Am J Transl Res 2025;17(6):4764-4773
www.ajtr.org /ISSN:1943-8141/AJTR0164846

Original Article

Therapeutic efficacy of different sulperazon dosing regimens in carbapenem-resistant Klebsiella pneumoniae: a retrospective analysis of 209 cases

Yao Chen, Qingjiang Guo, Youbao Liang, Erhu Heng

Clinical Laboratory, Bengbu First People's Hospital, Bengbu 233000, Anhui, China

Received March 27, 2025; Accepted June 5, 2025; Epub June 15, 2025; Published June 30, 2025

Abstract: Objectives: Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections pose significant clinical challenges worldwide due to limited therapeutic options and high mortality. Sulperazon (cefoperazone/sulbactam) has demonstrated activity against multidrug-resistant (MDR) organisms; however, the optimal dosing regimen for CRKP remains unclear. This study aimed to evaluate the clinical efficacy, microbiological outcomes, and safety of different sulperazon dosing in CRKP infections. Methods: A retrospective analysis was conducted on 209 adult patients with CRKP infections treated with sulperazon for at least 48 hours at Bengbu First People's Hospital between January 2020 and December 2022. Patients were grouped into a standard-dose group (≤3 g/day, n=112) and a high-dose group (>3 g/day, n=97). Clinical cure, microbiological eradication, treatment failure, 28-day mortality, and incidence of adverse events were compared between groups. Results: The cohort was predominantly elderly (mean age 67.3 ± 15.2 years) and male (65.1%). The most frequent carbapenemase genes were *bla*_KPC-2 (65.6%) and *bla*_NDM-1 (23.0%). Virulence factors, including adhesins (72.2%), iron-acquisition systems (63.2%), capsule synthesis genes (58.9%), and the hypermucoviscosity regulator *rmpA* (42.6%) were frequently detected. Compared with the standard-dose group, the high-dose group showed significantly increased clinical cure rates (64.9% vs. 43.8%; P=0.002) and microbiological eradication rates (69.1% vs. 46.4%; P=0.001), along with lower rates of treatment failure (10.3% vs. 24.1%; P=0.011) and 28-day mortality (8.2% vs. 20.5%; P=0.015), without an increase in adverse events. Conclusion: High-dose sulperazon demonstrated superior clinical efficacy and equivalent safety to standard dosing in the treatment of CRKP infections, supporting dose optimization to improve patient outcomes.

Keywords: Carbapenem-resistant *Klebsiella pneumoniae*, sulperazon, antibiotic dosage, clinical efficacy, virulence factors

Introduction

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has emerged as a critical global public health threat, characterized by high morbidity, high mortality, and limited therapeutic options [1-3]. CRKP generally refers to *K. pneumoniae* strains resistant to carbapenems - including meropenem, imipenem, and ertapenem - or those producing carbapenemase enzymes capable of hydrolyzing these antibiotics [2, 4]. Over the past decade, the global prevalence of CRKP has risen markedly, posing substantial challenges to healthcare systems by causing severe infections - such as pneumonia, bloodstream infections (BSIs), and urinary tract infections (UTIs) - particularly in critically ill patients [5, 6]. The rapid spread and broad -spectrum resistance of CRKP are largely driven by carbapenemase production, which compromises the efficacy of carbapenems [5, 7]. Among these enzymes, KPC-2 and NDM-1 are the most frequently reported worldwide, particularly in Asia [6]. Moreover, CRKP often co-harbors genes conferring resistance to multiple antibiotic classes, resulting in multidrug-resistant (MDR) or extensively drug-resistant (XDR) phenotypes, further complicating treatment [8].

CRKP infections are associated with significantly worse outcomes compared to infections caused by carbapenem-susceptible *Klebsiella pneumoniae* (CSKP). CRKP infections often correlate with prolonged hospital stays, increased healthcare costs, and elevated mortality rates, particularly in patients with comorbidities such

https://doi.org/10.62347/TZFB9853

as immunosuppression, chronic obstructive pulmonary disease, diabetes mellitus, or those requiring invasive procedures like mechanical ventilation and central venous catheterization [9-11]. Treatment failure is common and is attributed to delayed initiation of effective antimicrobial therapy, limited therapeutic options, and rapid emergence of resistance during treatment [9]. Clinicians therefore frequently rely on last-line agents such as colistin, tigecycline, and ceftazidime-avibactam, often administered in combination, to manage CRKP infections [10, 11]. However, rising resistance rates, adverse drug reactions, and the limited efficacy of monotherapy continue to hamper clinical outcomes [12]. Therefore, it is imperative to explore novel treatment strategies against CRKP.

Sulperazon, a fixed combination of cefoperazone, a third-generation cephalosporin, and sulbactam, a β-lactamase inhibitor, has emerged as an effective alternative for treating severe bacterial infections, including CRKP [13, 14]. Its efficacy stems from sulbactam's inhibition of class A β-lactamases and certain carbapenemases, which broadens and potentiates cefoperazone's activity against resistant pathogens [14]. Previous clinical studies have demonstrated favorable outcomes with sulperazon in hospital-acquired pneumonia, complicated urinary tract infections, and intra-abdominal infections, particularly when administered in combination regimens or at higher doses [10, 15]. However, evidence specifically evaluating sulperazon's efficacy against CRKP remains limited and inconsistent, necessitating further clinical assessment [12]. In addition, the optimal dosing strategy remains unclear due to variability in patient populations, infection severity, and underlying resistance mechanisms [9]. As clinical efficacy may be dose-depend, comprehensive studies are needed to establish standardized dosing guidelines [16]. Although sulperazon is generally well tolerated, potential adverse reactions, such as gastrointestinal disturbances, thrombocytopenia, and allergic responses, warrant thorough assessment [12]. Understanding the risk-benefit profile associated with different dosing regimens is crucial to ensuring both patient safety and therapeutic efficacy [15]. Therefore, defining optimal dosing strategies for sulperazon in CRKP management is essential, as dosage variations may significantly affect clinical outcomes, including bacterial clearance, clinical recovery, and adverse event rates [11].

In the current study, we retrospectively evaluated the therapeutic efficacy of different sulperazon dosages in the management of CRKP infections by reviewing 209 clinical cases. By assessing clinical outcomes, microbiological responses, and safety profiles across different dose groups, we aim to provide practical insights and recommendations to inform clinical decision-making, improve patient outcomes, and support antimicrobial stewardship and infection management practices.

Methods

Study design and patient enrollment

This retrospective study included 209 patients with culture-confirmed CRKP infections. Electronic medical records from January 2020 to December 2022 at Bengbu First People's Hospital were reviewed. Ethical approval was obtained from the Institutional Review Board of Bengbu First People's Hospital (Approval. No. BBYY202308), and the requirement for informed consent was waived due to the retrospective nature of the study. Patients were eligible for inclusion if they met all of the following criteria: 1) microbiological confirmation of CRKP infection; 2) treatment with sulperazon, either as monotherapy or in combination, for ≥48 hours; and 3) complete medical and laboratory records. Exclusion criteria: 1) sulperazon treatment for <48 hours; 2) CRKP colonization without clinical signs of infection; or 3) incomplete records. Based on these criteria, 209 eligible cases were included in the final analysis.

Data collection

Patient clinical information included demographics (age, sex), comorbidities, admission details, and disease severity [e.g., Acute Physiology and Chronic Health Evaluation (APACHE) II, Sepsis-related Organ Failure Assessment (SOFA)]. Additionally, microbiological data included isolate identification, resistance profiles, and antibiotic susceptibility patterns. Therapeutic data encompassed antibiotic regimen, dosages, treatment durations, and adverse events. Laboratory data, including white blood cell (WBC), C-reactive protein (CRP), and procalcitonin levels, were collected. Patient outcomes, including mortality, hospitalization duration, and clinical effectiveness, were also recorded.

Microbiological identification

Clinical specimens (blood, sputum, urine, and wound swabs) were collected aseptically and cultured on selective and differential media - blood agar, MacConkey agar, and CHROMagar KPC (CHROMagar, France) - to facilitate the isolation of carbapenem-resistant organisms via chromogenic substrate hydrolysis. After overnight incubation at 37°C, CRKP colonies typically exhibited a mucoid appearance with a metallic-blue hue. Initial identification was performed using the automated PH100 (BD, USA) and confirmed by conventional biochemical assays, including indole, methyl red, Voges-Proskauer, and citrate (IMViC) tests, as well as assessments of lactose fermentation, motility, urease activity, and lysine decarboxylation [7, 9].

Antibiotic susceptibility testing

Antibiotic susceptibility testing was performed using the broth microdilution according to Clinical and Laboratory Standards Institute (CLSI) guidelines [17]. Minimum inhibitory concentrations (MICs) were determined for sulperazon, carbapenems (imipenem, meropenem), ceftazidime-avibactam, tigecycline, polymyxin B, aminoglycosides, fluoroquinolones, and other relevant agents. Interpretive breakpoints were applied per CLSI standards. Serial two-fold dilutions of each agent were prepared in Mueller-Hinton broth, and a standardized bacterial inoculum [~10^5 colony-forming unit (CFU)/mL] was added to each dilution. After overnight incubation at 37°C, the MIC was recorded as the lowest antibiotic concentration that completely inhibited visible bacterial growth [9].

Detection of carbapenemase genes by multiplex polymerase chain reaction (PCR)

The presence of major carbapenemase genes (*bla*_KPC, *bla*_NDM, *bla*_OXA-48, *bla*_VIM, and *bla*_IMP) was assessed by multiplex PCR. Genomic DNA was extracted using the NucleoSpin Tissue kit (Macherey-Nagel, Germany) according to the manufacturer's instructions. Multiplex PCR was performed using gene-specific primers under the following cycling conditions: initial denaturation at 95°C for 5 min; 30 cycles of denaturation at 95°C for 30 s, annealing at primer-specific temperatures for 30 s, and extension at 72°C for 1 min; followed by a final extension at 72°C for 7 min. PCR products were separated by agarose gel electrophoresis and visualized under UV light, with band sizes compared to a molecular weight marker for gene identification [5].

Detection of virulence factors

Virulence-associated genes were detected by PCR, including those involved in capsular polysaccharide synthesis (*magA*, *k2A*), the hypermucoviscosity regulator *rmpA*, adherence factors (*fimH*, *mrkD*, *ycfM*), iron-acquisition systems (*iutA*, *iroN*, *entB*), and lipopolysaccharide synthesis (*wabG*, *uge*). Multiplex PCR was carried out under conditions similar to those used for carbapenemase gene detection, employing gene-specific primers and optimized cycling parameters. Amplified products were separated by agarose gel electrophoresis and visualized to confirm the presence of each virulence gene [5, 6].

Outcome assessment

Clinical outcomes were classified based on previous studies [10, 12] as follows: Clinical Cure: complete resolution of all signs and symptoms attributable to CRKP infection (e.g., fever, purulent secretions, hemodynamic instability), normalization of inflammatory markers (WBC count, CRP, procalcitonin), and no requirement for additional or rescue antibiotics after completion of the sulperazon regimen; Clinical Improvement: substantial reduction in infection-related signs and laboratory abnormalities without full normalization, requiring either an extension of sulperazon therapy or a short course of adjunctive antibiotics; Treatment Failure: persistence or worsening of clinical signs/symptoms after ≥72 h of therapy, need to switch to an alternative primary antibiotic regimen, or death directly attributable to CRKP infection.

Microbiological outcomes were classified as complete eradication (negative post-treatment culture), partial eradication (reduction or clearance of some organisms in polymicrobial infections), or microbiological failure (continued detection of the pathogen) [11, 17]. Secondary outcomes included all-cause mortality, length

Table 1. Demographic and clinical characteristics of patients (n=209)

Characteristics	Number (%) or Mean ± SD
Age (years), mean ± SD	67.3 ± 15.2
Age <65 years	96 (45.9%)
Male gender	136 (65.1%)
ICU admission	84 (40.2%)
Mechanical ventilation	91 (43.5%)
Central venous catheter	120 (57.4%)
APACHE II score, mean ± SD	17.5 ± 6.4
APACHE II score <15	97 (46.4%)
SOFA score, mean ± SD	7.1 ± 2.3
SOFA score <6	101 (48.3%)
Charlson comorbidity index, mean ± SD	4.6 ± 1.8
Charlson comorbidity index <4	101 (48.3%)
Length of hospital stay (days), mean ± SD	28.7 ± 14.2
Underlying Diseases	
Diabetes	92 (44.0%)
Cardiovascular disease	75 (35.9%)
Chronic obstructive pulmonary disease	60 (28.7%)
Chronic kidney disease	48 (23.0%)
Malignancy	42 (20.1%)

APACHE II, acute physiology and chronic health evaluation II; SOFA, sepsis-related organ failure assessment; ICU, intensive care unit.

of hospital stay, length of intensive care unit (ICU) stay, and adverse drug reactions associated with sulperazon use [10, 12].

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp.). Continuous variables were presented as mean ± standard deviation or median (interquartile range), and categorical variables as counts and percentages. Comparisons between sulperazon dosage groups were conducted using Student's t-test or the Mann-Whitney U-test for continuous variables, and the chi-square or Fisher's exact test for categorical variables. Variables with $P<0.05$ in univariate analysis were entered into a multivariate logistic regression model to identify independent predictors of treatment success or failure. A *p*-value <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

This retrospective cohort predominantly comprised elderly patients (mean age 67.3 years), underscoring heightened susceptibility of older adults to severe CRKP infections. Males comprised 65.1% of the cohort, suggesting a possible gender-related predisposition. ICU admission was required for 40.2% of patients, and 43.5% underwent mechanical ventilation, reflecting the severity of the infections. Elevated APACHE II (17.5 ± 6.4) and SOFA (7.1 ± 2.3) scores further indicated substantial illness severity in this cohort. Common comorbidities included diabetes (44.0%), cardiovascular disease (35.9%), chronic obstructive pulmonary disease (28.7%), chronic kidney disease (23.0%), and malignancy (20.1%), all of which may exacerbate patient vulnerability and complicate treatment outcomes. The details are shown in **Table 1**.

Microbiological characteristics and carbapenemase genes

Among the clinical specimens, sputum was the most common source of CRKP isolates (61.2%), indicating a predominance of respiratory tract infections. Blood cultures accounted for 16.7% of isolates, reflecting severe systemic involvement. Most isolates harbored multiple carbapenemase genes, with *bla*_KPC-2 being the most prevalent (65.6%), indicating the dominance of KPC-producing strains. *Bla*_NDM-1 was detected in 23.0% of isolates, underscoring its contribution to extensive drug resistance. Less common carbapenemase genes included *bla*_OXA-48 (5.7%), *bla*_VIM (3.3%), and *bla*_IMP (2.4%), highlighting the heterogeneity of resistance mechanisms and the complexity of managing CRKP infections. The details are shown in **Table 2**.

Virulence factor detection and antibiotic susceptibility profiles of CRKP isolates

Virulence factors were highly prevalent among CRKP isolates. Adhesion-related genes (*fimH*,

Table 2. Microbiological characteristics and carbapenemase genes (n=209)

Characteristics	Number (%)
Specimen sources	
Sputum	128 (61.2%)
Blood	35 (16.7%)
Urine	22 (10.5%)
Wound swabs	18 (8.6%)
Other	6 (2.9%)
Carbapenemase genes detected	
bla_KPC-2	137 (65.6%)
bla_NDM-1	48 (23.0%)
bla_OXA-48	12 (5.7%)
bla_VIM	7 (3.3%)
bla_IMP	5 (2.4%)

mrkD, *ycfM*) were the most frequent (72.2%), indicating strong adherence capabilities, an essential initial step in host colonization (**Figure 1A**). Lipopolysaccharide synthesis genes (*wabG*, *uge*; 68.4%) and iron-acquisition genes (*iutA*, *iroN*, *entB*; 63.2%) were also common, supporting bacterial survival by evading immune defenses and enhancing iron uptake, which is crucial for metabolism and virulence. Capsule-related genes (*magA*, *k2A*, *wcaG*) were detected in 58.9% of isolates, contributing to protection against phagocytosis. The hypermucoviscosity regulator *rmpA*, associated with severe invasive infections, was detected in 42.6% of isolates, underscoring their potential for causing serious disease. Additionally, the hemolysin gene *hly* was detected in 25.8% of isolates, further indicating their cytotoxic potential. See **Figure 1A** for details.

All isolates exhibited resistance to carbapenems (imipenem, meropenem; 100%), consistent with the CRKP definition. Resistance to alternative agents varied: low resistance rates to last-resort antibiotics, including ceftazidime-avibactam (2.9%), polymyxin B (4.8%), and tigecycline (7.2%), suggest these drugs remain viable treatment options. In contrast, high resistance rates to ciprofloxacin (73.7%) and amikacin (38.8%) significantly limit available therapies, underscoring the critical need for effective antibiotic stewardship (**Figure 1B**).

Clinical and microbiological outcomes by sulperazon dosage

High-dose sulperazon (>3 g/day) was associated with significantly better clinical and microbiological outcomes. The clinical cure rate was markedly higher in the high-dose group than in the standard-dose group (64.9% vs. 43.8%), while the treatment failure rate was significantly lower (10.3% vs. 24.1%) (**Figure 2A**). Similarly, microbiological eradication rate was significantly higher in the high-dose group (69.1% vs. 46.4%) (**Figure 2B**). Moreover, 28-day mortality decreased from 20.5% in standard-dose group to 8.2% in the high-dose group. Patients receiving high-dose sulperazon also experienced shorter hospital stays (24.6 ± 11.3 vs. 32.1 ± 16.5 days) and faster clinical resolution (10.2 ± 4.7 vs. 15.4 ± 5.8 days) ($P<0.05$). These results demonstrate a clear dose-response relationship and underscore the clinical advantages for higher sulperazon dosing in the management of severe CRKP infections.

Analysis of predictors associated with clinical cure

To identify factors influencing clinical outcomes, univariate analyses of clinical, microbiological, and therapeutic variables were performed (**Table 3**). Several factors were significantly associated with improved clinical cure rates: age <65 years, absence of ICU admission, absence of mechanical ventilation, lower severity scores (APACHE II <15; SOFA <6), lower comorbidity burden (Charlson index <4), high-dose sulperazon treatment, and infection with *rmpA*-negative (non-hypermucoviscous) isolates. In contrast, gender and the presence of specific carbapenemase genes (*bla*_KPC-2, *bla*_NDM-1) were not significantly correlated with clinical cure. Variables with *p*-values <0.05 in the univariate analysis were included in the multivariate logistic regression analysis to identify independent predictors of clinical cure.

Multivariate analysis demonstrated that high-dose sulperazon therapy (>3 g/day) independently increased the odds of clinical cure by approximately 2.5-fold (**Table 4**). Absence of mechanical ventilation was also an independent predictor, tripling the likelihood of cure. Furthermore, infection with *rmpA*-negative isolates was associated with a 2.9-fold increase in cure odds, underscoring the impact of microbial virulence. Finally, lower baseline disease severity (APACHE II score <15) independently raised the likelihood of clinical cure by nearly 2.5-fold, highlighting the importance of early intervention (**Table 4**).

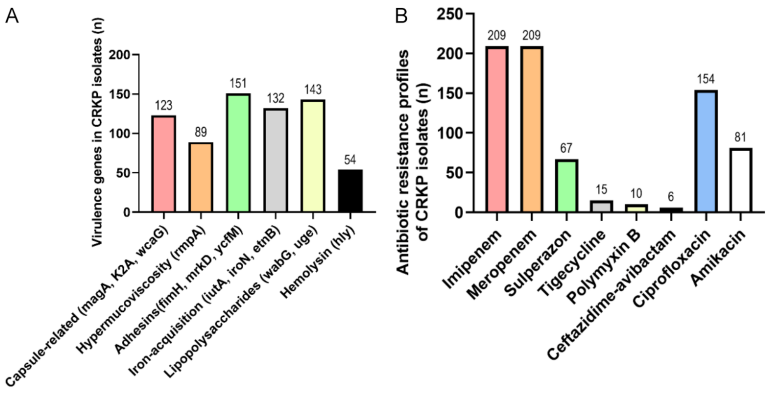

Figure 1. Virulence factor detection and antibiotic susceptibility profiles of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) isolates (n=209). A. Number of virulent genes in CRKP isolates; B. Number of antibiotic resistant CRKP isolates.

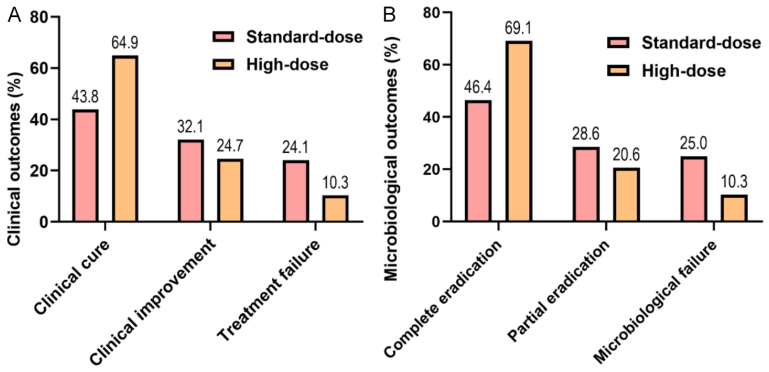

Figure 2. Comparison of clinical and microbiological outcomes between different dosage groups (n=209). A. Clinical outcomes; B. Microbiological outcomes.

Adverse events during sulperazon treatment

The incidence of adverse drug reactions did not differ significantly between dosage groups, suggesting that high-dose sulperazon therapy did not increase safety concerns of the treatment and was well-tolerated clinically (**Table 5**).

Discussion

CRKP has emerged as a global public health threat, posing significant challenges to healthcare providers due to its high morbidity, elevated mortality, and limited treatment options [2, 5, 18]. In this retrospective analysis of 209 patients with CRKP infection, we evaluated the efficacy of varying sulperazon (cefoperazone/sulbactam) dosing regimens. Our results provide key insights into patient demographics, resistance profiles, virulence factors, clinical and microbiological outcomes, and treatment-related adverse events, offering valuable guidance for optimizing CRKP management.

Patients affected by CRKP infections were predominantly older adults with comorbidities such as diabetes, cardiovascular disease, and chronic respiratory disorders, consistent with previous reports [19, 20]. Approximately 40% required ICU admission, and nearly half needed mechanical ventilation, underscoring the severity and complexity of these infections. These findings align with earlier studies indicating that CRKP disproportionately affects vulnerable, critically ill populations [9, 21-23]. Microbiological analysis revealed that respiratory tract specimens, especially sputum, were the primary source of CRKP isolates, followed by bloodstream infections [21]. The predominance of respiratory and bloodstream isolates corresponds with previous reports that hospital-acquired pneumonia and bacteremia are the most common clinical presentations of CRKP, particularly among ICU patients [2, 6, 24, 25]. Accordingly, interventions targeting respiratory and bloodstream infections should be prioritized to reduce CRKP transmission and improve patient outcomes.

An important finding of this study is the distribution of carbapenemase genes among the CRKP isolates. The predominance of *bla*_KPC-2 and *bla*_NDM-1 underscores the substantial presence of both serine β-lactamases (KPC-type) and metallo-β-lactamases (NDM-type). Similar prevalence patterns have been reported in studies from Asia and other regions, reflecting geographic variation in resistance gene epidemiology [26, 27]. This genetic diversity complicates treatment and infection-control measures, necessitating antibiotic regimens tailored to local resistance profiles. Moreover, a comprehensive assessment of virulence fac-

Table 3. Univariate analysis of predictors associated with clinical cure in carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections (n=209)

Variables	Clinical Cure (n=112)	Non-cure (n=97)	X^2 (df=1)	*p*-value
Age <65 years	62 (55.4%)	34 (35.1%)	7.83	0.003
Male gender	75 (67.0%)	61 (62.9%)	0.22	0.539
ICU admission	37 (33.0%)	47 (48.5%)	4.52	0.023
Mechanical ventilation	33 (29.5%)	58 (59.8%)	18.24	<0.001
Central venous catheter	56 (50.0%)	64 (66.0%)	4.79	0.019
APACHE II score <15	68 (60.7%)	29 (29.9%)	18.63	<0.001
SOFA score <6	71 (63.4%)	30 (30.9%)	20.66	<0.001
Charlson comorbidity index <4	69 (61.6%)	32 (33.0%)	15.92	<0.001
High-dose Sulperazon	63 (56.2%)	34 (35.1%)	8.56	0.002
Absence of hypermucoviscosity (rmpA negative)	76 (67.9%)	44 (45.4%)	9.86	0.001
bla_KPC-2 positive	69 (61.6%)	68 (70.1%)	1.31	0.195
bla_NDM-1 positive	23 (20.5%)	25 (25.8%)	0.54	0.356

APACHE II, acute physiology and chronic health evaluation II; SOFA, sepsis-related organ failure assessment; ICU, intensive care unit.

Table 4. Multivariate analysis of independent predictors for clinical cure (n=209)

Variables	Adjusted OR (95% CI)	Wald χ^2	*p*-value
High-dose Sulperazon	2.54 (1.38-4.69)	8.73	0.003
Absence of mechanical ventilation	3.12 (1.52-6.40)	9.77	0.002
Absence of hypermucoviscosity gene (rmpA)	2.89 (1.56-5.35)	12.10	<0.001
APACHE II score (<15)	2.46 (1.32-4.57)	8.27	0.004

APACHE II, acute physiology and chronic health evaluation II.

Table 5. Adverse events associated with sulperazon (n=209)

Adverse Events	Standard-dose (n=112)	High-dose (n=97)	X^2 (df=1)	*p*-value
Rash	4 (3.6%)	5 (5.2%)	0.05	0.577
Diarrhea	6 (5.4%)	8 (8.2%)	0.31	0.414
Thrombocytopenia	2 (1.8%)	4 (4.1%)	0.35	0.428
Elevated liver enzymes	5 (4.5%)	7 (7.2%)	0.31	0.4
Renal impairment	2 (1.8%)	3 (3.1%)	0.03	0.668

tors revealed that CRKP isolates frequently harbored multiple determinants, including capsule biosynthesis genes, the hypermucoviscosity regulator *rmpA*, adhesion factors, iron-acquisition systems, and lipopolysaccharide synthesis genes [28]. These virulence attributes enhance invasiveness, promote immune evasion, and improve bacterial survival, thereby contributing substantially to the pathogenicity and severity of CRKP infections [5, 29]. Notably, the high prevalence of the hypermucoviscosity phenotype gene *rmpA* is particularly concerning, as strains harboring this gene are linked to rapid disease progression, metastatic infections, and increased mortality [29]. Therefore, routine molecular surveillance for high-virulence CRKP isolates is essential to guide aggressive clinical management and reinforce infection-control measures.

One of the pivotal results of this study concerns the dose-dependent efficacy of sulperazon treatment. The high-dose regimen demonstrated significant improvements in clinical outcomes, including higher clinical cure rates and markedly reduced treatment failure compared to the standard-dose regimen. These clinical benefits were paralleled by substantial microbiological advantages, including higher complete bacterial eradication rates and lower rates of micro-

biological failure. Furthermore, high-dose sulperazon significantly reduced mortality. Compared with previous studies, our results show that sulperazon exhibited MICs against CRKP strains ranging from 1.5 to 16 mg/L and inhibited 100% of ceftazidime-resistant isolates, supporting the conclusions of Lim and Halijah et al. and confirming the potent activity of the cefoperazone/sulbactam combination against extended-spectrum β-lactamase-producing Gram-negative bacilli [11]. Mechanistically, sulbactam irreversibly binds the active site of serine β-lactamases, including plasmid-encoded variants, thereby protecting cefoperazone from hydrolysis and enabling its subsequent binding to penicillin-binding proteins to inhibit cell-wall synthesis [2]. Recent studies of β-lactam/β-lactamase inhibitor combinations, such as imipenem/relebactam, have similarly demonstrated that co-administration of a targeted inhibitor can restore activity against carbapenemase-producing *Enterobacteriaceae* [30]. Therefore, the observed improvements in clinical cure and microbiological eradication with higher sulperazon doses indicate that optimizing inhibitor exposure is a key strategy for overcoming diverse β-lactamase-mediated resistance. These findings underscore the importance of tailoring antibiotic dosing in managing multidrug-resistant infections, especially when confronting pathogens with complex resistance and virulence profiles like CRKP [11, 31].

Despite the markedly improved clinical outcomes with higher sulperazon doses, the incidence of adverse events, including rash, diarrhea, thrombocytopenia, elevated liver enzymes, and renal impairment, did not differ significantly between dosage groups. This finding indicates that high-dose sulperazon is both safe and effective, corroborating prior studies that have reported a favorable safety profile even at elevated doses [15, 32]. Consequently, clinicians should consider high-dose sulperazon regimens when managing severe CRKP infections, particularly in critically ill patients. From a broader perspective, our findings align with existing evidence supporting the efficacy of β-lactam/β-lactamase inhibitor combinations, such as cefoperazone/sulbactam, against CRKP, especially strains producing class A carbapenemases (KPC types) [15, 33]. They further reinforce recommendations to employ optimized dosing strategies or combination therapies for complicated multidrug-resistant Gram-negative infections [11, 31]. Nevertheless, continuous surveillance of local resistance patterns remains essential, given geographic variability in resistance mechanisms and epidemiological trends.

Our study also has limitations inherent to retrospective analyses. Despite careful screening and selection of patient records, the retrospective design may introduce selection bias and limit our ability to control confounding factors comprehensively. Additionally, the single-center nature of this study may restrict the generalizability of our findings. Therefore, prospective, multicenter studies are needed to validate these results and further inform clinical practice guidelines.

Conclusions

In summary, our study demonstrates that high-dose sulperazon is both efficacious and safe for treating severe CRKP infections. The widespread detection of carbapenemase genes and virulence factors underscores the importance of routine molecular surveillance to guide targeted therapy. High-dose sulperazon should be considered a preferred regimen for critically ill or high-risk patients. Concurrently, robust antimicrobial stewardship, continuous resistance surveillance, stringent infection-control practices, and further research are essential to mitigate the escalating global threat of CRKP.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Qingjiang Guo, Clinical Laboratory, Bengbu First People's Hospital, No. 229 Tushan Road, Yuhui District, Bengbu 233000, Anhui, China. Tel: +86-0552-4018124; E-mail: guoqingjiang124@163.com

References

[1] Xu L, Sun X and Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant Klebsiella pneumoniae. Ann Clin Microbiol Antimicrob 2017; 16: 18.

[2] Lei TY, Liao BB, Yang LR, Wang Y and Chen XB. Hypervirulent and carbapenem-resistant Klebsiella pneumoniae: a global public health threat. Microbiol Res 2024; 288: 127839.

[3] Yang Y, McNally A and Zong Z. Call for prudent use of the term hypervirulence in carbapenem-resistant Klebsiella pneumoniae. Lancet Microbe 2025; 6: 101090.
[4] Wang M and Wang H. Carbapenem-resistant hypervirulent Klebsiella pneumoniae: where is it headed in the tug-of-war between virulence and resistance? EBioMedicine 2025; 114: 105649.
[5] Gu D, Dong N, Zheng Z, Lin D, Huang M, Wang L, Chan EW, Shu L, Yu J, Zhang R and Chen S. A fatal outbreak of ST11 carbapenem-resistant hypervirulent Klebsiella pneumoniae in a Chinese hospital: a molecular epidemiological study. Lancet Infect Dis 2018; 18: 37-46.
[6] Jin X, Chen Q, Shen F, Jiang Y, Wu X, Hua X, Fu Y and Yu Y. Resistance evolution of hypervirulent carbapenem-resistant Klebsiella pneumoniae ST11 during treatment with tigecycline and polymyxin. Emerg Microbes Infect 2021; 10: 1129-1136.
[7] Candan ED and Aksöz N. Klebsiella pneumoniae: characteristics of carbapenem resistance and virulence factors. Acta Biochim Pol 2015; 62: 867-874.
[8] Ernst CM, Braxton JR, Rodriguez-Osorio CA, Zagieboylo AP, Li L, Pironti A, Manson AL, Nair AV, Benson M, Cummins K, Clatworthy AE, Earl AM, Cosimi LA and Hung DT. Adaptive evolution of virulence and persistence in carbapenem-resistant Klebsiella pneumoniae. Nat Med 2020; 26: 705-711.
[9] Yang D. Analysis of drug resistance and clinical characteristics of carbapenem-resistant Klebsiella pneumoniae bloodstream infection. Shaoxing University 2023.
[10] Huang SD. Clinical efficacy study of Sulperazon combined with antibiotics for severe pulmonary infection. Chin J Antituberc 2024; 91-92.
[11] Lim VK and Halijah MY. In vitro activity of sulperazon against recent isolates of ceftazidime-resistant bacteria. Med J Malaysia 2001; 56: 365-369.
[12] Lv M, Xu Q, Ye X and Yu Q. Sulperazon-induced acute reactive thrombocytopenia during treatment of systemic lupus erythematosus: a case report. Eur J Hosp Pharm 2023; 30: e18.
[13] Huang SD. Observation on therapeutic effect of Sulperazon on hospital-acquired pneumonia. Chin J Antituberc 2003; 13: 131-132.
[14] Yoshida T, Oono Y, Toyoda M, Sawa T and Yokoyama H. Efficacy of sulbactam/cefoperazone in respiratory tract infections in elderly patients with underlying respiratory diseases. Jpn J Antibiot 1996; 49: 710-714.
[15] Zhuang Z, Fang Y, Zhu CH and Gu HB. Effect of Sulperazon on elderly patients with pulmonary infection. Chin Prac Med 2018; 13: 131-132.
[16] Yang XW. Clinical manifestations and prognostic factors of carbapenem-resistant Klebsiella pneumoniae bloodstream infection. PLA Medical College 2018.
[17] Pa W. Clinical and Laboratory Standards Institute: Performance standards for antimicrobial susceptibility testing: 20th informational supplement. CLSI document M100-S20 2010.
[18] Zhong C, Lin S, Li Z and Yang X. Characterization of carbapenem-resistant Klebsiella pneumoniae in bloodstream infections: antibiotic resistance, virulence, and treatment strategies. Front Cell Infect Microbiol 2025; 15: 1541704.
[19] Li D, Huang X, Rao H, Yu H, Long S, Li Y and Zhang J. Klebsiella pneumoniae bacteremia mortality: a systematic review and meta-analysis. Front Cell Infect Microbiol 2023; 13: 1157010.
[20] Qian Y, Bi Y, Liu S, Li X, Dong S and Ju M. Predictors of mortality in patients with carbapenem-resistant Klebsiella pneumoniae infection: a meta-analysis and a systematic review. Ann Palliat Med 2021; 10: 7340-7350.
[21] Chen TA, Chuang YT and Lin CH. A decade-long review of the virulence, resistance, and epidemiological risks of Klebsiella pneumoniae in ICUs. Microorganisms 2024; 12: 2548.
[22] Gadisa E, Egyir B, Fekede E, Adu B, Danso J, Oclu A, Owusu-Nyantakyi C, Amuasi GR, Bortey A, Disasa G and Tessema TS. Epidemiology, antimicrobial resistance profile, associated risk factors and management of carbapenem resistant Klebsiella pneumoniae in children under 5 with suspected sepsis in Ethiopia. BMC Infect Dis 2024; 24: 1458.
[23] Zeng Z, Ye C, Hao J, Tang M, Xiao X, Jian C, Guo J, Ding Y and Liu J. Molecular epidemiological analysis of bla(NDM-5)-producing Klebsiella pneumoniae ST2407-K25 causing infection outbreaks in pediatric patients based on whole genome sequencing. Ann Clin Microbiol Antimicrob 2024; 23: 91.
[24] Rani K, Tripathi S, Sharma A, Sharma S, Sheba P and Samuel Raj V. Solithromycin in combination with other antimicrobial agents against the carbapenem resistant Klebsiella pneumoniae (CRKP). Indian J Microbiol 2024; 64: 540-547.
[25] Ding L, Yang Z and Sun B. Understanding blaNDM-1 gene regulation in CRKP infections: toward novel antimicrobial strategies for hospital-acquired pneumonia. Mol Med 2024; 30: 29.
[26] van Duin D and Paterson DL. Multidrug-resistant bacteria in the community: an update. Infect Dis Clin North Am 2020; 34: 709-722.
[27] Liao Y, Gong J, Yuan X, Wang X, Huang Y and Chen X. Virulence factors and carbapenem-re-

sistance mechanisms in hypervirulent Klebsiella pneumoniae. Infect Drug Resist 2024; 17: 1551-1559.

[28] Wang Q, Chen M, Ou Q, Zheng L, Chen X, Mao G, Fang J, Jin D and Tang X. Carbapenem-resistant hypermucoviscous Klebsiella pneumoniae clinical isolates from a tertiary hospital in China: antimicrobial susceptibility, resistance phenotype, epidemiological characteristics, microbial virulence, and risk factors. Front Cell Infect Microbiol 2022; 12: 1083009.

[29] Yang AX. Analysis of 178 cases of carbapenem-resistant Klebsiella pneumoniae and efficiency of tigecyline with different sensitivity. Shandong University 2021.

[30] Papp-Wallace KM, Barnes MD, Alsop J, Taracila MA, Bethel CR, Becka SA, van Duin D, Kreiswirth BN, Kaye KS and Bonomo RA. Relebactam is a potent inhibitor of the KPC-2 β-lactamase and restores imipenem susceptibility in KPC-producing Enterobacteriaceae. Antimicrob Agents Chemother 2018; 62: e00174-18.

[31] Huang SD. Observation of the efficacy of Shupushen in the treatment of hospital-acquired pneumonia. Journal of Clinical Pulmonary Medicine 2004; 9: 195.

[32] Wu SD. Shupushen combined with antibiotics in patients with severe lung infections efficacy studies. Chin J Antituberc 2024; 46: 91-93.

[33] Shangguan ZF, Chen HL, Li YF, Shi N and Mao QF. In vitro antibacterial effect of reduning combined with polymyxin on carbapenem resistant Klebsiella pneumoniae. Infect Drug Resist 2025; 18: 227-237.