneumonia; or the presence of urinary symptoms, pyuria (≥10 WBC/hpf in the urinalysis), and $\geq 10^5$CFU/ml for urinary tract infection (UTI). Treatment given after susceptibility data had become available was defined as definitive therapy. Clinical response was defined as a clinician-documented improvement in signs and symptoms of infection, and clinical failure was defined as persistence or deterioration in clinical parameters or death at the end of therapy (EOT). Cases were reviewed independently by two investigators to validate the classification as a clinical response or failure. Microbiological clearance was evaluated for patients who had follow-up cultures during antibiotic treatment. Patients were defined as having baseline renal insufficiency if the initial serum creatinine (Scr) level was ≥1.6 mg/dl or they had reported chronic kidney or end-stage renal disease or received hemodialysis. Nephrotoxicity due to PMB was defined as a decrease in baseline creatinine clearance (CrCl) of ≥50% or doubling of baseline Scr in patients with normal renal function or an increase of baseline Scr of ≥50% or decrease of CrCl of 20% in patients with abnormal baseline renal function [16].

Statistical analysis

Initial univariate comparisons were conducted using Chi-square or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Variables with *P* values of ≤0.05 were included in a stepwise (backward selection) conditional multivariate logistic regression model to identify predictors associated with in-hospital mortality. We used Kaplan-Meier product limit estimates and a log-rank test to compare distribution of survival time between polymyxin B plus active *vs.* inactive agent(s) groups. All analyses were performed using SPSS, version 21 (SPSS Inc., Chicago, IL).

Results

From 2007 to 2014, a total of 170 patients with CRKP isolates were identified from a hospital-wide microbiology report generated by our clinical microbiology laboratory. Sixty-two patients with CRKP infections with isolates susceptible to PMB and treated with PMB as backbone therapy in combination with *in vitro* active or inactive agent(s) qualified for study inclusion and were evaluated. The number and reasons for exclusion are summarized in (Figure 1). The main reasons for exclusion were due to the following: CRKP isolate was resistant to PMB (n=17), CRKP colonization (n=16), having hospital stay prior to initiation of EHR (n=16), and other infections

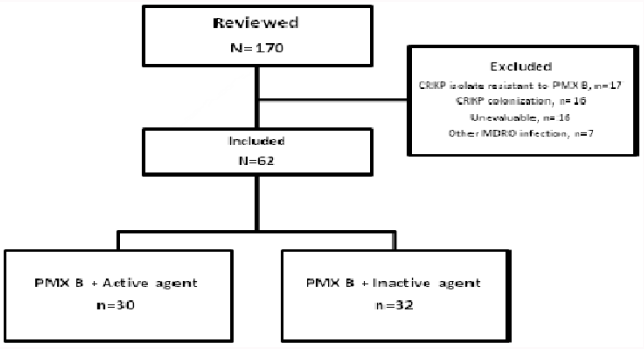

Figure 1: The number and reasons for exclusion are summarized.

Table 1: Characteristics of patients with infections caused by CRKP.

	All (N=62)	PMB + Active (n=30)	PMB + Inactive (n=32)
Age (years), median (range)	78 (31-93)	79 (37-90)	77 (31-93)
Male	35 (57)	20 (67)	15 (47)
Body weight (kg), median (IQR)	72.9 (60.1-82.8)	73.4 (59.2-80.3)	72.1 (64.7-84.6)
Comorbidities			
Cardiovascular disease	39 (63)	17 (57)	22 (69)
Diabetes mellitus	21 (34)	12 (40)	9 (28)
Solid tumor	19 (31)	9 (30)	10 (31)
Hematological malignancy	9 (15)	4 (13)	5 (16)
Charlson morbidity index, median (range)	4 (0-12)	4 (0-12)	3 (0-10)
Baseline renal insufficiency	24 (39)	10 (33)	14 (44)
Immunosuppressive therapy	17 (27)	8 (27)	9 (28)
Prior CRKP infection within 1 year	12 (19)	6 (20)	6 (19)
Antibiotic use within 30 days	57 (92)	27 (90)	30 (94)
Cephalosporin	24 (39)	13 (43)	11 (34)
Carbapenem	23 (37)	12 (40)	11 (34)
Piperacillin-tazobactam	20 (32)	10 (33)	10 (31)
ICU stay	47 (76)	23 (77)	23 (72)
Septic shock	37 (60)	19 (63)	18 (56)
mAPACHE score, median (range)	18 (5-29)	18 (5-28)	17 (6-29)
CPIS for pneumonia (PNA)	7 (2-8)	6.5 (5-7)	7 (2-8)
Mechanical ventilation (MV)	36 (58)	19 (63)	18 (56)
CRRT or HD	17 (27)	10 (33)	7 (22)
Polymicrobial infection (same site)	27 (44)	9 (30)	18 (56)
Indwelling devices			
Central venous catheter (CVC)	45 (73)	23 (77)	22 (69)
Foley catheter	45 (73)	25 (83)	20 (63)
Overall LOS, days, median (range)	39 (8-472)	44 (8-472)	39 (8-248)
ICU LOS, days, median (range)	22 (2-219)	20 (3-134)	24 (2-219)
LOS prior to culture, days, median (range)	11 (0-172)	11 (1-161)	12 (0-172)
MV for PNA, days, median (range)	25 (2-219)	26 (3-121)	25 (2-219)

All values shown as n (%) unless otherwise specified. All *P* values were >0.05 when comparing treatment regimens as determined using Mann-Whitney U, Chi-square or Fisher's Exact Tests except polymicrobial infection (same site) *P*=0.044; CPIS for PNA (n=22); ICU LOS (n=47); MV for PNA (n=36); CPIS, clinical pulmonary infection score; ICU, intensive care unit; CRRT or HD, continuous renal replacement therapy or hemodialysis.

with multi-drug resistant (MDR) isolates (n=7). Of the 62 patients who were evaluated, 30 patients were treated with PMB plus *in vitro* active agent(s), and 32 patients with PMB plus *in vitro* inactive agent(s).

PMB dosing at our institution was revised in January 2009. Prior to 2009, PMB dosing was based on 15,000 to 25,000 units/kg of ideal body weight/day in two divided doses, with adjustment for renal function at the treating prescriber's discretion. From January 2009 onwards, PMB dosing was based on the hospital protocol established by our antimicrobial stewardship program: a loading dose of 25,000 units/kg was given on day 1, followed by 25,000 units/kg given every 24 h in patients with normal renal function. Subsequent doses and the dosing interval were adjusted based on CrCl [16].

Clinical Characteristics

Baseline characteristics are summarized in (Table 1). The median age of patients was 78 years (31-93 years), mAPACE score was 18 (5-29), 76% of patients required intensive care unit (ICU) stay, and 60% had septic shock. There were no significant differences between treatment groups except for polymicrobial infection, which was more common in patients treated with PMB plus inactive agent(s) (56% *vs.* 30%, P = 0.044) (*Enterococcus* spp. [n=10], *Pseudomonas aeuroginosa* [n=8], *Acinetobacter baumanii* [n=6], *Staphylococcus aureus* [n=5], *Proteus* spp [n=3], Enterobacteriaceae [n=3], and *Providencia* [n=1]). Among 62 infections, there were 22 (35.5%) pneumonias, 11 (17.7%) secondary bacteremias (sources of bacteremia were unknown [n=7], urinary [n=2], and skin and soft tissue infections [n=2] sources), 10 (16.1%) catheter-related bloodstream, 10 (16.1%) urinary, 4 (6.5%) skin and soft tissue infection, 3 (9.7%) intra-abdominal infections, and 2 (4.8%) cases of osteomyelitis. Median length of hospital stay was 39 days in patients treated with PMB plus *in vitro* active agent(s) *vs.* 44 days (P=0.56) in patients treated with PMB plus *in vitro* inactive agents(s).

Table 2: Treatment Characteristics.

	All (N=62)	PMB + Active (n=30)	PMB + Inactive (n=32)
PMB daily dose, units, median (IQR)	768,750 (468,750-1,059,822)	751,250 (377,143-1,070,000)	782,500 (500,000-1,085,000)
PMB daily dose per body weight, units/kg/day, median (IQR)	11,740 (6,708-15,220)	11,885 (5,660-15,199)	11,628 (7,206-14,957)
PMB cumulative dose, units, median (IQR)	7,385,000 (4,000,000-10,525,000)	7,385,000 (4,093,750-10,625,000)	7,425,000 (4,095,000-9,937,500)
PMB + tigecycline	37/62 (60)	29/30 (97)	8/32 (25)
PMB + meropenem	21/62 (34)	1/30 (3)	20/32 (63)
Prolonged infusion	3/62 (5)	0	3/32 (9)
PMB + cefepime	8/62 (13)	2/30 (7)	6/32 (19)
PMB + aminoglycoside	7/62 (11)	4/30 (13)	3/32 (9)
Gentamicin	4/62 (7)	2/30 (13)	2/32 (6)
Amikacin	2/62 (3)	1/30 (3)	1/32 (3)
Tobramycin	1/62 (2)	1/30 (3)	0

All values shown as n (%) unless otherwise specified. [1]All *P* values were >0.05 when comparing treatment regimens as determined using Chi-square or Fisher's Exact Tests except PMB + tigecycline *P*=0.0005; PMB + meropenem *P*=0.001.

Microbiology Data

Of the 62 CRKP isolates, 23 isolates tested by Kirby-Bauer disk diffusion were susceptible to PMB and an additional 39 isolates were also susceptible to PMB with a median MIC of 1 mg/L (range, 0.5 to 2 mg/L) by Etest. There were no significant differences between groups for susceptibilities except there were more CRKP isolates with PMB MIC <1.5 mg/L in the PMB plus *in vitro* inactive agent(s) group (64% [16/25] *vs.* 21% [3/14]) compared to the PMB plus *in vitro* active agent(s) group, (P = 0.02). However, PMB MIC data was reported for only 39 (63%) CRKP isolates from total of 62 treatment courses. Twenty-three remaining isolates were susceptible to PMB with unknown MIC since testing was performed by Kirby-Bauer disk diffusion. Fifteen isolates tested by Kirby-Bauer disk diffusion were susceptible to tigecycline and an additional 24 isolates were also susceptible with a median MIC of 2 mg/L (range, 0.5 to 2 mg/L) by Etest. Of the 62 CRKP isolates, a vast majority were resistant to ciprofloxacin (97%), tobramycin (98%), amikacin (90%) and cefepime (87%). The median MIC for amikacin was 64 mg/L (range, 2 to 64 mg/L), and gentamicin was 8 mg/L (range, 1 to 16 mg/L), respectively.

Treatment Course

Details of the treatment course are summarized in (Table 2). For both PMB plus *in vitro* active and inactive agent(s) groups, the median length of hospital stay prior to CRKP-positive culture (11 days *vs.* 12 days, P=0.85), median time to start of PMB from day of positive culture (3 days *vs.* 4 days, P=0.83), and median duration of PMB therapy (10 days *vs.* 10 days, P=0.71) was comparable. The total number of patients who received PMB dosing regimen prior to 2009 (47% [14/30] *vs.* 31% [10/32], P = 0.30) was comparable for *in vitro* active and inactive agent(s) groups. For both PMB plus *in vitro* active and inactive agent(s) groups, median daily dose (751,250 units *vs.* 782,500 units, P=0.92), median daily dose per body weight (11,885 units/kg/day *vs.* 11,628 units/kg/day, P = 0.90) and cumulative dose (7,385,000 units *vs.* 7,425,000 units, P = 0.69) were comparable (Table 2). Nineteen (31%) patients developed nephrotoxicity (33% [10/30] PMB + active agent(s) *vs.* 28% [9/32] PMB + inactive agent(s), P = 1.00).

Definitive therapy was selected at the discretion of the attending prescriber based on susceptibility results provided by our clinical laboratory. For definitive treatment, the most common regimen in the PMB plus *in vitro* active agent(s) was tigecycline (97%) and an aminoglycoside was the least common regimen utilized (13%). The total daily dose was 100mg loading dose followed by 50mg administered every 12 h for tigecycline. In the PMB plus *in vitro* inactive agent(s) group, combination with meropenem was the most common (63%) and PMB plus an aminoglycoside was the least common regimen utilized (9%). For patients who received meropenem, high dose 2 g every 8 h was used when indicated and only 3 patients (9.4%) received prolonged infusion dosing over 180 minutes. Aminoglycosides were administered once daily; 5mg/kg for

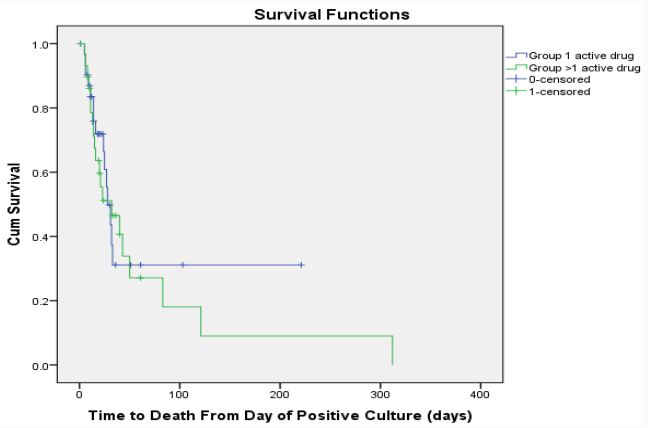

Figure 2: Kaplan-Meier survival estimates of patients with CRKP infections according to treatment regimens: polymyxin B plus in vitro active agent(s) (green line) versus polymyxin B plus in vitro inactive agent(s) (blue line). P = 0.64 (log rank test).

Table 3: Treatment outcomes.

Outcome	Overall	PMB + Active	PMB + Inactive
In-hospital mortality	35/62 (57)	20/30 (67)	15/32 (47)
Microbiologic failure	21/47 (44)	10/26 (39)	11/21 (52)
Clinical failure (EOT)[1]	31/62 (50)	17/30 (57)	14/32 (44)
Clinical deterioration	26/30 (83)	15/17 (88)	11/14 (79)
Death	5/30 (17)	2/17 (12)	3/14 (21)

All values shown as n (%). [1]Median duration of therapy was 14 days. All *P* values were >0.05 when comparing treatment regimens as determined using Chi-square or Fisher's Exact Tests. EOT. end of treatment.

Table 4: Univariate and multivariate analysis associated with in-hospital mortality in patients with CRKP infections.

	Univariate analysis				Multivariate analysis	
	Nonsurvivors (n=35)	Survivors (n=27)	*P* value	Odds Ratio (95% CI)	*P* value	Odds Ratio (95% CI)
Age of ≥65 years	28 (80)	18 (67)	0.26	2.0 (0.632-6.33)	--	--
ICU admission[1]	32 (91)	14 (52)	0.001	9.9 (2.4-40.32)	0.004	11.55 (2.15-62.01)
Comorbidities						
Cardio-vascular disease	23 (66)	16 (59)	0.79	1.3 (0.47-3.72)	--	--
Diabetes mellitus	9 (26)	12 (44)	0.18	0.4 (0.15-1.27)	--	--
Baseline renal insufficiency	14 (40)	10 (37)	1.00	1.1 (0.40-3.19)	--	--
Hospital-onset CRKP[1]	32 (91)	16 (59)	0.005	7.3 (1.79-30.01)	0.36	2.5 (0.36-17.15)
Characteristics on day of positive culture						
Septic shock[1]	28 (80)	9 (33)	0.0005	8.0 (2.53-25.31)	0.11	3.3 (0.78-13.7)
mAPACHE score. median (range)[1]	19 (9-28)	15 (5-29)	0.013	1.9 (0.64-5.69)	0.46	0.95 (0.84-1.08)
CVC[1]	32 (91)	13 (48)	0.0005	11.5 (2.83-46.8)	0.41	2.4 (0.31-18.52)
Inappropriate empiric therapy	27 (77)	20 (74)	1.00	1.2 (0.37-3.80)	--	--
Source of Infection						
Pneumonia	13 (37.1)	9 (33.3)	0.80	1.2 (0.41-3.39)	--	--
Secondary bacteremia	9 (25.7)	2 (7.4)	0.094	4.3 (0.85-22.03)	--	--
Catheter-related BSI[1]	9 (26)	1 (4)	0.033	9.0 (1.06-76.21)	0.07	9.4 (0.81-0.863)
Urinary tract infection[1]	1 (3)	9 (3)	0.002	0.059 (0.007-0.5)	0.037	0.09 (0.009-0.863)
Polymicrobial infection	15 (42.9)	12 (44.4)	1	0.938 (0.34-2.58)	--	--
Treatment Course						
PMB plus active agent(s)[1]	10 (37)	20 (57)	0.133	2.3 (0.81-6.34)	0.28	2.1 (0.55-8.08)
Loading dose	21 (60)	16 (59.3)	1	1.03 (0.371-2.896)	--	--
PMB regimen prior to 2009	14 (40)	10 (37)	1	1.13 (0.403-3.185)	--	--
PMB daily dose. units. median (IQR)	869.231 (412.500-1.250.000)	710.526 (500.000-975.000)	0.153	--	--	--
PMB daily dose per body weight. units/kg/day. median (IQR)	12.019 (6.221-15.684)	10.635 (6.870-14.771)	0.72	--	--	--
Cumulative dose. units. median (IQR)	7.800.000 (4.000.000-11.300.000)	7.000.000 (4.125.000-8.700.000)	0.375	--	--	--

Data are presented as n (%) unless otherwise specified. [1]Variable selected for multivariate analysis.

gentamicin or tobramycin and 15mg/kg for amikacin. Dosages were adjusted to creatinine clearance when indicated.

Treatment Outcomes

Overall, in-hospital mortality was 57% (35/62). In patients treated with PMB plus *in vitro* active *vs.* inactive agent(s), mortality was 67% (20/30) *vs.* 47% (15/32), P=0.13. Median time to death from the day of PMB initiation was 16 days (IQR 8-30 days): 15 days (IQR 8-44 days) in patients treated with PMB plus *in vitro* active agent(s), and 17days (IQR 7-28 days) in patient treated with PMB plus inactive agent(s). Kaplan-Meier survival estimation showed no significant difference in distribution of survival time for patients who received PMB plus *in vitro* active *vs.* inactive agents (P=0.64) (Figure 2).

Forty-seven patients had follow-up culture data, and 21 of 47 patients (44%) had failure of documented microbiologic clearance. In patients treated with PMB plus *in vitro* active *vs.* inactive agent(s), failure of microbiologic clearance was 39% *vs.* 52%, P = 0.34. Thirty-one patients had a subsequent isolate with CRKP a median of 12 days after completing the treatment course. Among these 31 patients, 17 (65%) had isolates tested for PMB susceptibility, of which 11 isolates had increased PMB MIC or were reported as resistant to PMB.

Thirty-one of 62 (50%) patients failed to attain clinical cure at the EOT, 57% (17/30) *vs.* 44% (14/32), P = 0.45 treated with *in vitro* active *vs.* inactive agent(s), respectively (Table 3). A total of 26 patients had documented clinical deterioration at EOT: 15 patients were treated with PMB plus *in vitro* active agent(s) and 11 patients were treated with PMB plus *in vitro* inactive agent(s). A total of 5 patients died at EOT at a median of 14 days: 2 patients were treated with PMB plus *in vitro* active agent(s), and 3 patients were treated with PMB plus *in vitro* inactive agent(s).

Predictors of In-Hospital Mortality

Clinical characteristics of survivors and non-survivors were compared to identify predictors of in-hospital mortality (Table 4). Age, gender, baseline renal insufficiency, Charlson score, median days to appropriate therapy, polymicrobial infection, and definitive treatment regimens were similar between the two groups. Additionally, the proportion of patients who received PMB dosing prior to 2009 was also similar among non-survivors and survivors (40% *vs.* 37%, OR, 1.13; 95% CI 0.403-3.185, P = 1.00). Of note, median daily and cumulative PMB doses were comparable between both treatment groups (Table 2) as well as between non-survivors and survivors (Table 4). Patients who required ICU admission (odds ratio (OR), 9.9; 95% confidence interval (CI), 2.4 to 40.32), presented with septic shock (OR, 8.0; 95% CI, 2.53 to 25.31), presented with

higher mAPACE scores (OR, 1.9; 95% CI, 0.64 to 5.69), had hospital-onset CRKP infections (OR, 7.3; 95% CI, 1.789 to 30.01), had central venous catheters (OR 11.5; 95% CI, 2.82 to 46.76), and had catheter-related blood stream infections [BSIs]as the source of infection (OR, 4.3; 95% CI, 0.85 to 22.03) were observed to have a higher probability of death. Patients who presented with CRKP urinary tract infection (OR, 0.059; 95% CI 0.007 to 0.50) were more likely to survive. In univariate analysis, these differences were statistically significant. In a multivariable analysis, ICU admission (OR, 11.55; 95% CI, 2.15 to 62.01) was identified as an independent predictor of death, and urinary tract infection was associated with survival (OR, 0.09; 95% CI, 0.009 to 0.863) (Table 4).

Discussion

Treatment of patients with CRKP infections represents a significant clinical challenge especially when PMB is the only *in vitro* active agent based on the susceptibility profile. To our knowledge, this single center retrospective cohort study is the first to report outcomes of patients with only CRKP infections treated with PMB as the backbone therapy in combination with *in vitro* active (n=30) *vs.* inactive (n=32) agent(s). In our study, an overall in-hospital mortality rate was 57%. This finding is similar to previous published studies supporting the high mortality rate associated with CRKP infections [2,8]. ICU stay was identified as the only independent predictor of mortality, and this finding is consistent with previous reports [2,8,17].

The decision to add *in vitro* inactive agent(s) to PMB backbone therapy in critically ill patients with CRKP infections susceptible only to PMB still presents a therapeutic dilemma. Few pharmacokinetic/pharmacodynamic (PK/PD) *in vitro* evaluations demonstrated synergistic activity when PMB was administered in combination with other antimicrobials, such as meropenem, tigecycline, cefepime, or aminoglycosides [10,18]. Yet, it remains unknown if *in vitro* findings translate into clinical efficacy. Our findings suggest similar in-hospital mortality (67% *vs.* 47%, P= 0.13), microbiological failure (39% *vs.* 52%, P=0.34), and clinical failure (57% *vs.* 44%, P=0.45) rates in patients treated with combination of PMB plus *in vitro* active agent(s) as compared to *in vitro* inactive agent(s).

Although this was not the objective of this study, comparing PMB monotherapy to PMB combination with *in vitro* inactive agent(s) would be necessary to evaluate the potential value of adding *in vitro* inactive agent(s). Our institution previously reported outcomes of patients with CRKP infections treated with PMB monotherapy [19]. In this monotherapy study, ICU stay and septic shock were reported only in 53% and 25% of patients, respectively and a majority of patients had either BSI (45%) (sources of bacteremia were catheter ((n=3), urinary (n=4), pulmonary (n=4), and intra-abdominal (n=3)) or urinary tract infection (30%) as the primary sources of infection. In the current study, our patient population was more critically ill and a higher percentage of our patients had either BSIs (34%) or pneumonia (36%) as the source of infection. In our previous monotherapy study, a majority of patients achieved clinical and microbiologic cure and overall in-hospital mortality was only 28% as compared to 57% in our current study. These findings provide insight that providers may be more likely to prescribe PMB combination therapy for critically ill patients. Therefore, a direct comparison of PMB monotherapy *vs.* combination therapy in the patients with the same degree of critical illness might not be possible.

A number of limitations are appreciable in our study including a small sample size from a single center in New York City that has a high prevalence of CRKP isolates. Secondly, our study had a retrospective design and the study time frame spanned over 7 years. Our results may not be applicable to other institutions because our hospital's PMB dosing protocol may not be in accordance to dosing strategies at other institutions. Although our PMB dosing changed, *in vitro* studies showed bactericidal activity of PMB is concentration-dependent related to AUC/MIC and altering the dosing schedule with identical daily doses does not appear to influence PMB bactericidal activity or resistance suppression [20]. Also, our study excluded patients who received monotherapy, included patients with polymicrobial infections, and definitive therapy was selected by the treating prescribers's discretion. Lastly, susceptibility testing for PMB was determined by Kirby-Bauer disk diffusion and Etest, which may result in variation in susceptibilities compared to broth microdilution.

In conclusion, in this single center cohort of patients, CRKP infections were associated with a high mortality rate and clinical failure. Our findings suggest ICU admission is associated with treatment failure and CRKP UTI as the source of infection is associated with survival. Our findings suggest that mortality, microbiological, and clinical failure was comparable between patients with CRKP infections treated with PMB in combination with *in vitro* active *vs.* inactive agent(s). Larger studies are needed to compare treatment efficacy of PMB backbone therapy in combination based on *in vitro* activity to define the potential value of using *in vitro* inactive agents.

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