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

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**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

**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 challenge as 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 carbapenemases 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 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 (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.](image-url)
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), mAPACHE 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 aeruginosa* [n=8], *Acinetobacter baumannii* [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 (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 agent(s).

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N=62)</th>
<th>PMB + Active (n=30)</th>
<th>PMB + Inactive (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>78 (31-93)</td>
<td>79 (37-90)</td>
<td>77 (31-93)</td>
</tr>
<tr>
<td>Male</td>
<td>35 (57)</td>
<td>20 (67)</td>
<td>15 (47)</td>
</tr>
<tr>
<td>Body weight (kg), median (IQR)</td>
<td>72.9 (60.1-82.8)</td>
<td>73.4 (59.2-80.3)</td>
<td>72.1 (64.7-84.6)</td>
</tr>
</tbody>
</table>

Comorbidities

- Cardiovascular disease: 39 (63) vs. 17 (57) vs. 22 (69)
- Diabetes mellitus: 21 (34) vs. 12 (40) vs. 9 (28)
- Solid tumor: 19 (31) vs. 9 (30) vs. 10 (31)
- Hematological malignancy: 9 (15) vs. 4 (13) vs. 5 (16)
- Charlson morbidity index, median (range): 4 (0-12) vs. 4 (0-12) vs. 3 (0-10)
- Baseline renal insufficiency: 24 (39) vs. 10 (33) vs. 14 (44)
- Immunosuppressive therapy: 17 (27) vs. 8 (27) vs. 9 (28)
- Prior CRKP infection within 1 year: 12 (19) vs. 6 (20) vs. 6 (19)
- Antibiotic use within 30 days: 57 (92) vs. 27 (90) vs. 30 (94)
- Cephalosporin: 24 (39) vs. 13 (43) vs. 11 (34)
- Carbapenem: 23 (37) vs. 12 (40) vs. 11 (34)
- Piperacillin-tazobactam: 20 (32) vs. 10 (33) vs. 10 (31)
- ICU stay: 47 (76) vs. 23 (77) vs. 23 (72)
- Septic shock: 37 (60) vs. 19 (63) vs. 18 (56)
- mAPACHE score, median (range): 18 (5-29) vs. 18 (5-28) vs. 17 (6-29)
- CPIS for pneumonia (PNA): 7 (2-8) vs. 6.5 (5-7) vs. 7 (2-8)
- Mechanical ventilation (MV): 36 (58) vs. 19 (63) vs. 18 (56)
- CRRT or HD: 17 (27) vs. 10 (33) vs. 7 (22)
- Polymicrobial infection (same site): 27 (44) vs. 9 (30) vs. 18 (56)

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.
Table 2: Treatment Characteristics.

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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsurvivors (n=35)</td>
<td>Survivors (n=27)</td>
</tr>
<tr>
<td>Age of &gt;65 years</td>
<td>28 (80)</td>
<td>18 (67)</td>
</tr>
<tr>
<td>ICU admission*</td>
<td>32 (91)</td>
<td>14 (52)</td>
</tr>
</tbody>
</table>

Comorbidities

- Cardio-vascular disease: 23 (66) vs. 16 (59) (P=0.39)
- Diabetes mellitus: 9 (26) vs. 12 (44) (P=0.18)
- Baseline renal insufficiency: 14 (40) vs. 10 (37) (P=0.10)
- Hospital-onset CRKP*: 32 (91) vs. 16 (59) (P=0.001)

Characteristics on day of positive culture

- Septic shock*: 28 (80) vs. 9 (33) (P=0.001)
- nAPACHE score. median (range)*: 19 (9-28) vs. 15 (5-29) (P=0.013)
- CVC*: 32 (91) vs. 13 (48) (P=0.001)
- Inappropriate empiric therapy: 27 (77) vs. 20 (74) (P=0.005)

Source of Infection

- Pneumonia: 13 (37.1) vs. 9 (33.3) (P=0.80)
- Secondary bacteremia: 9 (25.7) vs. 2 (7.4) (P=0.50)
- Catheter-related BSI*: 9 (26) vs. 1 (4) (P=0.33)
- Urinary tract infection*: 1 (3) vs. 9 (3) (P=0.02)
- Polymicrobial infection: 15 (42.9) vs. 12 (44.4) (P=0.005)

Treatment Course

- PMB plus active agent(s)*: 10 (37) vs. 20 (57) (P=0.133)
- Loading dose: 21 (60) vs. 16 (59.3) (P=1.03)
- PMB regimen prior to 2009: 14 (40) vs. 10 (37) (P=1.13)
- PMB daily dose. units. median (IQR): 869.231 vs. 710.526 (412.500-1,250.000) vs. (500.000-975.000) (P=0.153)
- PMB daily dose per body weight. units/kg/day. median (IQR): 10.835 vs. 10.938 (6.870-14.771) vs. (4.000-8.700) (P=0.72)

Data are presented as n (%) unless otherwise specified. Variables 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 17 days (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 (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 dosages 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 mAPACHE 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 multivariate 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.

**References**


