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ORIGINAL RESEARCH

Comparison of Efficacy and Safety of Colistimethate Sodium and Polymyxin B in the Treatment of Bloodstream Infection Caused by Carbapenem-Resistant Gram-Negative Bacteria: A Retrospective Study

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Background: This study aimed to compare the efficacy and safety of colistimethate sodium (CMS) and polymyxin B (PMB) in treating carbapenem-resistant Gram-negative bacteria (CR-GNB)-induced bloodstream infection (BSI) based on real-world data. While international studies on CMS and PMB have yielded conflicting results, there is a lack of direct comparative data from Chinese cohorts, where the pathogen distribution may influence outcomes.

Methods: A retrospective analysis was conducted on 373 Chinese patients with CR-GNB-induced BSI who received CMS-containing therapy (n=132) or PMB-containing therapy (n=241) between Dec 2021 and Dec 2023. Propensity score matching was used to balance the two groups at a ratio of 1:2. The primary outcome was clinical success. The secondary outcomes included inpatient days, in-hospital mortality, 28-day all-cause mortality, and incidence of adverse events. Statistical analysis was performed with Wilcoxon rank sum test, Student's *t*-test, chi-square test, and Fisher's exact test as appropriate.

Results: In this cohort, Acinetobacter baumannii was the predominant pathogen (53.4%). No significant differences were observed in efficacy outcomes between the two groups ($p>0.05$). For safety, the difference in hyperpigmentation incidences between the two groups was statistically significant (CMS vs PMB: 0.0% vs 6.36%, $p=0.04$). Incidences of hypersensitivity, neurotoxicity, and nephrotoxicity were similar between groups ($p>0.05$). A longer treatment course (>12 days), while associated with a higher incidence of hyperpigmentation, was linked to significantly improved clinical outcomes, including higher success rate, reduced in-hospital mortality, and lower 28-day all-cause mortality ($p<0.05$).

Conclusion: This study provides the first large, real-world comparative evidence from a Chinese cohort with CR-GNB BSIs. In this setting, CMS and PMB demonstrated comparable efficacy. The critical difference lay in the safety profile, with CMS associated with a markedly lower incidence of hyperpigmentation. This finding provides a tangible basis for antibiotic stewardship, positioning CMS as a valuable first-line polymyxin option.

Keywords: bloodstream infection, colistimethate sodium, carbapenem-resistant Gram-negative bacteria, polymyxin B

Introduction

Bloodstream infections (BSIs) are a significant public health concern, characterized by high morbidity, rapid progression, and elevated mortality rates. In hospitalized patients, BSIs rank as the second most common infection after respiratory tract infections in China, with a morbidity rate of 4.57–6.50 per thousand.[1] A major challenge in managing BSIs is the

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rise of drug-resistant pathogens, particularly carbapenem-resistant Gram-negative bacteria (CR-GNB), which have become a prevalent cause of these infections.[2,3] Effective treatment options for CR-GNB-induced BSIs are limited, and polymyxins emerge as a potential last line of clinical defense. Polymyxins, specifically polymyxin B (PMB) and polymyxin E (colistin, administered as colistimethate sodium-CMS), belong to a class of antibiotics known as cationic peptides. They exhibit potent activity against certain gram-negative bacteria, including CR-GNB strains.[4] Although polymyxins fell out of favor due to concerns over toxicity and the availability of more effective antibiotics, they have resurfaced as viable treatment options in the era of antibiotic resistance. The reevaluation of polymyxins has led to improved dosing strategies and a better understanding of their role in combating CR-GNB-induced infections.[5,6] National and international guidelines provide consensus recommendations for the management of CR-GNB-induced BSI, emphasizing the importance of evidence-based approaches and the judicious use of antibiotics. Both CMS and PMB can be used to treat BSIs caused by multidrug-resistant/pan-drug-resistant bacteria, and the guidelines do not specify which polymyxin is more effective or safer.[7,8]

CMS is a prodrug that requires conversion to its active form, colistin, after intravenous administration to exert antibacterial activity. In contrast, PMB does not require this conversion process. Consequently, PMB is believed to achieve bactericidal concentrations in the bloodstream more rapidly after administration, potentially offering a quicker onset of action in treating bloodstream infections (BSI).[9] However, the comparative clinical efficacy and safety of CMS and PMB in treating CR-GNB induced BSIs remain subjects of debate.[10,11] The available evidence is confined to international studies characterized by limited BSI sample sizes, which report conflicting data on nephrotoxicity and mortality. For instance, while some studies have reported a significantly higher incidence of nephrotoxicity with CMS compared to PMB (eg, 55.3% vs 21.1%;[12] 38.3% vs 12.7%[13]), others have found no statistically significant difference in acute kidney injury.[14] Similarly, mortality rates have shown no consistent advantage for either agent, with some studies reporting comparable mortality[12,14] and others noting a non-significant trend favoring CMS.[13] A leading hypothesis for these discrepant findings centers on the fundamental pharmacological difference between the two drugs: CMS is an inactive prodrug that must be converted to colistin in the body, potentially leading to variable and suboptimal plasma levels in BSIs, whereas PMB is administered as the active compound. This has led to persistent clinical uncertainty over whether one agent is superior for achieving treatment success in bloodstream infections. Furthermore, this critical question has not been specifically addressed in a Chinese population with domestically manufactured formulations. Therefore, this study aims to address this gap by comparing the efficacy and safety of CMS and PMB in the treatment of CR-GNB-induced BSI, using real-world data from China.

Methods

Study Design and Population

This is a retrospective study and data were collected between Dec 2021 and Dec 2023 from hospitalized patients (n=8161). Inclusion criteria include: patients with age 18–85 years; patients hospitalized with confirmed primary/secondary bloodstream infections defined as an infection with a positive blood culture for CR-GNB including carbapenem-resistant acinetobacter baumannii (CRAB), carbapenem-resistant pseudomonas aeruginosa (CRPA), carbapenem-resistant klebsiella pneumoniae (CRKP) and Escherichia coli; patients were administered CMS (intravenous [IV]) or PMB (IV) for a duration of at least three days. Exclusion criteria include: patients with estimated creatinine clearance <30 mL/min; patients with Child-Pugh liver function rating of class C; patients were immunocompromised and at risk for opportunistic pathogen infections, including but not limited to the following: 1) history of HIV (AIDS or CD4 <200); 2) radiotherapy within the previous 3 months; 3) immunosuppressive therapy including maintenance corticosteroid therapy for 30 days (0.5 mg/kg prednisone per day or other equivalent hormone or more); 4) absolute neutrophil count <500/mm3; 5) significantly missing data from the primary study (such as missing test data, sample baseline information, medication regimen, and medication adjustment records). This study was performed by the approval of ethical committee of the institutes.

Eligible patients were initially divided into a CMS-containing treatment group and a PMB-containing treatment group. To minimize selection bias and improve the comparability of these non-randomized groups, we performed a 1:2

propensity score matching (PSM). Propensity scores were calculated using key baseline covariates known to influence outcomes, including gender, age, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, a validated system for classifying disease severity.[15] The matching procedure successfully created well-balanced groups for subsequent analysis.

Outcomes

The primary outcomes of this study were clinical success at the end of treatment, defined as complete remission or significant improvement of infection signs and symptoms, with the patient not requiring additional antimicrobial therapy. Clinical success was evaluated by assessing the resolution of clinical symptoms and the patient's overall clinical status at the conclusion of the treatment period. The secondary outcomes included inpatient days, in-hospital mortality, 28-day all-cause mortality and adverse events (AEs), including nephrotoxicity,[16] neurotoxicity,[16] hypersensitivity reactions, and hyperpigmentation.[17]

For nephrotoxicity, according to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline,[18] renal impairment is diagnosed when any of these three criteria is met: 1) blood creatinine increase ≥26.5μmol/L within 48 hours(h); 2) blood creatinine increase more than 1.5 times of the basal value within 7 days and above; 3) decrease in urine output (< 0.5 mL/kg/h) and the duration is more than 6h. Neurotoxicity include dizziness, ataxia, sensory abnormalities, mental status changes (such as somnolence) or seizures. Hypersensitivity reaction includes drug urticarial and generalized itching etc. Hyperpigmentation is diagnosed according to the Felix von Luschan skin color scale[19] or the clinical diagnosis of hyperpigmentation.[20]

Procedures

This was a retrospective, non-interventional post-marketing study, and the type of therapeutic measures that physicians administer to their patients is not influenced by this study. The specific treatment regimen was also at the discretion of the physician based on the patient's actual condition and is not affected by this study. The cases included in this study were hospitalized patients with confirmed BSIs due to CR-GNB, and the study did not require actions outside of conventional medical treatment. Cases were screened by physicians based on inclusion and exclusion criteria. Required evaluation items included, but were not limited to: demographic information, disease diagnosis, medical history, test and assay results, and prior/combined medications.

Statistical Analysis

A quantitative indicator was tested for normality. Comparison between two groups was tested by Wilcoxon rank sum test for data not meeting normal distribution. Comparison between two groups was tested by *t*-test if data was normally distributed. The statistical description includes mean, standard deviation, median, and upper and lower quartiles. The frequency and its percentage were listed in the statistical description of the qualitative or categorical indicators. Comparisons of unordered categorical indicators were made using the chi-square test or the exact probability method (Fisher's method). To identify independent factors associated with clinical efficacy, a multifactorial logistic regression analysis was conducted on the matched cohort. The model included treatment group (CMS vs PMB), along with other clinically relevant variables such as treatment days and surgery status. The results were reported as odds ratios (OR) with their corresponding 95% confidence intervals (CI). All statistical tests were two-sided and a p-value less than or equal to 0.05 was considered statistically significant for the difference being tested.

Results

Patient Baseline Characterization

As shown in Figure 1 and Table 1, the CMS group included 132 patients and the PMB group included 241 patients before PSM. Among a total of 373 patients, the median age was 59 years, and 71.05% were male. Median BMI was 22.61 (interquartile range [IQR]: 20.21–25.45) kg/m^2. The patients had combined therapy with carbapenems, tigecycline or ceftazidime-avibactam occupied 63.54%, 52.01%, and 26.54%, respectively. Acinetobacter baumannii (53.35%) was the

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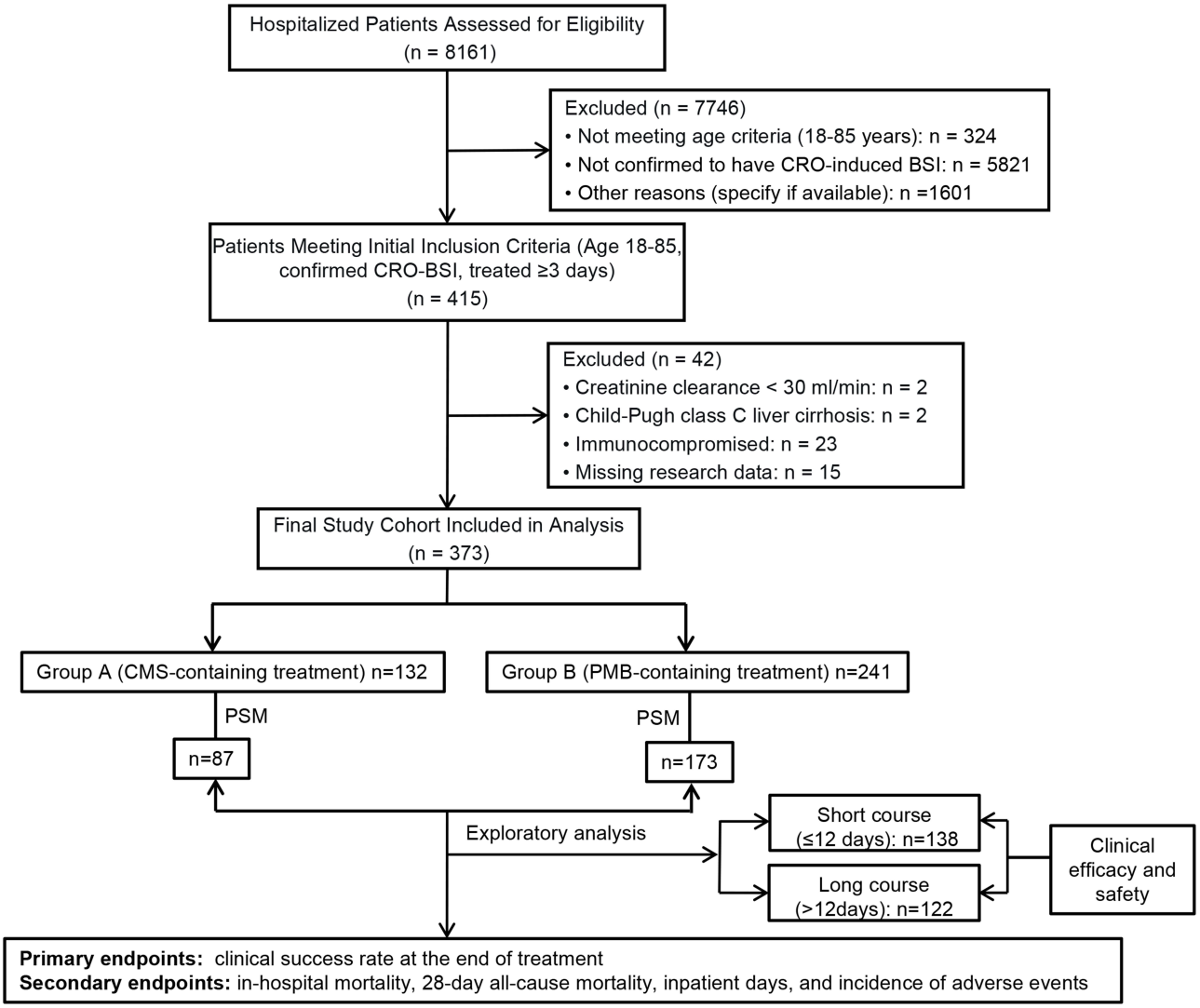

Figure 1 Patient disposition.
Abbreviations: CMS, Colistimethate sodium; PMB, polymyxin B; CR-GNB, carbapenem-resistant Gram-negative bacteria.

most common pathogen, followed by Pseudomonas aeruginosa (30.03%), Klebsiella pneumonia (28.69%) and Escherichia coli/others (26.27%). The median treatment days (polymyxin therapy) was 12 (IQR: 7.00–20.00) and the median inpatient days were 32 (IQR: 20.00–49.00). For CMS group patients, median dose administered (CMS) was 300 mg colistin base activity (CBA) per day (IQR: 150.00 ~ 300.00). For PMB group patients, median dose (PMB) was 1 million U per day (IQR: 100.00 ~ 125.00). Both drugs were administrated according to the international consensus guidelines.[7]

Before PSM, the difference in age between the two groups was statistically significant, with a median age of 56.00 years in the CMS group being lower than 60.00 years in the PMB group. The difference in APACHE II between the two groups was also statistically significant, with a median APACHE II of 20.00 in the CMS group being lower than 23.00 in the PMB group (Table 1). To minimize selection bias and balance potential confounders, we performed a 1:2 PSM. After matching, the final analysis cohort consisted of 87 patients in the CMS group and 173 in the PMB group. As summarized in Table 1, PSM successfully balanced the two groups, with no statistically significant differences in key baseline characteristics remaining, including age and APACHE II score, which were imbalanced prior to matching.

Table 1 Patient Baseline Characteristics Before and After PSM

Variables	Total N=373 Median (IQR)/n (%)	Before PSM			After PSM		
		CMS (n=132)	PMB (n=241)	P value	CMS (n=87)	PMB (n=173)	P value
Age, years	59.00 (48.00–70.00)	56.00 (42.00–69.25)	60.00(50.00–71.00)	0.048	56.00 (46.50–67.50)	59.00(48.00–70.00)	0.408
Gender (Male)	265 (71.05%)	89 (67.42%)	176 (73.03%)	0.254	64 (73.56%)	126 (72.83%)	0.9
BMI, kg/m^2	22.61 (20.21–25.45)	23.47 (21.50–26.12)	21.78(19.59–24.99)	0.012	23.35 (21.49–27.66)	22.40(19.43–24.89)	0.041
Temperature	38.00 (37.12–38.58)	38.00 (37.23–38.60)	37.95(37.08–38.50)	0.292	38.00 (37.20–38.50)	37.80(37.00–38.50)	0.631
Systolic pressure	123.00(110.50–136.00)	124.00(111.00–135.50)	123.00(110.00–136.00)	0.792	124.00(112.00–136.00)	124.50(110.75–137.00)	0.959
Diastolic pressure	69.00 (61.00–77.00)	71.00 (63.00–81.00)	69.00 (60.00–76.00)	0.038	71.00 (63.00–81.00)	69.50 (61.75–76.00)	0.219
Laboratory results							
PCT, ng/mL	1.37 (0.36–4.80)	0.71 (0.19–4.17)	1.50 (0.45–5.35)	0.008	0.69 (0.25–3.46)	1.15 (0.38–4.25)	0.118
WBC, 10–9/L	9.28 (4.69–13.84)	7.47 (2.17–10.89)	10.60 (6.22–14.81)	<0.001	8.41 (3.70–12.07)	9.60 (6.25–13.88)	0.043
Albumin, g/L	34.02 (30.90–37.52)	34.00 (30.85–37.55)	34.05 (30.90–37.50)	0.602	34.50 (31.10–37.10)	34.50 (31.20–37.70)	0.529
CRP, mg/L	88.20 (44.96–141.18)	72.26 (32.11–123.28)	90.78(47.47–144.31)	0.067	74.11(29.73–123.48)	85.77(45.30–141.18)	0.19
Creatinine, μmol /L	78.45 (53.05–148.00)	72.40 (50.00–126.50)	85.00(54.85–151.00)	0.185	78.00 (53.70–126.50)	79.00(52.30–135.50)	0.693
Combination drug therapy							
Carbapenems	237 (63.54%)	82 (62.12%)	155 (64.32%)	0.674	58 (66.67%)	125 (72.25%)	0.352
Tigecycline	194 (52.01%)	64 (48.48%)	130 (53.94%)	0.313	34 (39.08%)	80 (46.24%)	0.272
Ceftazidime-avibactam	99 (26.54%)	33 (25.00%)	66 (27.39%)	0.618	14 (16.09%)	26 (15.03%)	0.823
Pathogen, n (%)							
Acinetobacter baumannii	199 (53.35%)	56 (42.42%)	143 (59.34%)	0.002	36 (41.38%)	99 (57.23%)	0.016
Klebsiella pneumoniae	107 (28.69%)	28 (21.21%)	79 (32.78%)	0.018	20 (22.99%)	61 (35.26%)	0.044
Pseudomonas aeruginosa	112 (30.03%)	28 (21.21%)	84 (34.85%)	0.006	18 (20.69%)	62 (35.84%)	0.013
Escherichia coli/others	98 (26.27%)	64 (48.48%)	34 (14.11%)	<0.001	42 (48.28%)	25 (14.45%)	<0.001
Basic chronic disease, n (%)							
High blood pressure	147 (39.41%)	32 (24.24%)	115 (47.72%)	<0.001	21 (24.14%)	81 (46.82%)	<0.001
Diabetes	103 (27.61%)	29 (21.97%)	74 (30.71%)	0.071	21 (24.14%)	54 (31.21%)	0.235
Hyperlipidemia	45 (12.06%)	11 (8.33%)	34 (14.11%)	0.102	10 (11.49%)	21 (12.14%)	0.88
Coronary heart disease	31 (8.31%)	8 (6.06%)	23 (9.54%)	0.244	4 (4.60%)	11 (6.36%)	0.566
Surgery, n (%)				0.725			0.888
Level II	40 (10.72%)	9 (6.82%)	31 (12.86%)		8 (9.20%)	24.0 (13.87%)	
Level III	22 (5.90%)	7 (5.3%)	15 (6.22%)		5 (5.75%)	11.0 (6.36%)	
Level IV	50 (13.40%)	13 (9.85%)	37 (15.35%)		10 (11.49%)	29.0 (16.76%)	
Malignancies, n (%)							
Solid	18 (4.83%)	8 (6.06%)	37 (15.35%)	0.008	3 (3.45%)	23 (13.29%)	0.013
Haematological	45 (12.06%)	10 (7.58%)	8 (3.32%)	0.067	3 (3.45%)	8 (4.62%)	0.906
Scores							
APACHE II scores	21.00 (17.00–26.00)	20.00 (15.00–23.00)	23.00 (19.00–26.00)	<0.001	20.00 (17.00–23.00)	21.00 (17.00–25.00)	0.141
SOFA scores	6.00 (5.00–7.00)	6.00 (5.00–7.00)	6.00 (5.00–7.00)	0.705	6.00 (5.00–7.00)	6.00 (5.00–7.00)	0.204
Inpatient days (days)	32.00 (20.00–49.00)	31.00 (22.00–47.25)	33.00 (19.00–50.00)	0.959	31.00(22.00–49.00)	34.00 (20.00–50.00)	0.831
Length of ICU stay (days)	26.00 (14.00 ~ 38.00)	28.00 (19.00–39.00)	27.00 (15.00–42.00)	0.615	27.00(18.00–38.00)	27.00 (15.00–42.00)	0.693
Days of treatment (days)	12.00 (7.00–20.00)	11.00(7.00–21.25)	12.00 (6.00–20.00)	0.321	11.00(7.00–21.00)	12.00 (6.00–19.00)	0.327
Mechanical ventilation duration (hours)	390.00(213.75–640.75)	410.00(142.00–663.00)	369.00(236.00–631.00)	0.831	370.50(144.50–584.25)	363.00(216.50–633.50)	0.864

Notes: Surgery level, level II surgery refers to surgeries with moderate risk, average process complexity and moderate technical difficulty; level III surgery refers to surgeries with high risk, relatively complex procedures, and significant technical difficulty; level IV refers to surgeries with very high risk, complex procedures, and high technical difficulty.

Abbreviations: PSM, propensity score matching; CMS, colistimethate sodium; PMB, polymyxin B; IQR, interquartile range; BMI, body mass index; PCT, procalcitonin; WBC, white blood count; CRP, C-reactive protein; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; ICU, intensive care unit.

Efficacy

The primary analysis of the matched cohort revealed no statistically significant differences in clinical efficacy between CMS and PMB. Specifically, the clinical success rate was 68.97% in the CMS group compared to 70.52% in the PMB group (p=0.796). Similarly, there were no significant differences in in-hospital mortality (29.89% vs 27.75%, p=0.831), 28-day all-cause mortality (24.14% vs 23.70%, p=0.938), or inpatient days (Table 2 and Supplemental Figure 1). When analyzing the factors related to the clinical efficacy, univariate logistic regression analysis showed that clinical efficacy was significantly associated treatment days and surgery (Table 3). Further multifactorial logistic regression analysis

Table 2 Comparison of Clinical Outcomes Between Two Groups

	CMS (N=87)	PMB (N=173)	p-value
Clinical success rate, n (%)	60 (68.97%)	122 (70.52%)	0.796
Inpatient days, median (IQR)	31.00 (22.00 ~ 49.00)	34.00 (20.00 ~ 50.00)	0.831
In-hospital mortality	26 (29.89%)	48 (27.75%)	0.718
28-day all-cause mortality	21 (24.14%)	41 (23.70%)	0.938

Table 3 Univariate Analysis of Factors Affecting Clinical Efficacy in All Patients After PSM

Variables	Clinical Efficacy*		OR (95% CI)	p-value
	1 (N=182)	0 (N=78)		
Gender	134 (73.63%)	56 (71.79%)	1.10(0.61~1.98)	0.760
Age	57.00 (46.00 ~ 69.00)	59.50 (49.25 ~ 69.00)	0.99(0.97~1.01)	0.376
Acinetobacter baumannii	96 (52.75%)	39 (50.00%)	1.12(0.66~1.90)	0.685
Klebsiella pneumoniae	53 (29.12%)	28 (35.90%)	0.73(0.42~1.29)	0.280
Pseudomonas aeruginosa	60 (32.97%)	20 (25.64%)	1.43(0.79~2.59)	0.242
Other Bacteria	47 (25.82%)	20 (25.64%)	1.01(0.55~1.85)	0.975
Inpatient days	33.00 (21.00 ~ 49.75)	31.00 (20.00 ~ 48.75)	1.00(0.99~1.01)	0.578
Treatment Days	13.00 (7.00 ~ 21.00)	8.00 (5.00 ~ 14.75)	1.03(1.00~1.05)	0.039**
Hypertension	71 (39.01%)	31 (39.74%)	0.97(0.56~1.67)	0.912
Diabetes	50 (27.47%)	17 (21.79%)	1.36(0.73~2.55)	0.338
Hyperlipidemia	22 (12.09%)	4 (5.13%)	2.54(0.85~7.64)	0.096
Coronary Artery Disease	11 (6.04%)	4 (5.13%)	1.19(0.37~3.86)	0.772
Malignant tumor	27 (14.84%)	11 (14.10%)	1.06(0.50~2.26)	0.878
Albumin	34.50 (30.85 ~ 37.77)	34.42 (31.95 ~ 37.30)	0.99(0.94~1.04)	0.660
Creatinine	74.00 (50.55 ~ 134.00)	85.55 (57.45 ~ 133.50)	1.00(1.00~1.00)	0.513
CRP	80.88 (50.96 ~ 120.45)	80.88 (57.46 ~ 87.79)	1.00(1.00~1.01)	0.168
PCT	1.04 (0.31 ~ 3.96)	1.04 (0.53 ~ 3.02)	1.01(0.99~1.04)	0.240
WBC	8.41 (4.94 ~ 12.87)	10.88 (5.05 ~ 13.95)	0.99(0.96~1.02)	0.551
Surgery	53 (29.12%)	34 (43.59%)	0.53(0.31~0.92)	0.024**
APACHE II	21.00 (17.25 ~ 24.00)	21.00 (16.25 ~ 24.00)	1.01(0.96~1.06)	0.749
SOFA	6.00 (5.00 ~ 7.00)	6.00 (5.00 ~ 7.00)	1.00(0.83~1.20)	1.000
Body temperature	37.90 (37.20 ~ 38.50)	37.90 (37.00 ~ 38.20)	1.20(0.89~1.62)	0.226
Systolic pressure	124.00 (111.00 ~ 137.00)	124.00 (113.50 ~ 134.25)	1.00(0.99~1.02)	0.474
Diastolic pressure	70.00 (63.00 ~ 78.00)	70.00 (62.00 ~ 75.00)	1.01(0.99~1.03)	0.502
Ceftazidime Avibactam	49 (26.92%)	16 (20.51%)	1.43(0.75~2.71)	0.275
Tigecycline	96 (52.75%)	36 (46.15%)	1.30(0.77~2.22)	0.330
Carbapenems	112 (61.54%)	53 (67.95%)	0.75(0.43~1.32)	0.326
ICU	171 (93.96%)	71 (91.03%)	1.53(0.57~4.11)	0.397
MV	147 (80.77%)	66 (84.62%)	0.76(0.37~1.56)	0.461

Notes: *Clinical efficacy refers to clinical success. **P value < 0.05. Ceftazidime avibactam, tigecycline, and carbapenems are coadministered after the use of polymyxins.

Abbreviations: OR, odds ratio; CRP, C-reactive protein; PCT, Procalcitonin; WBC, white blood cell; ICU, Intensive care unit; MV, mechanical ventilation; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment.

revealed that the treatment days (OR=1.03, 95% CI: 1.00–1.05) was an independent protective factor affecting the clinical efficacy, and the patients' surgery status (OR=0.52, 95% CI: 0.30–0.91) was an independent risk factor (Supplemental Table 1).

Safety

The safety profiles of the two drugs were largely similar, with one key exception. The incidence of hyperpigmentation was significantly higher in the PMB group (6.4% [11/173]) compared to the CMS group (0.0% [0/87], p=0.04). In contrast, no statistically significant differences were observed in hypersensitivity reactions (p=0.37), neurotoxicity (p=0.23) and nephrotoxicity (p=0.69, Table 4).

Impact of Treatment Duration: An Exploratory Analysis

Given the finding that treatment duration was an independent factor for clinical efficacy, we performed an exploratory analysis. All matched patients (n=260) were categorized into short-course (≤12 days, n=138) and long-course (>12 days, n=122) groups. Statistical analysis revealed no significant differences between the two groups in terms of age, gender, or baseline APACHE II scores (Supplemental Table 2). When comparing the outcomes between the two groups, patients who received a longer course of therapy (>12 days) were associated with better clinical outcomes, including a higher clinical success rate (p<0.001), lower in-hospital mortality rate (p=0.02) and reduced 28-day all-cause mortality rate (p<0.001, Supplemental Table 3). Regarding safety, the long-course group had a higher incidence of hyperpigmentation (p=0.02), but no significant differences in other adverse events (Supplemental Table 4).

Discussion

To our knowledge, this is the first large real-world study comparing the efficacy and safety of CMS and PMB in Chinese patients with CR-GNB-induced BSIs. We found both drugs equally effective in treating BSIs, with similar clinical success rate, and no differences in in-hospital or 28-day all-cause mortality. Our study also revealed important distinctions between the two groups. The CMS group showed no hyperpigmentation, a significant advantage over the PMB group. Furthermore, after PSM, we found that longer treatment courses (>12 days) significantly improved clinical efficacy while reducing in-hospital and 28-day all-cause mortality compared to shorter courses (≤12 days). This suggests that the duration of antibiotic administration is an independent protective factor for clinical efficacy.

Most clinicians consider CMS a prodrug that requires conversion to active colistin after intravenous infusion, leading to a preference for PMB in treating CR-GNB-induced conditions.[4,6] However, research data directly comparing the efficacy of the two drugs is still limited. Our real-world study found comparable clinical efficacy between CMS and PMB in treating CR-GNB-induced BSIs. This aligns with Vieceli's study, which reported no difference in 30-day mortality and acute kidney injury rates among patients with carbapenem-resistant Klebsiella pneumonia (CRKP) induced BSI treated with either drug.[21] Regarding safety, Oliveira'et al found both polymyxins have similar efficacy and renal toxicity for the treatment of serious infections caused by carbapenem-resistant Acinetobacter spp.[22] In another prospective study, colistin was found to have more nephrotoxic than PMB, depending on the does.[23] Skin hyperpigmentation, a rare side effect of PMB, was observed in 6% of PMB-treated patients in our study, while no cases were reported in the CMS group. This supports previous case reports in the literature[24] and provides valuable information for clinical use. Our finding of comparable efficacy between CMS and PMB adds a critical data point to an ongoing international debate. The existing

Table 4 Comparison of Adverse Events Between Two Groups

	CMS (N=87)	PMB (N=173)	p-value
Hyperpigmentation	0 (0.0%)	11 (6.36%)	0.038
Hypersensitivity reactions	10 (11.49%)	27 (15.61%)	0.37
Neurotoxicity	8 (9.20%)	25 (14.45%)	0.23
Nephrotoxicity	20 (22.99%)	36 (20.81%)	0.687

literature presents a conflicting picture, with studies reporting higher nephrotoxicity for CMS[12,13] while others show no difference,[14] and mortality outcomes that are similarly inconsistent. This heterogeneity is likely not random but stems from several key factors. First, significant dosing variability exists between studies and regions, influenced by evolving pharmacokinetic/pharmacodynamic (PK/PD) data and local guidelines, which directly impacts both efficacy and toxicity. Second, the distribution of causative pathogens varies considerably; for instance, our cohort was predominantly Acinetobacter baumannii, whereas other studies may be enriched with Klebsiella pneumoniae or Pseudomonas aeruginosa. These species have differing intrinsic susceptibility to polymyxins and are often treated with different concomitant antibiotics, which could profoundly influence outcomes. Furthermore, the absence of carbapenem-resistant Enterobacter cloacae in our cohort may reflect regional resistance patterns or the impact of local antibiotic stewardship programs that utilize different agents for AmpC-producing organisms. Finally, emerging resistance mechanisms, such as mobile colistin resistance (mcr) genes, though not assessed in this study, may have varying prevalence across regions and time periods, further complicating cross-study comparisons. The significantly higher incidence of hyperpigmentation observed with PMB, while not fully understood, can be contextualized by several proposed biological mechanisms. Several case studies and reviews have suggested that PMB may stimulate melanocytes either directly or through the release of inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) following drug-induced cutaneous inflammation. This is supported by the observation that PMB, but not colistin, is more commonly associated with skin discoloration, particularly in areas exposed to pressure or friction. The precise mechanism is not fully clarified, but hypotheses include direct toxic effects on melanocytes, secondary post-inflammatory changes, or PMB's influence on skin microvasculature.[17,24,25]

This study has several limitations inherent to its retrospective, single-center design. First, the findings are subject to the potential biases and unmeasured confounding factors typical of observational research, despite our use of propensity score matching (PSM) to minimize known confounders. A further limitation of PSM is its tendency to exclude participants who cannot be matched with suitable controls, potentially reducing the sample size and statistical power. Second, our exploratory analysis revealed a strong association between longer polymyxin treatment duration (>12 days) and improved patient outcomes. However, this finding must be interpreted with caution, as it is susceptible to significant confounding. Patients who are responding well to therapy and are clinically stable are more likely to survive long enough to complete a longer treatment course. Therefore, the observed association may not be causal, and we cannot conclude that prolonging therapy independently improves survival. This analysis should be considered hypothesis-generating, and the optimal treatment duration for CR-GNB BSIs remains a critical question for future prospective studies to address. Third, the retrospective design also necessitated the application of specific exclusion criteria, which, while improving cohort homogeneity, may introduce selection bias and limit the generalizability of our results to excluded populations (eg, immunocompromised patients). Finally, the single-center, Chinese setting of our study, while a strength for internal consistency, limits its generalizability. The applicability of our findings to other healthcare systems may be influenced by several region-specific factors. Antibiotic stewardship practices and the availability of newer agents like ceftazidime-avibactam can vary widely, affecting treatment pathways and the severity of cases referred for polymyxin therapy. The local pathogen distribution, dominated by CRAB in our cohort, differs from the CRKP-dominant epidemiology seen in many other parts of the world. Moreover, the prevalence of specific resistance mechanisms (eg, metallo-β-lactamases vs KPC enzymes) in China could influence the effectiveness of polymyxin-based combination regimens. Therefore, while our results are highly relevant for the Chinese clinical context, their extrapolation to regions with differing microbial epidemiology, resistance patterns, and stewardship protocols should be done cautiously. It is essential to emphasize the need for future prospective, multi-center studies, and ultimately randomized controlled trials, to validate these findings in a larger, more diverse cohort and to establish more robust evidence for the comparative efficacy of these treatments.

In summary, this real-world study demonstrates that CMS and PMB have comparable efficacy in treating CR-GNB BSIs, but CMS is associated with a significantly lower risk of hyperpigmentation. This finding provides a compelling safety consideration for clinicians when choosing between these last-line agents, potentially favoring CMS in patients for whom cosmetic outcomes are a concern. These conclusions are tempered by the study's limitations, including its retrospective, single-center design in China and a safety evaluation focused primarily on readily identifiable adverse

events. To validate these results, future research should consist of larger, multicenter randomized controlled trials that include more comprehensive safety monitoring. Ultimately, our data offer valuable evidence to guide antibiotic stewardship, supporting that either polymyxin is an effective choice, with the decision potentially hinging on their distinct safety profiles rather than presumed differences in efficacy.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This retrospective study was approved by the Ethics Committee of The First Affiliated Hospital of Soochow University (IRB No. 2024–190), granting a waiver of informed consent due to its retrospective design and use of de-identified data. We confirm that all patient data were kept confidential. The study was performed in accordance with the 2008 Declaration of Helsinki and its later amendments.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of work.

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Disclosure

All authors declare that they have no conflicts of interest in this work.

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