JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Real-world data on the effects of colistin sulfate and polymyxin B sulfate in the treatment of pneumonia induced by CR-GNB

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Abstract

Introduction: The aim of this study was to compare the efficacy and safety of colistin sulfate (CS) with polymyxin B sulfate (PMB) in the treatment of pneumonia induced by carbapenem-resistant Gram-negative bacteria (CR-GNB).

Methodology: Patients diagnosed with pneumonia caused by CR-GNB and admitted to the intensive care unit (ICU) from January 2020 to September 2022 were enrolled in this study. The patients were divided into the CS group and the PMB group according to their medication regimens. Group-wise demographic data, clinical efficacy, prognosis, and adverse events were analyzed and compared.

Results: A total of 120 patients (68 in the CS group and 52 in the PMB group) with pneumonia were included in the study. The majority of the pathogens were CR-*Acinetobacter baumannii*, followed by CR-*Klebsiella pneumoniae*, and CR-*Pseudomonas aeruginosa*. The clinical response rates in the CS and PMB groups after treatment were 62.0% and 65.4%, bacterial clearances were 44.0% and 36.5%, 28-day mortality rates were 16.0% and 13.5%, respectively; no significant differences between the two treatments were found. Nevertheless, the adverse effects were significantly less common in the CS group than in the PMB group, especially when treatments were administered intravenously.

Conclusions: CS, a novel polymyxin E formulation, is as effective as PMB in treating pneumonia induced by CR-GNB while causing less side effects.

Key words: polymyxin; colistin sulfate; polymyxin B sulfate; carbapenem-resistant Gram-negative bacteria; pneumonia.

J Infect Dev Ctries 2024; 18(7):1050-1057. doi:10.3855/jidc.18887

(Received 13 July 2023 – Accepted 08 November 2023)

Introduction

Carbapenems are recognized as the most effective antimicrobial agents against multidrug-resistant Gram-negative bacteria (MDR-GNB). The increase of bacterial resistance, and the emergence and prevalence of carbapenem-resistant GNB (CR-GNB) are great challenges to the prevention and treatment of nosocomial infections [1]. Carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA); *Acinetobacter baumannii* (CR-AB); and Enterobacteriaceae (CRE), mainly carbapenem-resistant *Klebsiella pneumoniae* (CR-KP), are the most important pathogens which directly lead to high mortality in infected patients [2]. The World Health Organization (WHO) lists these resistant bacteria as critical pathogens requiring urgent drug research and development [3]. Since the 1990s, the polymyxins, mainly including polymyxin B sulfate (PMB) and colistin methanesulfonate (CMS), have been widely used in clinical practice because of their effect on these CR-GNB, and their efficacy and safety have also been partly acknowledged [4,5]. Colistin sulfate (CS) is a new form of polymyxin originally developed in China and is currently accessible exclusively in China [6]. Its active ingredient is colistin (polymyxin E); it is completely distinct from CMS, which is inactive and requires conversion to colistin *in vivo*. Because of the early confusion in terminology, people frequently confuse colistin with CMS, but CS is a water-soluble drug that is directly active *in vivo*, and its chemical structure, metabolism and efficacy are close to those of PMB. At present, PMB and CS are most extensively used in China. PMB has more evidence-based guidelines and recommendations [7]. Due to the fact that the application of CS was discontinued for 10 years in China before being remarketed in 2018, there are limited reports on CS.

More than a decade ago, our research team demonstrated that CS has good efficacy againts CR-GNB infections as a salvage therapy [8]. Recently, CS has obtained more attention in China [9,10]. Considering that bacterial pneumonia is the most prevalent type of infection in intensive care units (ICUs), a retrospective comparative study of CS and PMB in the treatment of pneumonia induced by CR-GNB was conducted to evaluate the effectiveness and safety of CS.

Methodology

Study design and patient inclusion criteria

Critically ill adult patients admitted to general and respiratory ICUs from January 2020 to September 2022 were enrolled. The inclusion criteria were as follows: primary or secondary pneumonia caused by CR-GNB, two or more positive reports of bacterial culture in deep sputum or bronchoalveolar lavage fluid and evidence of *in vitro* susceptibility testing, and treatment with CS or PMB for ≥ 72 hours. The exclusion criteria were: use of CS or PMB for < 3 days or death within three days, CR-GNB considered as colonization strains according to the history, combined deep fungal infection, combined extrapulmonary CR-GNB infection, and combined pneumonia caused by other pathogens.

Grouping and therapeutic regimens

The patients were divided into the CS group (trade name: Feng weiling, 500,000 IU/bottle, Shanghai Sph New Asia Pharmaceutical Co., Ltd. Shanghai, China) and PMB group (trade name: Ya le, 500,000 IU/bottle, Shanghai Biochemical Pharmaceutical Co., Ltd. Shanghai, China) according to the medication regimens. In the case of intravenous (IV) administration of CS, the recommended loading dose is 1.0–1.5 million IU, and the maintenance dose is 1.0–1.5 million IU/d, divided into 2–3 dosages. The recommended dose for nebulization is 0.5–1.0 million IU daily, divided into 2 dosages. For IV administration of PMB, the recommended loading dose is 20,000–25,000 IU/kg and the maintenance dose is 20,000–25,000 IU/kg/d, divided into 2–3 dosages. The recommended dose for nebulization is 0.5–1.0 million IU/d, divided into 2 doses [7]. During treatment with polymyxins, other nephrotoxic drugs should be avoided as much as possible. Patients of both groups were further divided into three subgroups according to the different routes of administration: vibrating mesh nebulization group (referred to as nebulization group), IV combined nebulization treatment group (referred to as IV+ nebulization group), and IV administration group (referred to as IV group).

Data collection

The baseline characteristics and clinical data, including patients' general condition, primary illness, comorbidity, chronic disease, acute organ dysfunction, site of infection, bacterial culture, and drug regimens were collected. The 28-day mortality rate, clinical responses, and microbiological responses of different regimens were recorder; changes in acute physiology and chronic health status II (APACHE II) score and clinical pulmonary infection score (CPIS) [8] before and after drug administration, as well as duration of mechanical ventilation and length of hospital stay were also recorded.

The clinical response to treatment was classified as cure (resolution of symptoms and free from antibiotics), improvement (partial resolution of symptoms but not free from antibiotics), or failure (persistent symptoms or death). Both cure and improvement were defined as good clinical responses [12].

Microbiological responses were divided into four categories: eradication (no growth of causative pathogens in at least two consecutive respiratory specimens), persistence (persistent growth of causative pathogens in respiratory specimens), recurrence (re-isolation of causative pathogens within 14 days of eradication), and undetermined (follow-up specimen unavailable or only one specimen with no growth) [12].

Evaluation of adverse effects

Nephrotoxicity, neurotoxicity, skin pigmentation, and allergic reactions such as dermatitis, pruritus, and drug fever were monitored during treatment. All observed adverse effects were evaluated and their relationship to drug administration was determined by physicians after multidisciplinary consultation. Creatinine exceeding the baseline level of 88.4 μmol/L or more while excluding other causative factors was defined as drug-related renal injury.

Statistical analysis

The statistical analysis was carried out using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The quantitative data were tested for normality. If they were in accord with the normal distribution, they were expressed by the mean ± SD and compared by t-test; if not, they were expressed by median (IQR) and compared by a nonparametric rank sum test. Categorical variables were expressed as numbers (%) and compared using the Chi-square test. Fisher's exact

test was used for small samples, as applicable. Multiple dependent variables among different groups were analyzed using multivariate analysis of variance (MANOVA). *p* value less than 0.05 was considered statistically significant.

Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University (RJ2019NO1-3), Shanghai, China. Informed consent was not required in this study because of its retrospective nature.

Results

Participant baseline characteristics

Demographic characteristics and baseline data of the CS group (n = 68) and PMB group (n = 52) are summarized in Table 1. There was no significant difference in gender, age, and body mass index (BMI) between the two groups. The APACHE II score, comorbidity, and acute organ dysfunction evaluation were additional characteristics that we used to assess the severity of disease at the time of ICU admission; however, there was no discernible difference between the two groups. The severity of disease at the time of CS or PMB administration are presented in Table 2. The APACHE II score, CPIS, renal function, and anti-infection therapy before drug administration showed no significant difference between the two groups.

In the CS group, there were 29, 10, and 24 patients with CR-AB, CR-PA, and CR-KP single strain infection, respectively, three with CR-AB + CR-KP mixed infection, and two with CR-AB + CR-PA mixed infection. In the PMB group, there were 22, 8, and 19 patients with CR-AB, CR-PA, and CR-KP single strain infection, respectively, on1 with CR-AB + CR-KP mixed infection, and two with CR-AB + CR-PA mixed infection (Supplementary Table 1). The results of bacterial susceptibility tests are presented in Supplementary Table 2.

Table 1. Demographic and clinical data.

	CS group (n = 68)	PMB group (n = 52)	*p* value
Age (mean ± SD) in years	71.0 ± 11.6	69.9 ± 14.7	0.657
Gender, n (%)			
Male	46 (67.6)	41 (78.8)	0.854
Female	22 (32.4)	11 (21.2)	
BMI (mean ± SD)	22.7 ± 4.3	22.4 ± 3.8	0.686
APACHE II Score (mean ± SD)	10.4 ± 2.7	12.4 ± 7.4	0.064
Primary disease, n (%)			
Pneumonia	39 (57.4)	22 (42.3)	0.102
Hematologic neoplasm	3 (4.4)	3 (5.8)	0.933
Stroke	9 (13.2)	5 (9.6)	0.540
Trauma	5 (7.4)	2 (3.8)	0.675
Tumor	3 (4.4)	4 (7.7)	0.714
AMI	2 (2.9)	5 (9.6)	0.249
Cardiac arrest	2 (2.9)	2 (3.8)	0.811
Pancreatitis	1 (1.5)	4 (7.7)	0.219
Others	4 (5.9)	5 (9.6)	0.675
Comorbidity, n (%)			
Hypertension	35 (51.5)	28 (53.8)	0.796
Diabetes	19 (27.9)	13 (25.0)	0.718
COPD	5 (7.4)	3 (5.8)	0.980
Coronary heart disease	10 (14.7)	11 (21.2)	0.357
Post-stroke state	11 (16.2)	5 (9.6)	0.295
Chronic kidney disease	7 (10.3)	6 (11.5)	0.828
History of malignancy	5 (7.4)	4 (7.7)	0.780
Autoimmune disease	3 (4.4)	1 (1.9)	0.811
Tracheostomy Status	6 (8.8)	2 (3.8)	0.475
Parkinsonism	4 (5.9)	2 (3.8)	0.933
Hematologic Disease	5 (7.4)	5 (9.6)	0.658
Chronic heart failure	3 (4.4)	2 (3.8)	0.759
Acute organ dysfunction, n (%)			
NIV/HFNC	17 (25.0)	6 (11.5)	0.063
Mechanical ventilation	37 (54.0)	36 (69.2)	0.099
Septic shock	27 (39.7)	21 (40.4)	0.940
Acute kidney injury	19 (27.9)	20 (38.5)	0.223
Acute heart failure	4 (5.9)	2 (3.8)	0.612
Acute hepatic dysfunction	8 (11.8)	4 (7.7)	0.461
Consciousness disorder	3 (4.4)	6 (11.5)	0.263

AMI: acute myocardial infarction; APACHE: acute physiology and chronic health evaluation; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CS: colistin sulfate; HFNC: high-flow nasal canula PMB: polymyxin B sulfate; NIV: non-invasive ventilation.

Table 2. Clinical features before treatment.

	CS group (n = 68)	PMB group (n = 52)	*p* value
APACHE II score (mean ± SD)	11.57 ± 2.72	12.52 ± 3.80	0.113
CPIS (mean ± SD)	7.38 ± 1.37	7.13 ± 1.36	0.320
AKI/CKD acute exacerbation, n (%)	14 (20.6)	16 (30.8)	0.288
RRT, n (%)	8 (11.8)	8 (15.4)	0.759
Broad-spectrum antibiotics, n (%)	43 (63.2)	39 (75.0)	0.240
Length of hospitalization (mean ± SD)	31.2 ± 26.1	33.7 ± 27.5	0.614

AKI: acute kidney injury; APACHE: acute physiology and chronic health evaluation; CKD: chronic kidney disease; CPIS: clinical pulmonary infection score; CS: colistin sulfate; PMB: polymyxin B sulfate; RRT: renal replacement therapy.

Therapeutic regimens

Seventeen patients in the CS group were treated with nebulization, 25 with IV combined nebulization, and 26 with IV therapy alone (Table 3). Fifty-one patients received IV therapy, with a loading dose of 1.05 ± 0.18 million IU, and a maintenance dose of 2.16 ± 0.64 million IU/Kg/d for 12.84 ± 6.99 days. Forty-two patients received nebulization therapy, with a maintenance dose of 0.69 ± 0.25 million IU/d, and a treatment course of 10.64 ± 9.82 days.

In the PMB group, 13 patients were treated with nebulization, 27 with IV combined nebulization, and 12 with IV therapy only. Thirty-nine patients received IV therapy, with a loading dose of 1.30 ± 0.42 million IU, and a daily maintenance dose of 2.19 ± 0.62 million IU/Kg/d, for a treatment course of 16.18 ± 8.23 days. Forty patients received nebulization therapy, with a maintenance dose of 0.68 ± 0.24 million IU/d, and a treatment course of 15.05 ± 8.66 days.

The comparison between the two groups showed that the loading dose of PMB was higher than that of CS in IV therapy patients ($p < 0.001$), and the treatment course of PMB was significantly longer than that of CS in both IV and nebulization therapy patients ($p = 0.042$ and 0.031).

In both groups, most patients were treated with combined antibiotics (77.9% in CS group and 80.8% in PMB group). Carbapenems were combined the most frequently, followed by cefoperazone–sulbactam, tigecycline, and ceftazidime–avibactam. There was no significant difference in the combined antibiotics between the two groups.

Clinical efficiency and prognosis

There was no significant difference in the incidence of secondary bloodstream infection, use of vasoactive drugs, and new renal replacement therapy (Table 4). APACHE II score and CPIS changes between the two groups before and after treatment also showed no difference. The good clinical response rates after treatment were 62.0% and 65.4% in the CS and PMB groups, respectively, the bacterial clearances were 44.0% and 36.5%, the 28-day mortality were 16.0% and 13.5%, and the final mortality were 26.5% and 30.8% in the CS and PMB groups, respectively. There were no significant differences between the two groups. Additionally, the MANOVA analysis revealed that there were no differences in clinical response, bacterial clearance, or 28-day mortality rates between subgroups based on the routes of medication administration (Supplementary Table 3).

Adverse effects

The incidence of adverse events was listed in Table 5. Among the adverse effects associated with IV polymyxins, the incidence of pigmentation was significantly higher in the PMB group than that in the CS group (25.6% vs 0). Patients in PMB group experienced more drug-related renal damage than the patients in CS group did (20.5% vs 5.9%), although the

Table 3. Medication dosage and course.

	CS group (n = 68)	PMB group (n = 52)	*p* value
Intravenous	n = 51	n = 39	-
Loading dose (million IU) (mean ± SD)	1.05 ± 0.18	1.30 ± 0.42	< 0.001
Daily dose (million IU/Kg) (mean ± SD)	2.16 ± 0.64	2.19 ± 0.62	0.823
Course (d) (mean ± SD)	12.84 ± 6.99	16.18 ± 8.23	0.042
Nebulization	n = 42	n = 40	
Daily dose (x 10^4 IU) (mean ± SD)	0.69 ± 0.25	0.68 ± 0.24	0.855
Course (d) (mean ± SD)	10.64 ± 9.82	15.05 ± 8.66	0.031
Combined therapy, n (%)			
Amikacin	6 (8.8)	2 (3.8)	0.475
Carbapenems	14 (20.6)	9 (17.3)	0.827
Cefoperazone/sulbactam	7 (10.3)	7 (13.5)	0.804
Tigecycline	10 (14.7)	5 (9.6)	0.578
Ceftazidime/avibactam	2 (2.9)	1 (1.9)	0.813
Piperacillin/tazobactam	4 (5.8)	4 (7.7)	0.980

CS: colistin sulfate; PMB: polymyxin B sulfate.

Table 4. Clinical efficacy and prognosis.

	CS group (n = 68)	PMB group (n = 52)	*p* value
Clinical changes			
Secondary bloodstream infection, n (%)	9 (13.2)	13 (25.0)	0.099
Vasoactive agents, n (%)	17 (25.0)	21 (40.4)	0.073
New RRT, n (%)	6 (8.8)	7 (13.46)	0.648
Change in APACHE II score (mean ± SD)	2.08 ± 4.65	2.52 ± 2.64	0.513
Change in CPIS (mean ± SD)	3.53 ± 1.86	3.39 ± 1.80	0.677
Bacteriological changes			
Bacterial clearance, n (%)	30 (44.1)	19 (36.5)	0.402
Replacement of other resistant organisms, n (%)	8 (11.8)	5 (9.6)	0.707
Prognosis			
Good clinical reponse, n (%)	42 (61.8)	34 (65.4)	0.683
28-day mortality, n (%)	11 (16.2)	7 (13.5)	0.680
All-cause mortality, n (%)	18 (26.5)	16 (30.8)	0.605

APACHE: acute physiology and chronic health evaluation; CPIS: clinical pulmonary infection score CS: colistin sulfate; PMB: polymyxin B sulfate; RRT: renal replacement therapy.

difference was not statistically significant. One patient in the CS group and four patients in the PMB group had drug dose decreases because of renal impairment. The incidences of other adverse effects such as neurotoxicity, rash, and eosinophilia were not significantly different between the two groups. Among the patients treated with nebulization, there was one case of mild bronchospasm in each group, which was relieved after treatment and did not discontinue the therapy.

Discussion

Polymyxins have taken the place of first-line antibiotics due to the paucity of effective antibiotics against CR-GNB over the past 20 years [13]. The subjects of this study were all patients with pneumonia caused by CR-GNB; excluding the interference of multiple site infections and mixed bacterial infections, the basic data in the two groups were homogeneous. The majority of the pathogens were CR-AB, followed by CR-KP and CR-PA. These pathogens continue to be highly sensitive to polymyxins. The clinical response rates under the treatment of CS and PMB were 62.0% and 65.4%, the bacterial clearance rates were 44.0% and 36.5%, and 28-day mortality rates were 16.0% and 13.5%, respectively, in the CS and PMB groups. There was no difference in the therapeutic efficacy between the two groups.

PMB and CS used in this study were both made in China. The pharmacokinetics and pharmacodynamics (PK/PD) of PMB have been thoroughly investigated [14]. However, the PK/PD of CS is almost unknown. Notably, it is wrong to use CS based on the evidence of CMS. A recent study on the population pharmacokinetics of CS showed that a dose of 750,000 U every 12 h could attain probability of target attainment (PTA) > 90% for pathogens with minimum inhibitory concentration (MIC) ≤ 1 μg/mL, and the dosage recommended by the label inserts had a risk of subtherapeutic exposure for pathogens with MIC ≥ 2 μg/mL. Although individuals with acute renal insufficiency were exposed to colistin at greater levels, dose reduction was not recommended [15]. As a result, when CS was delivered intravenously, the PK parameters were comparable to those of PMB [16].

The clinical efficacy of PMB in previous reports was about 35–70% [17,18]. Lu *et al.* also reported a clinical efficacy of 57.2% with our domestic PMB [19]. Two recent reports imply that CS has a good clinical response of 73–94% and bacterial clearance rate of 50–74% [20,21]. However, the clinical and bacteriological efficacy of CS and PMB in our study were generally consistent (62.0% vs 65.4% and 44.0% vs 36.5%), but marginally lower than the above reports. This means that CS and PMB exhibit almost identical

Table 5. Adverse effects, n (%).

	CS group	PMB group	*p* value
Intravenous administration	n = 51	n = 39	
Drug-related renal injury	3 (5.9)	8 (20.5)	0.076
Skin pigmentation	0	10 (25.6)	< 0.001
Neurotoxicity	0	2 (5.1)	0.185
Rash	3 (5.9)	4 (10.3)	0.711
Eosinophils increased	0	1 (2.6)	0.440
Total	6	25	< 0.001
Nebulization administration	n = 42	n = 40	
Bronchospasm	1 (2.4)	1 (2.5)	0.612

CS: colistin sulfate; PMB: polymyxin B sulfate.

pharmacokinetic properties, and their clinical efficacy on pneumonia induced by CR-GNB is acceptable.

The dosage, administration method, course of treatment, and drug combination may all have a significant impact on a drug's effectiveness. Firstly, three routes of administration were included in this study: nebulization alone, IV + nebulization, and IV alone. Earlier studies have shown that IV + nebulization of PMB and CMS is significantly more effective than IV administration in the treatment of pneumonia caused by drug-resistant bacteria [22,23]. Current guidelines recommend nebulization of CMS to achieve higher drug concentrations in the alveolar epithelium [24]. However, CS nebulization has also been used in China. There are only three reports of CS available on the use of CS. Hao *et al.* reported that CS treated intravenously alone can get a clinical response of 73.1% and bacterial clearance of 50% [21]. Yu *et al*. reported an overall clinical efficacy of 59.5% in 42 patients, of whom half were treated intravenously alone and the other half were treated intravenously combined with nebulization [15]. Bao *et al.* observed that combined CS nebulization on the basis of conventional antibacterial drugs can significantly improve clinical efficacy [20].

However, the efficacy of nebulization is closely tied to nebulizer and operation management and requires more clinical attention. We did not find any differences in clinical and bacteriological efficacy among the three routes of administration in subgroup analysis, indicating that all three routes of administration are feasible. Secondly, the dose and course of treatment were also crucial to the therapy. Additionally, nebulized CS had a similar daily dose as PMB, but its course of treatment was much shorter. The relationship between a high dose and a prolonged PMB treatment course, and clinical benefit has been hypothesized [19]. Our dosage has been verified in accordance with CS's recommendations, and the recommended treatment schedule is consistent with the results of Yu *et al*. and Hao *et al*. [15,21]. Although the loading dose was not discussed in the two articles above, it appeared that clinical efficacy with a standardized CS application was sufficient. The ideal dosage and treatment plan are still being investigated.

Additionally, polymyxins (PMB and CMS) in combination with other antibiotics are generally regarded as superior to monotherapy and have a considerable mortality reduction effect [25–27]. The choice of potent antibacterial medications in combination with polymyxins might not only boost the antibacterial action but also lessen the heterogeneous resistance of polymyxins, according to susceptibility tests or combined susceptibility in vitro. Due to the high drug resistance of pathogens and medical insurance coverage issues, carbapenems (mainly meropenem) and tigecycline were frequently used in combination with polymyxins in China. In fact, there are great differences in epidemic strains in each region and hospital. For example, in the study of Hao *et al.* 91% of AB were sensitive to tigecycline, 69% of PA were sensitive to amikacin, and 64% of KP were sensitive to amikacin [21]. These data were much higher than the susceptibilities test results in our study. Polymyxins combined with other sensitive antimicrobial agents can significantly improve their effect, which may be the reason why the clinical response reported by Hao *et al.* is much higher than ours [21].

It is important to highlight that the bacterial clearance was low in both groups in this study (44.0% in CS group and 36.5% in PMB group, respectively), both lower than the data reported in other studies [15,20,21]. Previous reports have shown that the floating range of the bacterial clearance of PMB and CMS was very large [28]. As mentioned in the previous discussion, the combination of sensitive or synergistic antibiotics may improve clinical efficacy and bacterial clearance. In addition, CHINET data in 2022 showed that KP ranked first among respiratory tract detected samples in China and that the resistance of KP increased year after year. Meanwhile, CR-KP itself had higher colonization and pathogenicity and was challenging to completely eradicate in the state of invasive mechanical ventilation (intubation or tracheotomy) [29]. Of course, issues including insufficient dosage of polymyxin, substandard plasma concentration, nonstandard nebulization operations, and heterogeneous drug resistance also have an impact on the bacterial clearance.

The adverse effects of polymyxins, especially nephrotoxicity, have been the focus of attention. Compared to CMS, PMB has better pharmacokinetic features and a decreased risk of nephrotoxicity, according to the International Consensus 2019. However, PMB also has various side effects, including neurotoxicity and skin pigmentation [30]. Falagas *et al.* recently reviewed that the all-cause nephrotoxicity rate in 2,994 patients (from 28 studies) treated with intravenous PMB was 40.7% (95% CI 35.0–46.6%) [28]. The incidence of CS-related renal damage in the other two reports varied from 9.7% to 23.1% [15,21]. In our research, 14 (20.6%) patients in the CS group and 16 (30.8%) patients in the PMB group had acute kidney injury (AKI) or an acute exacerbation of chronic kidney disease (CKD) before administration; while after

treatment, three patients (5.9%) in the CS group and 8 (20.5%) in the PMB group experienced drug-related renal injury, while other cases improved or stayed stable during treatment. In contrast, the incidence of renal injury in CS group patients was lower than in PMB group patients.

PMB was also associated with significant skin pigmentation in 25.6% of patients and neurotoxicity in 10.3% (another three cases of neurotoxicity were excluded from the study because the patients quit the medication within three days), while no pigmentation or neurotoxicity occurred in patients using CS. In addition, rashes occurred in a relatively low proportion of patients in both groups. Bronchospasm was mainly observed in patients with nebulization therapy, with one case in each group. With the prophylactic use of bronchodilators in recent years, the incidence of bronchospasm has decreased significantly, and no deaths associated with it have been observed. In general, CS was linked to fewer negative side-effects than PMB.

Limitations

Our study had several limitations:

1. The pharmacokinetics of CS are still not very clear, and the dose of IV administration according to the package insert is 1–1.5 million IU/day, which is suitable for Asian populations with standard weights; there is no recommended dose for the obese population or other ethnic cohorts with higher body weights.

2. The loading dose for CS is not mentioned in the package insert, and the recommended loading dose of PMB is 20,000–25,000 IU/kg. The CS loading dose in our study was significantly lower than PMB, which may be a little conservative. However, it is difficult to assess the area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio (AUC/MIC) because of the lack of drug concentration monitoring.

3. The combination of certain sensitive drugs (mainly tigecycline and ceftazidime-avibactam) may significantly enhance clinical efficacy and affect the efficacy assessment of polymyxin. However, the proportion of tigecycline and ceftazidime-avibactam used in this study was very low in both groups.

4. PMB may have a nephrotoxicity effect because its treatment duration is substantially longer than that of CS, but this is difficult to pin down in this study.

Conclusions

CS is a new polymyxin E formulation, and our study showed that CS has comparable clinical and bacteriological efficacy to PMB in the treatment of pneumonia induced by CR-GNB. The clinical efficacy and the 28-day mortality rates of CS and PMB showed no significant difference when administered via different routes. In IV administration, the nephrotoxicity of CS seemed slightly lower than PMB; however, this needs further verification. Patients in the CS group also showed no skin pigmentation or neurotoxicity, which were common after long-term use of PMB. In nebulization administration, the incidence of airway spasm caused by CS and PMB was rare. Thus, CS and PMB are both effective in the treatment of pneumonia induced by CR-GNB, and CS appeared to have fewer adverse effects.

Authors' contributions

Study design: HQ, DC, JH; data collection: DL, JF, YD; data analysis: DL, JH; writing, review, and editing: DL, JH.

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Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

Supplementary Table 1. Pathogenic bacteria data, n (%).

	CS group (n = 68)	PMB group (n = 52)	*p* value
CR-AB	29 (42.6)	22 (42.3)	0.915
CR-PA	10 (14.7)	8 (15.4)	0.918
CR-KP	24 (35.3)	19 (36.5)	0.888
CR-AB + CR-KP	3 (4.4)	1 (1.9)	0.811
CR-AB + CR-PA	2 (2.9)	2 (3.8)	0.811

CS: colistin sulfate; PMB: polymyxin B sulfate; CR-AB: carbapenem-resistant *Acinetobacter baumannii*; CR-PA: carbapenem-resistant *Pseudomonas aeruginosa*; CR-KP: carbapenem-resistant *Klebsiella pneumoniae*.

Supplementary Table 2. Antibiotic resistance of isolated pathogens (%).

	***Acinetobacter Baumannii* (n = 5)**	***Pseudomonas Aeruginosa* (n = 22)**	***Klebsiella pneumoniae* (n = 47)**
Imipenem	100	100	100
Meropenem	100	100	100
Amikacin	79.7	95.5	85.1
Gentamicin	100	100	100
Ampicillin	100	100	100
Piperacillin	100	100	100
Cefuroxime	100	100	100
Ceftazidime	100	100	100
Cefepime	100	100	93.6
Cefoperazone–sulbactam	76.3	90.9	97.9
Piperacillin–tazobactam	100	86.4	100
Ciprofloxacin	93.2	86.4	100
Trimethoprim–sulfamethoxazole	64.4	NA	89.4
Polymyxin B	0	0	0
Ceftazidime/avibactam	NA	NA	6.4

Notes: intermediate assigned to resistance category. NA: not available.

Supplementary Table 3. Comparison of the six subgroups classified by different routes of drug administration.

	CS group			PMB group			*p* value
	A (n = 17)	B (n = 25)	C (n = 26)	A (n = 13)	B (n = 27)	C (n = 12)	
Clinical efficacy	10 (58.8)	15 (60.0)	17 (65.4)	7 (53.8)	19 (70.4)	8 (66.7)	0.919
28-day mortality	2 (11.8)	5 (20.0)	4 (15.4)	2 (15.4)	3 (11.1)	2 (16.7)	0.966
Bacterial clearance	7 (41.2)	11 (44.0)	12 (46.2)	4 (30.8)	11 (40.7)	4 (33.3)	0.945

A: nebulization; B: intravenous + nebulization; C: intravenous.