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Efficacy and Safety of Different Colistin Administration Routes for Nosocomial Pneumonia Caused by Carbapenem-Resistant Organisms: A Single Centre, Open Label, Prospective Cohort Study

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Background: The role of inhaled colistin as either an adjunctive or substitution for nosocomial pneumonia (NP) caused by carbapenem-resistant organisms (CRO) is highly debated due to conflicting clinical evidence. Given the limitations of intravenous therapy, the optimal administration strategy remains a critical, unresolved question. This study aimed to compare the efficacy and safety of three colistin-based regimens administered via different routes.

Methods: In this prospective cohort study, 127 intensive care unit (ICU) patients diagnosed with CRO-related NP and treated with colistin were enrolled. Patients were classified into three groups according to the route of administration: inhalation (IH group), intravenous colistin with adjunctive inhalation (IV+IH group), and intravenous (IV group) therapy. The primary endpoint was clinical efficacy at the end of treatment. Key secondary outcomes included microbiological eradication and nephrotoxicity.

Results: Clinical efficacy was achieved in 72.1% of the IH group, 67.4% of the IV+IH group, and 65% of the IV group, with no statistically significant difference among groups (P=0.786). The IH group demonstrated a significantly higher microbiological eradication rate compared with the IV group (P=0.004). No significant differences were observed in 28-day all-cause mortality, hospital stay duration, or incidence of acute kidney injury (AKI). Moreover, the development of AKI during treatment was strongly associated with clinical failure, suggesting it may serve as a prognostic marker for poor outcomes.

Conclusion: In critically ill patients with CRO-associated NP, inhaled colistin monotherapy provided comparable clinical efficacy to systemic administration. It achieved superior microbiological eradication and showed a favorable safety profile regarding nephrotoxicity, suggesting it represents a viable and potentially safer therapeutic strategy.

Keywords: carbapenem-resistant Gram-negative bacteria, colistin, inhalation therapy, intravenous administration, nosocomial pneumonia

Introduction

Nosocomial pneumonia (NP), encompassing hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), is a leading cause of morbidity and mortality in critically ill patients, a challenge compounded by profound pathophysiological alterations that significantly impact antibiotic pharmacokinetics and pharmacodynamics.[1] The global rise of multidrug-resistant (MDR) microorganisms has emerged as a major threat to public health, with the burden being particularly pronounced in developing countries.[2] Within hospital settings, refractory infections and the growing prevalence of

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MDR pathogens further complicate infection control, especially in intensive care units (ICUs).[3,4] Furthermore, a recent Global Burden of Disease analysis estimated that MDR pneumonia accounts for roughly 2.3 million deaths worldwide each year.[5] Carbapenem-resistant Gram-negative bacteria (CR-GNB) are strongly linked to high mortality among infected patients. Their resistance arises mainly from the production of carbapenemases, increased activity of efflux pumps, and reduced permeability due to loss or modification of outer membrane porins.[6,7]

Polymyxins, despite their known nephrotoxicity and neurotoxicity, have re-emerged as essential agents for treating infections caused by MDR Gram-negative bacteria.[8] Owing to the global escalation of antimicrobial resistance, colistin is once again frequently used in severe infections, particularly in critically ill patients.[9] In its intravenous form, however, colistin demonstrates limited penetration into pulmonary tissues, largely due to its physicochemical properties, raising concerns about suboptimal drug exposure at the site of lung infection.[10] Inhaled administration has therefore been proposed as an alternative strategy. Pharmacokinetic studies have shown that aerosolized colistin achieves markedly higher concentrations in the epithelial lining fluid than in plasma,[11] suggesting the potential to enhance local antibacterial activity while reducing systemic toxicity. These theoretical advantages have led to increasing clinical use of inhaled colistin.[12,13]

Nevertheless, clinical evidence supporting the optimal route of colistin administration remains inconsistent. For instance, one study in patients with VAP reported that adjunctive inhaled colistin significantly improved both clinical cure and microbiological eradication rates compared to IV monotherapy.[14] In contrast, another matched case-control study found no significant differences in any efficacy endpoint between adjunctive therapy and IV colistin alone.[15] Further complicating the picture, a study comparing inhaled monotherapy against IV monotherapy found comparable efficacy but a dramatically lower rate of nephrotoxicity in the inhalation group.[16]

This evidentiary chaos is mirrored in the discordant recommendations from major international guidelines. The most recent 2024 Infectious Diseases Society of America (IDSA) guidelines advise against adjunctive inhaled antibiotics for pneumonia, citing a lack of proven clinical benefit in robust trials.[17] Similarly, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) does not support routine use.[18] In contrast, other expert bodies have adopted a more permissive stance: the 2019 international consensus guidelines favor adding inhaled colistin to IV therapy for extensively drug-resistant pneumonia,[19] while some European collaborative networks suggest inhaled monotherapy may be a viable "substitution" strategy when systemic options are limited.[20]

In CR-GNB nosocomial pneumonia—an infection associated with high mortality and limited therapeutic alternatives—identifying the colistin strategy that best balances efficacy with renal safety is clinically important. Therefore, this prospective study aimed to evaluate and compare the clinical outcomes and renal safety associated with three different colistin regimens—intravenous alone, inhaled alone, and combined intravenous plus inhaled therapy—in a real-world cohort of critically ill patients.

Material and Methods

Study Design and Setting

This prospective, single-center cohort study was conducted in the ICU of The First Affiliated Hospital of Ningbo University, Ningbo, China, between January 1, 2023, and September 30, 2025. The study protocol was reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Ningbo University (Approval No. 2024-R044-02). The trial was registered in ClinicalTrials.gov (Identifier: NCT06907069).

Study Population

Eligible participants were adult patients (≥18 years old) diagnosed with NP caused by carbapenem-resistant organisms (CRO) and treated with colistin for at least 72 hours. The diagnosis of NP was established based on clinical, radiological, and microbiological criteria, including the presence of new or progressive pulmonary infiltrates on chest imaging, purulent respiratory secretions, and compatible clinical features (eg, fever, leukocyte count abnormality, and hypoxemia). We only included respiratory isolates that tested non-resistant to colistin via standardized antimicrobial susceptibility testing.

Exclusion Criteria

Patients were excluded if they met any of the following conditions: (1) pregnancy or lactation; (2) known allergy to colistin; (3) incomplete or missing essential clinical data; or (4) participation in another interventional clinical trial within the preceding three months. For individuals who received multiple courses of colistin during the study period, only the first treatment episode was included in the analysis to avoid duplication and bias.

Dosing and Administration

Patients received colistin therapy via one of three administration routes—intravenous (IV) monotherapy, inhaled (IH) monotherapy, or IV therapy with adjunctive inhaled colistin (IV+IH)—based on clinical judgment, infection severity, and attending physician discretion. For intravenous therapy, colistin was administered at a total daily dose of 2.5–5.0 mg colistin base activity (CBA) per kilogram of body weight, divided into two equal doses. Dosage adjustments were made according to renal function, based on the creatinine clearance or ongoing renal replacement therapy status, following current international dosing guidelines. For inhalation therapy, 75 mg CBA of colistin was reconstituted in 3–5 mL of sterile 0.9% normal saline and delivered via a vibrating mesh nebulizer every 8 or 12 hours. The nebulizer was connected to the ventilator circuit or a standard mouthpiece, depending on patient ventilation status, ensuring particle sizes between 1 and 5 μm for optimal pulmonary deposition. In the adjunctive therapy group, inhaled colistin was administered at the same dose as in the monotherapy group; the intravenous dose was individualized based on renal function and infection severity.

Data Collection

All clinical data were retrieved from the institutional electronic medical record system. The initiation of colistin therapy was defined as Day 1 of treatment. A comprehensive range of potential confounding variables was collected, including demographic information, underlying disease, Clinical Pulmonary Infection Score (CPIS). The laboratory parameters included inflammation-related markers, total protein, albumin, and serum creatinine levels. The Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were assessed both before and after treatment. Additionally, microbiological findings, details of antimicrobial therapy, clinical and microbiological outcomes, adverse drug reactions, and 28-day all-cause mortality were also recorded.

Microbiological Testing

Respiratory specimens were cultured on Columbia blood agar plates at 35 °C for 18–24 hours. Bacterial identification was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Daltonics, Germany). The minimum inhibitory concentrations (MICs) of antibiotics were determined using the VITEK 2 Compact system (bioMérieux, France). Antimicrobial susceptibility results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2025). Quality control was performed using *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853.

Definitions and Outcomes

According to the Clinical Practice Guidelines for the Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia jointly issued by the American Thoracic Society and the Infectious Diseases Society of America in 2016, HAP and VAP are defined as follows. HAP refers to pneumonia that develops 48 hours or more after hospital admission, that was not present at the time of admission and is unrelated to mechanical ventilation. VAP refers to pneumonia that arises more than 48 hours after endotracheal intubation and initiation of mechanical ventilation.[21]

The primary outcome was clinical effectiveness at the end of colistin treatment. Clinical efficacy was defined as the resolution or alleviation of pneumonia-related symptoms and signs following the completion of therapy. Clinical failure was characterised by the persistence or worsening of pneumonia symptoms or signs at the end of treatment. Clinical cure or improvement was determined based on patient survival, resolution of fever, decreased need for sputum suction,

improvement or resolution of radiographic findings, stabilization or improvement in the PaO_2/FiO_2 ratio, and reduction or normalization of infection markers.

Secondary outcomes included 28-day all-cause mortality, microbiological outcomes, nephrotoxicity, and the duration of ICU and hospital stay. Sputum, endotracheal aspirates, or bronchoalveolar lavage fluid served as the sources of all microbiological isolates. Microbiological eradication was defined as the absence of the original causative pathogen in cultures obtained from the primary infection site after treatment. When clinical resolution made specimen collection infeasible — such as the inability to expectorate sputum — or when invasive procedures were not justified in recovering patients, the outcome was classified as presumed eradication. The microbiological eradication rate was calculated as follows: (number of eradications + number of presumed eradications)/total number of patients × 100%. Because most ICU patients were sedated, neurological side effects could not be reliably assessed. In contrast, nephrotoxicity was more readily identifiable and occurred more frequently,[22] making it the primary adverse effect of interest. Nephrotoxicity was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as the occurrence of acute kidney injury (AKI) during colistin therapy, meeting at least one of the following conditions: (1) An increase in serum creatinine of more than 26.5 μmol/L (0.3 mg/dL) within 48 hours; (2) An increase in serum creatinine to more than 1.5 times the baseline within 7 days; (3) Urine output less than 0.5 mL/(kg h).[23]

Statistical Analyses

All statistical analyses were performed using SPSS (version 27.0, IBM Corporation, Armonk, NY, USA). A P value of less than 0.05 was considered statistically significant. Continuous variables with a normal distribution were expressed as the mean ± standard deviation (SD), and comparisons were conducted using the t-test or one-way analysis of variance (ANOVA). Continuous variables that did not follow a normal distribution were presented as median (P25, P75) and analysed using the Mann–Whitney U-test for two-group comparisons or the Kruskal–Wallis test for comparisons among multiple independent groups. Categorical variables were reported as frequencies or percentages and analysed using the chi-square test or Fisher's exact test, as appropriate. Post hoc pairwise comparisons were adjusted using the Bonferroni correction method. Kaplan-Meier curves were generated to compare 28-day cumulative survival rates among the IV, IH, and IV+IH groups. Variables potentially associated with clinical resolution were first screened using univariate analysis. Variables with a P value < 0.10 and/or considered clinically relevant based on prior literature were entered into the multivariate logistic regression model to identify factors independently associated with clinical resolution. To ensure the model's robustness, collinearity was assessed using the variance inflation factor (VIF), and the model's goodness-of-fit was confirmed with the Hosmer-Lemeshow test.

Result

Patient Characteristics and Baseline Clinical Data

This single-centre prospective study analyzed 127 patients diagnosed with NP caused by CRO who received colistin therapy between January 2023 and September 2025. Figure 1 presents the flow diagram for patient enrollment and exclusion. Among the enrolled patients, 61 received inhaled colistin monotherapy, 46 received intravenous therapy with adjunctive inhaled colistin, and 20 received intravenous colistin monotherapy. The overall study population included 94 male (74.0%) and 33 female (26.0%) patients.

Carbapenem-resistant *Acinetobacter baumannii* (60.0%) was the most frequently isolated pathogen. No significant difference was observed in microbial distribution among the three groups (P=0.329). A combination therapy approach was common in our cohort. Beyond the core colistin treatment, the most prevalent co-administered antibiotics were meropenem (29.8%) and cefoperazone-sulbactam (26.8%), with piperacillin-tazobactam (19.6%) and tigecycline (9.5%) also frequently used. The distribution of these concomitant agents (eg, meropenem, cefoperazone-sulbactam, piperacillin-tazobactam, ceftazidime-avibactam) was comparable across the three study groups, with no significant differences observed ($P > 0.05$ for all comparisons). Similarly, no significant were found in baseline demographic or clinical characteristics, including age, sex, body mass index (BMI), comorbidities, and pretreatment APACHE II, SOFA, or CPIS scores. However, a statistically significant difference was observed in baseline serum creatinine levels, with the

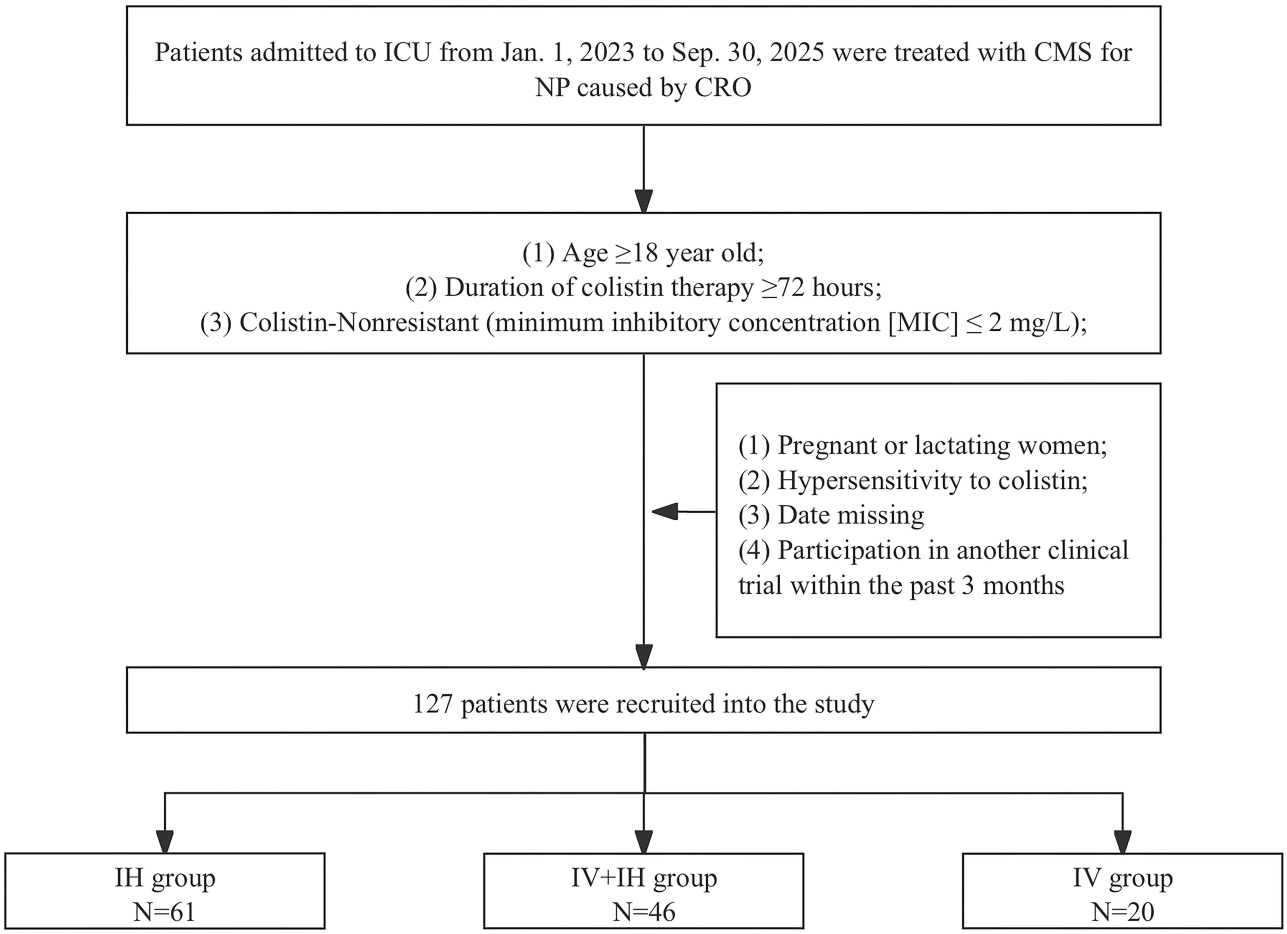

Figure 1 Flow chart of participant selection.

intravenous group showing lower values than the inhalation group (P=0.015). Comprehensive demographic and baseline clinical characteristics are summarized in Table 1.

Assessment of Inflammatory Biomarkers and Clinical Severity Scores

Given that the median duration of CMS therapy was 9 to 10 days, inflammatory biomarkers and disease severity scores were primarily evaluated on days 3, 7, and at the end of treatment. Prior to enrolment, 89% of patients required mechanical ventilation, and more than two-thirds presented with concomitant respiratory failure. After 7 days of CMS therapy, the PaO_2/FiO_2 ratio demonstrated an overall upward trend with intermittent fluctuations (Figure 2A), reaching a mean of 351.62 in the intravenous monotherapy group; however, the difference among the three groups was not statistically significant (P=0.193). In addition, both APACHE II and SOFA scores exhibited decreasing trends on days 3 and 7, though no significant differences were observed among the three cohorts (all P>0.05) (Table 2). Notably, both C-reactive protein (CRP) and white blood cell (WBC) counts showed a fluctuating but overall downward trend throughout the course of treatment (Figure 2B and C). Additionally, on day of the treatment, no statistically significant differences were observed in body temperature, total protein, or albumin among the groups (Figure 2D–F).

Clinical Outcomes

The rates of clinical efficacy were comparable among the IH (72.1%), IV+IH (67.4%), and IV (65.0%) groups, with no statistically significant difference observed (P=0.786). Patients who received nebulized antibiotic therapy demonstrated a markedly higher rate of microbiological eradication. In the IV+IH group, 29 patients (63%) achieved negative culture results after treatment, compared with only 45% in the IV monotherapy group (P=0.014). Regarding prognosis, there

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Table 1 Demographic and Clinical Characteristic of Study Patients

	IH (n=61)	IV+IH (n=46)	IV (n=20)	*P* Value
Demographic				
Age, years	66.92 ± 15.12	71.11 ± 13.22	63.00 ± 12.12	0.080
Male, n (%)	48 (78.7)	35 (76.1)	11 (55.0)	0.103
BMI, kg/m^2	23.56 ± 3.91	22.51 ± 4.10	23.78 ± 2.50	0.314
Underlying disease, n (%)				
Diabetes mellitus	16 (26.2)	16 (34.8)	2 (10.0)	0.112
Hypertension	33 (54.1)	27 (58.7)	10 (50.0)	0.788
CHD	9 (14.8)	6 (13.0)	0 (0)	0.232
COPD	8 (13.1)	10 (21.7)	1 (5.0)	0.213
Cerebrovascular disease	7 (11.5)	7 (15.2)	1 (5.0)	0.529
Isolated pathogen at diagnosis, n (%)				
CRAB	40 (65.6)	26 (56.5)	15 (75.0)	0.329
CRPA	12 (19.7)	13 (28.3)	3 (15.0)	0.438
CRKP	8 (13.1)	7 (15.2)	4 (20.0)	0.708
Carbapenem-resistant *Serratia marcescens*	2 (3.3)	3 (6.5)	0 (0)	0.574
Carbapenem-resistant *Klebsiella aerogenes*	1 (1.6)	1 (2.2)	0 (0)	1.000
Polymyxins MIC distribution ≤0.5 mg/L, n (%)	35 (57.4)	21 (45.7)	8 (40.0)	0.291
Duration of nebulized CMS therapy, days	10 (7, 14)	10 (6, 14)	0 (0,0)	0.736
Duration of systemic CMS therapy, days	0 (0,0)	9.5 (6, 13)	9 (5.3, 12)	0.721
Concomitant antibiotic therapy, n (%)				
Meropenem	24 (39.3)	16 (34.8)	10 (50.0)	0.509
Cefoperazone-Sulbactam	16 (26.2)	21 (45.7)	8 (40.0)	0.103
Piperacillin-Tazobactam	19 (31.1)	8 (17.4)	6 (30.0)	0.249
Tigecycline	12 (19.7)	4 (8.7)	0 (0)	0.042*
Ceftazidime-Avibactam	5 (8.2)	2 (4.3)	1 (5.0)	0.882
Others	10 (16.4)	4 (8.7)	2 (10.0)	0.459
Baseline laboratory results and vital signs				
T, °C	38.1 (37.7, 38.5)	38.0 (37.4, 38.4)	38.1 (37.8, 39.1)	0.194
PaO_2/FiO_2, mmHg	293.24 ± 108.66	247.05 ± 88.96	282.15 ± 107.76	0.070
WBC, $10^9/L$	11.6 (8.6, 15.7)	11.9 (7.3, 16.3)	11.8 (7.1, 14.7)	0.868
CRP, mg/L	93.0 (61.6, 153.7)	81.9 (40.3, 139.0)	48.4 (27.4, 173.3)	0.467
PCT, ng/mL	1.00 (0.31, 2.16)	0.56 (0.25, 3.00)	1.33 (0.19, 6.92)	0.695
Total protein, g/L	59.34 ± 6.71	57.79 ± 6.02	57.15 ± 5.24	0.271
Albumin, g/L	30.04 ± 3.20	29.34 ± 3.41	30.05 ± 2.81	0.502
Serum creatinine, μmol/L	72.0 (51.0, 104.0)[a]	72.5 (43.5, 89.0)	50.0 (37.3, 85.4)[b]	0.029*
Severity of disease				
APACHE II score	20.39 ± 4.99	21.58 ± 4.27	21.20 ± 5.31	0.442
SOFA score	7 (5, 9)	7 (5, 9)	8 (5, 13)	0.582
CPIS score	7 (6, 8)	7 (6, 8)	7 (5, 9)	0.627
Mechanical ventilation, n (%)	53 (86.9)	43 (93.5)	17 (85.0)	0.436

Notes: *$P<0.05$ was considered statistically significant. Different letters (a, b) denote significant differences by Bonferroni post hoc test ($P < 0.05$).
Abbreviations: BMI, body mass index; CHD, coronary heart disease; COPD, Chronic Obstructive Pulmonary Disease; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; MIC, minimum inhibitory concentration; WBC, White blood cell count; CRP, C-reactive protein; PCT, procalcitonin; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CPIS, Clinical Pulmonary Infection Score.

were no statistically significant differences in 28-day all-cause mortality among the groups (P=0.352) (Table 3). Similarly, Kaplan-Meier survival analysis revealed no significant difference in 28-day mortality across the three groups (P=0.386) (Figure 3). After excluding patients who undergone renal replacement therapy before the initiation of colistin (9 in the IH cohort, 3 in the IV+IH cohort, and 6 in the IV cohort), the incidence of AKI was 28.8% in the IH cohort, 44.2% in the IV+IH cohort, and 42.9% in the IV cohort, with no statistically significant difference (P=0.266).

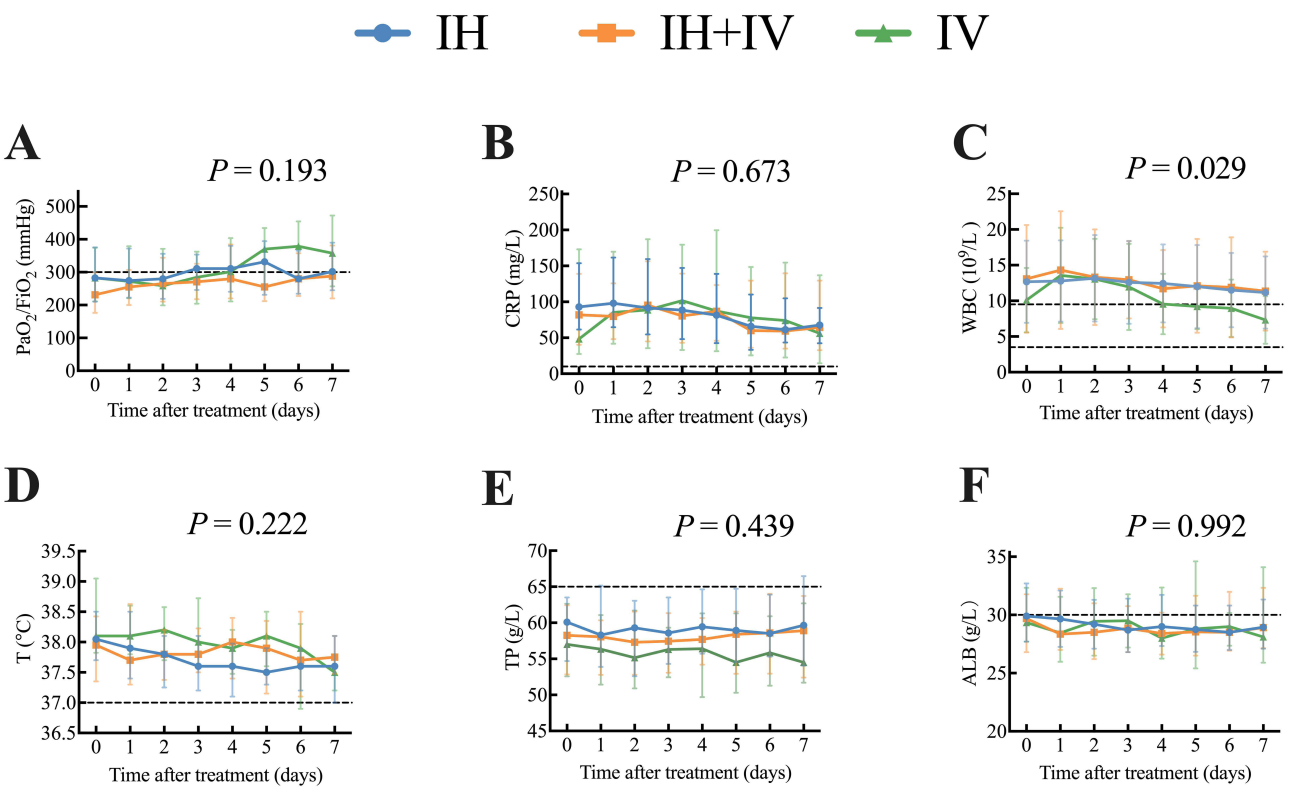

Figure 2 Dynamic profile of key clinical and laboratory parameters across the three treatment groups over time. The panels display trends in: (**A**) the oxygenation index (PaO2/FiO2 ratio), (**B**) C-reactive protein (CRP), (**C**) white blood cell (WBC) count, (**D**) body temperature, (**E**) total protein (TP), and (**F**) albumin (ALB). Each dot represents the median value, and the error bars indicate the interquartile range (25th to 75th percentiles).

As shown in Table 4, univariate analysis identified age, sepsis, AKI, CPIS, and APACHE II score as variables associated with clinical resolution at a significance level of $P < 0.10$. These variables were selected for further multivariate analysis. Multicollinearity was assessed prior to model construction, and all variables demonstrated acceptable collinearity (all VIF values < 5). These variables were subsequently entered into the multivariate logistic

Table 2 Inflammatory Markers and Severity Scores Across Treatment Timeline

	IH (n=61)	IV+IH (n=46)	IV (n=20)	*P* Value
On the third day of treatment				
APACHE II score	20 (18, 24)	21 (18, 23)	21 (20, 22)	0.721
SOFA score	6 (5, 9)	7 (5, 10)	7 (5, 10)	0.473
T, °C	37.6 ± 0.6	37.9 ± 0.5	38.1 ± 0.8	0.015*
PaO_2/FiO_2, mmHg	304.13 ± 93.02	275.28 ± 94.57	277.10 ± 94.21	0.240
WBC, 10^9/L	12.1 (7.6, 16.0)	11.8 (8.6, 17.8)	12.7 (6.2, 14.0)	0.772
CRP, mg/L	94.0 (51.0, 157.4)	84.7 (43.3,147.5)	82.8 (27.4, 178.0)	0.658
PCT, ng/mL	1.13 (0.68, 2.50)	1.22 (0.40, 4.13)	1.51 (0.29, 5.70)	0.703
Total protein, g/L	59.03 ± 7.21	57.20 ± 5.94	56.61 ± 5.13	0.211
Albumin, g/L	28.98 ± 3.20	28.76 ± 3.10	29.80 ± 3.62	0.486
On the seventh day of treatment				
APACHE II score	20 (18, 22)	19 (16, 22)	22 (17, 23)	0.650
SOFA score	6 (5, 8)	6 (5, 8)	5 (4, 9)	0.458
T, °C	37.6 (37.0, 38.1)	37.8 (37.5, 38.1)	37.5 (37.2, 37.8)	0.222
PaO_2/FiO_2, mmHg	319.33 ± 93.42	294.93 ± 103.70	351.62 ± 131.20	0.193

(*Continued*)

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Table 2 (Continued).

	IH (n=61)	IV+IH (n=46)	IV (n=20)	*P* Value
WBC, 10^9/L	9.9 (7.5, 14.3)	9.6 (6.5, 15.2)	7.1 (6.0, 8.2)	0.029*
CRP, mg/L	66.8 (42.1, 90.7)	49.6 (28.8, 134.2)	53.5 (12.7, 142.7)	0.879
PCT, ng/mL	0.62 (0.25, 1.56)	1.04 (0.32, 2.42)	0.63 (0.21, 4.72)	0.886
Total protein, g/L	60.92 ± 8.98	58.77 ± 6.31	58.79 ± 9.65	0.439
Albumin, g/L	28.95 (27.10, 31.33)	28.90 (27.15, 32.33)	28.10 (25.90, 34.10)	0.992
End of treatment				
APACHE II score	17 (14, 21)	20 (16, 25)	20 (15, 24)	0.155
SOFA score	5 (3, 7)	6 (5, 9)	6 (4, 11)	0.071
T, °C	37.3 (37.0, 37.6)	37.2 (36.7, 37.7)	37.2 (37.0, 37.5)	0.293
PaO_2/FiO_2, mmHg	345.75 ± 112.22	322.02 ± 121.24	269.83 ± 99.95	0.040*
WBC, 10^9/L	9.5 (6.9, 15.0)	8.9 (7.4, 13.7)	6.1 (4.8, 10.6)	0.828
CRP, mg/L	10.2 (6.9, 15.1)	8.7 (6.9, 16.7)	8.1 (5.0, 16.5)	0.962
PCT, ng/mL	0.48 (0.15, 1.97)	1.16 (0.26, 5.72)	0.56 (0.17, 2.19)	0.031*
Total protein, g/L	61.79 ± 8.00	59.26 ± 7.50	59.36 ± 8.78	0.249
Albumin, g/L	30.42 ± 4.05	29.80 ± 3.63	31.67 ± 4.88	0.261

Notes: *P<0.05 was considered statistically significant.

Table 3 Outcomes in Patients Receiving Different Administration

	IH (n=61)	IV+IH (n=46)	IV (n=20)	*P* Value
Clinical efficacy, n (%)	44 (72.1)	31 (67.4)	13 (65)	0.786
Microbiological eradication, n (%)	48 (78.7)[a]	29 (63.0)	9 (45.0)[b]	0.014*
28-day mortality, n (%)	15 (24.6)	17 (37.0)	7 (35.0)	0.352
Length of hospital stay, days	30 (20, 43)	30 (21, 48)	25 (19, 36)	0.509
Length of ICU stay, days	26 (19, 40)	26 (19, 42)	28 (20, 36)	0.967
AKI, n (%)	15 (28.8)	19 (44.2)	6 (42.9)	0.266
AKI stage				
Stage 1	7 (46.7)	6 (31.6)	4 (66.7)	0.292
Stage 2	5 (33.3)	4 (21.1)	2 (33.3)	0.630
Stage 3	3 (20.0)	9 (47.4)	0 (0)	0.051

Notes: *P<0.05 was considered statistically significant. Different letters (a, b) denote significant differences by Bonferroni post hoc test ($P < 0.05$).
Abbreviation: AKI, acute kidney injury.

regression model. The model demonstrated good calibration, as confirmed by the Hosmer–Lemeshow test (P=0.404). After adjustment, the occurrence of AKI during colistin therapy remained independently associated with clinical efficacy (OR = 0.246, 95% CI: 0.093–0.646, P = 0.004).

Discussion

This study evaluated the clinical efficacy and nephrotoxicity of different colistin administration routes for the treatment of NP caused by CR-GNB. Compared with IV or IH monotherapy, IV+IH group did not demonstrate superior clinical efficacy, lower 28-day all-cause mortality rate, or a shorter length of hospital stay. However, the IH group achieved a significantly higher rate of bacterial eradication than the IV group (P<0.05). Importantly, the addition of inhaled therapy to systemic intravenous administration was not associated with an increased risk of nephrotoxicity.

Prior meta-analyses have yielded mixed findings on whether polymyxin-based adjunctive therapy improves outcomes such as mortality and clinical cure rates. The inconsistency across studies likely reflects variations in infection severity, nebulizer design and delivery efficiency, and differences in inhaled dosing regimens.[5,24–26] In most cases, inhaled colistin was administered as an adjunct to systemic therapy rather than as a standalone approach, making it difficult to isolate its

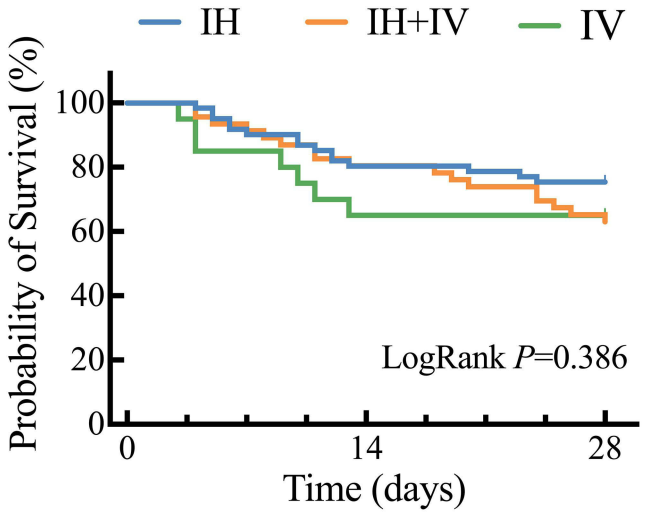

Figure 3 Kaplan–Meier survival analysis curve.

independent therapeutic contribution. The present study addressed this limitation by examining a relatively homogeneous cohort of critically ill patients with CRO-associated nosocomial pneumonia and by directly comparing inhaled colistin monotherapy with systemic administration. This design reduced treatment-related heterogeneity and allowed a more focused evaluation of the clinical role of inhaled therapy. Under these conditions, the addition of inhaled colistin did not result in higher rates of clinical success or improved 28-day survival. It should also be noted that the effectiveness of aerosolized antibiotic therapy is strongly influenced by technical and patient-specific factors, including nebulizer performance, ventilator settings, and airway pathology.[27] In our study, many patients undergoing bronchoscopy exhibited thick airway secretions, potentially impeding alveolar drug deposition and thereby limiting therapeutic efficacy. Although a vibrating mesh nebulizer-characterized by high pulmonary deposition efficiency, low residual volume, and short

Table 4 Univariate Analysis of Factors Associated with Clinical Efficacy

	Clinical Failure (n=39)	**Clinical Efficacy (n=88)**	***P* Value**
Demographic			
Age, years	75 (64, 81)	71 (56.5, 75.8)	0.026*
Male, n (%)	30 (76.9)	64 (72.7)	0.619
BMI, kg/m^2	23.28 ± 3.84	23.18 ± 3.61	0.887
Underlying disease, n (%)			
Diabetes mellitus	8 (20.5)	26 (29.5)	0.289
Hypertension	21 (53.8)	49 (55.7)	0.848
CHD	4 (10.3)	11 (12.5)	0.949
COPD	7 (17.9)	12 (13.6)	0.530
Cerebrovascular disease	5 (12.8)	10 (11.4)	1.000
Isolated pathogen at diagnosis, n (%)			
CRAB	21 (53.8)	60 (68.2)	0.121
CRPA	10 (25.6)	18 (20.5)	0.515
CRKP	8 (20.5)	10 (11.4)	0.173
Carbapenem-resistant *Serratia marcescens*	1 (2.6)	4 (4.5)	1.000
Carbapenem-resistant *Klebsiella aerogenes*	1 (2.6)	1 (1.1)	0.522
Polymyxins MIC distribution ≤0.5 mg/L, n (%)	21 (60.0)	43 (53.8)	0.535

(*Continued*)

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Table 4 (Continued).

	Clinical Failure (n=39)	Clinical Efficacy (n=88)	*P* Value
Concomitant antibiotic therapy, n (%)			
Meropenem	13 (33.3)	37 (42.0)	0.354
Cefoperazone-Sulbactam	16 (41.0)	29 (33.0)	0.380
Piperacillin-Tazobactam	7 (17.9)	26 (29.5)	0.169
Tigecycline	7 (17.9)	6(9.1)	1.000
Ceftazidime-Avibactam	3 (7.7)	5 (5.7)	0.973
Others			
Sepsis, n (%)	23 (59.0)	35 (39.8)	0.045*
AKI, n (%)	21 (63.6)	19 (25.0)	<0.001*
Microbiological eradication, n (%)	25 (64.1)	61 (69.3)	0.681
Mechanical ventilation, n (%)	36 (92.3)	78 (88.6)	0.755
CPIS score	7 (6, 8)	7 (6, 8)	0.053
APACHE II score (D0)	21.65 ± 4.84	20.77 ± 4.53	0.014*
SOFA score (D0)	8 (5, 9)	7 (5, 9)	0.113

Notes: *$P<0.05$ was considered statistically significant.

nebulization time-was used, achieving adequate drug concentrations in infected lung regions remains uncertain and warrants further pharmacokinetic investigation.[20] Furthermore, patients who developed AKI had a substantially lower likelihood of achieving clinical success compared with those without AKI. Consistent with our findings, previous studies have shown that elevated Simplified Acute Physiology Score II ($P=0.002$), higher SOFA score ($P=0.05$), septic shock ($P<0.001$), and AKI during polymyxin therapy ($P=0.04$) were all independently associated with poor clinical outcomes.[28] This may be due to dose adjustment or renal replacement therapy, which alters the pharmacokinetics of colistin and consequently leads to insufficient drug exposure.

Compared with IV administration, aerosolized colistin achieved significantly higher bacterial eradication rates ($P=0.004$), consistent with prior reports.[14,29,30] The enhanced local drug concentration delivered via inhalation may contribute to superior microbial clearance. Nonetheless, a retrospective matched case-control study involving 43 patient pairs with VAP caused by MDR Gram-negative pathogens found no significant differences between adjunctive therapy and IV monotherapy in terms of pathogen eradication ($P=0.679$), clinical cure ($P=0.100$), or mortality ($P=0.289$).[15] Similarly, another study focusing on MDR *Acinetobacter baumannii* also reported comparable outcomes across treatment regimens.[16] These discrepancies may reflect an incomplete understanding of antibiotic penetration from the airway lumen into infected parenchymal tissue. A key observation from our study was the apparent dissociation between microbiological eradication and clinical benefit ($P=0.681$). We propose several potential explanations for this finding. First, in this critically ill population, the ultimate clinical trajectory is often dictated by the primacy of the host's inflammatory response and the degree of organ dysfunction, rather than by microbial clearance alone. Second, while reducing the bacterial burden is a critical therapeutic goal, it may be insufficient to reverse severe, established structural lung injury. Finally, we must acknowledge the possibility that our study was statistically underpowered to detect a more modest, albeit potentially real, association between these two endpoints.

Nephrotoxicity remains a major concern with colistin use, often limiting its clinical application. In this study, physicians appeared more tolerant of mild creatinine elevations in patients receiving IH therapy alone, reflecting the perception of lower systemic exposure. Although the difference in AKI incidence among the three groups were not statistically significant, the IH-only group exhibited a numerically lower AKI rate. The reported incidence of colistin-associated AKI ranges from 20% to 60%. Studies have demonstrated that inhaled colistin results in a markedly reduced incidence of nephrotoxicity compared with systemic administration.[31,32] Furthermore, combined IV+IH therapy does not appear to significantly increase nephrotoxic risk compared with IV administration alone.[14] A separate meta-analysis

identified age >65 years, hypoalbuminemia, sepsis or septic shock, and concurrent use of vancomycin or vasopressors as independent risk factors for colistin-associated nephrotoxicity.[33]

Although nephrotoxicity is a well-recognized adverse effect of polymyxins, the associated rise in serum creatinine is often mild and reversible. Given the severity of infections in these patients, treatment discontinuation due to renal toxicity is uncommon. Prior studies have shown that AKI was reversible in 91.6% of patients treated with CMS and 79.0% of those receiving polymyxin B.[34] However, the long-term renal consequences of polymyxins exposure, particularly among elderly patients, remain underappreciated. A retrospective cohort study found that among survivors who received intravenous polymyxin therapy for severe infections developed AKI during hospitalization (29/72). At the 6-month follow-up, 75% (22/29) of these AKI survivors progressed to chronic kidney disease, which was substantially higher than the 27% (16/58) recorded in a matched cohort of sepsis-associated AKI patients without polymyxin exposure (P<0.001). Multivariate analysis identified polymyxin use (OR 8.86, 95% CI 2.8–27.8) and advanced age (OR 1.04, 95% CI 1.01–1.07) as independent predictors of chronic kidney disease progression.[35] These findings underscore the necessity of vigilant renal monitoring, particularly in elderly patients, to mitigate irreversible nephrotoxic injury.

Despite the emergence of several novel antimicrobials—such as aztreonam-avibactam, cefiderocol, and ceftazidime-avibactam—have emerged,[17,36,37] other innovative therapeutic strategies, including bacteriophage therapy, nanomaterials, and antimicrobial adjuvants, are also rapidly evolving.[38–40] Nonetheless, colistin remains an indispensable therapeutic option in many settings due to economic constraints and pathogen susceptibility patterns. Incorporating therapeutic drug monitoring into clinical practice may optimize the balance between efficacy and safety in critically ill patients.[41] Besides, the rapid and accurate detection of bacterial resistance genes is equally essential to guide precision antimicrobial therapy.[42,43]

This study has several limitations. First, being a single-centre investigation with a relatively small sample size—particularly in the IV group—selection bias cannot be excluded. Second, despite comparable baseline disease severity across groups, patients with better overall conditions were more likely to receive inhaled colistin alone. Third, ventilator parameters were not standardized, and factors such as airway obstruction or parenchymal consolidation, which could potentially influence the efficacy of inhaled therapy, were not systematically assessed. Fourth, potential unmeasured confounding factors could have affected our results. While we have attempted to account for important variables, the non-randomized design and reliance on physician judgment for treatment assignment may have led to residual confounding.

Conclusion

This prospective study evaluated the efficacy and nephrotoxicity of three different colistin administration routes in the treatment of NP caused by CRO. The findings demonstrated that adjunctive therapy offered no significant clinical advantage over either inhaled or intravenous monotherapy. In contrast, inhaled colistin therapy achieved a higher rate of bacterial eradication and was associated with lower nephrotoxicity, indicating its potential as an effective and safer alternative to intravenous administration. Nevertheless, as this study was observational, these results should be interpreted cautiously, as no conclusions on causality can be drawn. These results align with some previous studies suggesting that inhaled colistin may offer a safer alternative. Given the study's single-center design and limited sample size, large-scale, multicenter randomized controlled trials are warranted to further validate the comparative efficacy and safety of different colistin administration strategies in critically ill patients.

Abbreviations

NP, nosocomial pneumonia; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; MDR, multidrug-resistant; ICU, intensive care unit; CR-GNB, Carbapenem-resistant Gram-negative bacteria; CMS, Colistimethate sodium; CRO, carbapenem-resistant organisms; IV, intravenous; IH, inhalation; IDSA, Infectious Diseases Society of America; ESCMID, Infectious Diseases Society of America; the European Society of Clinical Microbiology and Infectious Diseases; CBA, colistin base activity; CPIS, Clinical Pulmonary Infection Score; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; MIC, the minimum inhibitory concentrations; CLSI, the Clinical and Laboratory Standards Institute; KDIGO, Kidney Disease: Improving Global Outcomes; AKI, acute kidney injury; VIF, variance inflation factor; BMI, body mass index; CRP, C-reactive protein; WBC, white blood cell; CRAB, carbapenem-

resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*.

Date Sharing Statement

The datasets used during the current study are available from the corresponding author, Heng Fan, upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of The First Affiliated Hospital of Ningbo University (No. 2024-R044-02). All participants provided informed consent. All procedures were performed in accordance with the ethical principles outlined in the Declaration of Helsinki and relevant guidelines and regulations.

Consent for Publication

All authors have read and approved the final version of the manuscript and consent to its publication in *Drug Design Development and Therapy.*

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Disclosure

The authors declare no competing interests. This paper has been uploaded to ResearchSquare as a preprint: https://doi.org/10.21203/rs.3.rs-6911404/v1

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