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Research Article

Polymyxin E Combination Regimens Versus Monotherapy for The Treatment of Pandrug-Resistant Acinetobacter Baumannii Pneumonia: Efficacy and Safety

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Abstract

Objective: To compare the clinical efficacy and safety of polymyxin E monotherapy versus combination regimens in the treatment of pandrug-resistant Acinetobacter baumannii (PDRAB) pneumonia. **Methods:** A retrospective study was conducted in which 26 patients with PDRAB pneumonia admitted to a tertiary hospital between July 2023 and June 2024 were divided according to their treatment regimens into a monotherapy group (13 cases, polymyxin E alone) and a combination-therapy group (13 cases, polymyxin E plus cefoperazone–sulbactam or tigecycline). Changes in infection markers including body temperature, white blood cell (WBC) count, procalcitonin (PCT), and C-reactive protein (CRP) before and after treatment were compared, and clinical efficacy was evaluated. Categorical variables were compared using Fisher's exact test, and continuous variables were compared using independent-samples t-tests or Mann–Whitney U tests as appropriate. A post-hoc power analysis was performed. **Results:** The overall response rate in the combination group was 76.9% (10/13) compared with 61.5% (8/13) in the monotherapy group (Fisher's exact test, P=0.673); the difference was not statistically significant. Decreases in WBC, PCT, and CRP were significantly greater in the combination group than in the monotherapy group (P=0.002, P=0.003, and P=0.002, respectively). The post-hoc power for the response-rate comparison was 13.6%, indicating that the study was underpowered to detect a difference of this magnitude. **Conclusion:** Polymyxin E–based combination therapy showed greater reductions in inflammatory markers compared with monotherapy, although the difference in clinical response rate did not reach statistical significance. These preliminary findings are hypothesis-generating and warrant confirmation in larger, prospective, randomized studies. No significant increase in adverse events was observed in this small sample.

Key words: Polymyxin E; Acinetobacter baumannii; Pneumonia; Cefoperazone–sulbactam; Tigecycline.

Introduction

Acinetobacter baumannii is a non-fermenting Gram-negative bacillus and an important pathogen of hospital-acquired infections. It mainly causes respiratory tract infections, and can also lead to bacteremia, urinary tract infections, and ventilator-associated pneumonia (VAP). Globally, there are about 1 million cases of infection caused by A. baumannii every year. Among hospitalized patients in China, A. baumannii accounts for about 6%–7% of infections, roughly twice the proportion seen in Europe and North America (1–2). With the widespread clinical use of broad-spectrum antibiotics such as carbapenems, the detection rate of pandrug-resistant Acinetobacter baumannii (PDRAB) has continued to rise and has become a major challenge in anti-infective therapy.

In 2024, the World Health Organization (WHO) released the updated "2024 Bacterial Priority Pathogens List" (3), categorizing carbapenem-resistant A. baumannii as a critical-priority pathogen. According to the 2024 CHINET China Bacterial Resistance Surveillance data (4), the resistance rates of A. baumannii to imipenem and meropenem are as high as 64.5% and 64.7%, respectively.

Polymyxins are bactericidal agents that bind to the lipopolysaccharides and phospholipids in the outer membrane of Gram-negative bacteria, competitively displacing divalent cations bound to the phosphate groups of membrane lipids. This disrupts the outer membrane, causes leakage of intracellular contents, and ultimately leads to bacterial death (5–7). They represent one of the last-line options for treating infections caused by multidrug-resistant Gram-negative bacteria. The polymyxins commonly used in China are polymyxin B and polymyxin E (colistin). However, polymyxin E monotherapy has limitations, including heterogeneous resistance, a relatively high mutant prevention concentration, and a relatively high rate of clinical failure, which may result in unsatisfactory treatment outcomes.

In recent years, combination regimens of polymyxin E with other antibiotics (such as sulbactam-containing combinations and tigecycline) have shown synergistic effects *in vitro* and in some clinical studies, potentially helping to overcome the limitations of monotherapy. Nevertheless, controlled clinical data within China on different polymyxin E combination regimens for PDRAB pneumonia remain scarce. This study therefore aimed to retrospectively compare the efficacy and safety of polymyxin E monotherapy versus combination regimens in treating PDRAB pneumonia, to provide preliminary evidence for optimizing clinical treatment strategies.

Methods

1. Study population

A total of 26 patients with PDRAB pneumonia admitted to the Department of Respiratory and Critical Care Medicine of a tertiary hospital (Lianjiang People's Hospital) between July 2023 and June 2024 were enrolled. The study was approved by the hospital ethics committee (approval No. LX2023-033-01). All patient data were anonymized.

Inclusion criteria:

(1) Age ≥18 years;

(2) Diagnosis of pneumonia in accordance with the "Guidelines for the Diagnosis and Treatment of Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia in Chinese Adults";

(3) A. baumannii infection confirmed by culture of airway secretions, with susceptibility testing demonstrating carbapenem resistance and susceptibility only to polymyxins and a few other agents, consistent with pandrug-resistant strains;

(4) Receipt of polymyxin E-based anti-infective therapy for ≥3 days.

Exclusion criteria:

(1) Known allergy to polymyxin E;

(2) Baseline creatinine clearance <15 mL/min;

(3) Concomitant uncontrolled fatal infections or end-stage diseases;

(4) Incomplete clinical data.

2. Grouping and treatment

The commonly used formulations of polymyxin E are colistin sulfate and colistin methanesulfonate (CMS). Colistin sulfate was used in this study because it is the formulation available at our institution. The dosing was 1,000,000–1,500,000 IU per day, administered intravenously in 2–3 divided doses. This corresponds to approximately 33–50 mg of colistin base activity (CBA) per day (1 mg CBA ≈ 30,000 IU). It should be noted that this dose is lower than the internationally recommended CBA dosing for CMS (2.5–5 mg/kg/day, see Discussion).

Patients were divided according to actual treatment regimens into two groups:

Monotherapy group (n=13): colistin sulfate for injection (National drug approval No. H31020822) as monotherapy at a total daily dose of 1,000,000–1,500,000 IU (≈33–50 mg CBA), administered intravenously in 2–3 divided doses.

Combination-therapy group (n=13): colistin sulfate plus one of the following:

(1) Cefoperazone–sulbactam for injection (3 g, q8h, IV), 6 cases;

(2) Tigecycline for injection (loading dose 100 mg, then 50 mg q12h, IV), 7 cases.

All anti-infective regimens were determined by physicians in the Department of Respiratory and Critical Care Medicine based on clinical judgment, considering factors such as disease severity, prior antibiotic exposure, drug susceptibility results, and organ function. Treatment assignment was not randomized. The criteria for choosing combination therapy over monotherapy included: (a) more severe disease presentation (e.g., higher APACHE II scores, septic shock); (b) failure of prior antibiotic therapy; and (c) physician preference based on local resistance patterns. Although baseline characteristics were broadly similar between groups (Table 1), the potential for selection bias due to non-random assignment is acknowledged (see Discussion).

3. Outcome measures

Clinical efficacy (assessed at the end of treatment):

Cure: complete resolution of infection-related symptoms and signs; near-complete radiologic resolution of pulmonary lesions; inflammatory markers returned to normal.

Improvement: marked alleviation of symptoms and signs; >50% absorption of radiologic lesions; major inflammatory markers decreased by >50% compared with baseline.

Treatment failure: no improvement or worsening of symptoms and signs despite adequate therapy duration.

Voluntary discharge: patients who left the hospital against medical advice before completing treatment, precluding efficacy assessment.

Death: in-hospital mortality attributable to any cause during the treatment period.

Overall response rate = (number cured + number improved) / total cases × 100%. For sensitivity analysis, a composite unfavorable outcome (treatment failure + voluntary discharge + death) was also reported.

Laboratory parameters: Data collected before treatment and at the end of treatment (or before discharge) included:

(1) Infection markers: body temperature, WBC, PCT, CRP;

(2) Liver and kidney function: total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, and estimated glomerular filtration rate (eGFR).

Safety assessment: All drug-related adverse events during treatment were recorded and graded according to CTCAE version 5.0. Acute kidney injury (AKI) was assessed using the KDIGO criteria (Stage 1: increase in serum creatinine ≥1.5 times baseline or ≥0.3 mg/dL increase; Stage 2: increase ≥2.0 times baseline; Stage 3: increase ≥3.0 times baseline or initiation of renal replacement therapy). Individual creatinine trajectories were reviewed to identify any AKI episodes, dose adjustments, or treatment discontinuations due to renal impairment.

4. Statistical analysis

Data were analyzed using SPSS 24.0 software. The normality of continuous variables was assessed

using the Shapiro–Wilk test. Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{x}\pm s$) and compared using independent-samples t-tests; non-normally distributed variables were expressed as median (interquartile range) and compared using the Mann–Whitney U test. Within-group pre- and post-treatment comparisons were made using paired t-tests or Wilcoxon signed-rank tests as appropriate. Categorical variables were expressed as number of cases (percentage) and compared using Fisher's exact test (given the small sample size and expected cell counts <5). Exact P-values were reported wherever possible. A P value <0.05 was considered statistically significant.

A post-hoc power analysis was performed for the primary outcome (overall response rate) using G*Power 3.1 and confirmed with R (package "pwr"), with a two-sided alpha of 0.05, to determine the statistical power afforded by the sample size.

Results

1. Baseline characteristics

There were no significant differences between the two groups in age, sex, APACHE II scores, baseline body temperature, infection markers (WBC, PCT, CRP), or liver and kidney function indices (all P>0.05; Fisher's exact test for categorical variables, t-tests for continuous variables). See Table 1.

2. Clinical efficacy

The overall response rate in the combination group was 76.9% (10/13) compared with 61.5% (8/13) in the monotherapy group; the difference was not statistically significant (Fisher's exact test, P=0.673). When the composite unfavorable outcome (treatment failure + voluntary discharge + death) was used, the rates were 38.5% (5/13) and 23.1% (3/13) in the monotherapy and combination groups, respectively (Fisher's exact test, P=0.673). Mortality did not differ significantly between groups (1/13 vs 1/13; Fisher's exact test, P=1.000). Among the non-response cases, voluntary discharge accounted for 2 cases in each group, and treatment failure accounted for 2 cases in the monotherapy group and 0 cases in the combination group. See Table 2.

3. Post-hoc power analysis

Given the observed response rates of 61.5% and 76.9% with 13 patients per group, the post-hoc statistical power was 13.6% at a two-sided alpha of 0.05, indicating that the study was substantially underpowered. To achieve 80% power to detect a difference of this magnitude, approximately 140 patients per group (280 total) would be required. These findings should be interpreted with caution given the high probability of type II error.

4. Infection markers before and after treatment

Body temperature, WBC, PCT, and CRP all decreased significantly after treatment in both groups (P<0.05). When comparing between groups after treatment, WBC, PCT, and CRP levels were significantly lower in the combination group than in the monotherapy group (P=0.002, P=0.003, and P=0.002, respectively), whereas post-treatment body temperature did not differ significantly between groups (P=0.103). See Table 3.

5. Liver and kidney function

There were no significant changes in total bilirubin, ALT, AST, serum creatinine, or eGFR before and after treatment in either group (all P>0.05). Post-treatment comparisons between groups also showed no significant differences (all P>0.05). These findings suggest that neither regimen caused significant hepatic or renal impairment and that their safety profiles were comparable. See Table 4.

6. Adverse events and renal safety

No adverse reactions were recorded in the monotherapy group. In the combination group, one patient developed coagulation abnormalities associated with cefoperazone–sulbactam, which improved after symptomatic management and did not affect continuation of treatment.

Table 1. Baseline characteristics of the two groups (x̄±s).

Variable	Monotherapy (n=13)	Combination (n=13)	P value
Age (year)	62.1 ± 8.7	62.5 ± 9.3	0.911
Male	8 (61.5%)	7 (53.8%)	1.000†
APACHE II score	16.2 ± 4.1	17.1 ± 3.8	0.562
Baseline Temp. (°C)	38.5 ± 0.6	38.4 ± 0.5	0.649
Baseline WBC (×10⁹/L)	13.6 ± 1.7	13.8 ± 1.6	0.760
Baseline PCT (μg/L)	2.5 ± 0.6	2.6 ± 0.7	0.699
Baseline CRP (mg/L)	71.5 ± 12.2	73.2 ± 12.8	0.732
Baseline total bilirubin (μmol/L)	32.2 ± 5.5	32.8 ± 5.9	0.791
Baseline ALT (U/L)	49.5 ± 9.3	51.2 ± 9.8	0.654
Baseline AST (U/L)	54.6 ± 7.6	55.3 ± 7.9	0.820
Baseline creatinine (μmol/L)	91.5 ± 11.8	90.3 ± 10.9	0.790
eGFR (mL/min)	93.8 ± 15.3	93.2 ± 16.0	0.923

†Fisher's exact test; all other P values are from independent-samples t-tests.

Table 2. Comparison of clinical efficacy (n (%)).

Group	Case	Cure	Improvement	Failure	Discharge	Death	ORR
Monotherapy	13	3 (23.1)	5 (38.5)	2 (15.4)	2 (15.4)	1 (7.7)	61.5
Combination therapy	13	5 (38.5)	5 (38.5)	0 (0.0)	2 (15.4)	1 (7.7)	76.9
P		0.673†	—	0.474†	1.000†	1.000†	0.673†

†Fisher's exact test. Overall response rate (ORR) = (Cure + Improvement) / total cases × 100%.

Table 3. Comparison of infection markers before and after treatment (x̄±s).

Group	Time	Temp (°C)	WBC (×10⁹/L)	PCT (μg/L)	CRP (mg/L)
Monotherapy	Before	38.5 ± 0.5	13.6 ± 1.7	2.5 ± 0.6	71.5 ± 12.2
	After	37.6 ± 0.8*	9.3 ± 2.0*	1.8 ± 0.7*	53.8 ± 14.5*
Combination therapy	Before	38.4 ± 0.6	13.9 ± 1.5	2.6 ± 0.7	73.2 ± 12.8
	After	37.1 ± 0.7*	6.7 ± 1.8*#	1.0 ± 0.5*#	35.8 ± 11.2*#

**P<0.05 vs pre-treatment in the same group (paired t-test); #P<0.05 vs monotherapy group after treatment (independent-samples t-test). Exact P values: WBC P=0.002, PCT P=0.003, CRP P=0.002, temperature P=0.103.*

Table 4. Liver and kidney function before and after treatment (x̄±s).

Group	Time	Total bilirubin (μmol/L)	ALT (U/L)	AST (U/L)	Creatinine (μmol/L)	eGFR (mL/min)
Monotherapy	Before	32.2 ± 5.5	49.5 ± 9.3	54.6 ± 7.6	91.5 ± 11.8	93.8 ± 15.3
	After	30.8 ± 5.2	48.2 ± 8.7	53.9 ± 7.2	92.1 ± 11.2	94.5 ± 14.8
Combination therapy	Before	32.8 ± 5.9	51.2 ± 9.8	55.3 ± 7.9	90.3 ± 10.9	93.2 ± 16.0
	After	31.5 ± 5.4	49.8 ± 9.0	54.5 ± 7.4	91.0 ± 11.3	94.0 ± 15.1

Regarding renal safety, individual creatinine trajectories were reviewed for all 26 patients. No patient met the KDIGO criteria for AKI (Stage 1 or above) in either group. No dose adjustments or

treatment discontinuations due to renal impairment were required. Although mean creatinine and eGFR values remained stable (Table 4), we acknowledge that the small sample size limits the ability to detect rare renal adverse events.

Discussion

1. Implication

A. baumannii was initially considered broadly susceptible to antibiotics, but it has gradually acquired resistance to most agents through intrinsic mechanisms such as production of β-lactamases, as well as acquired mechanisms including plasmid-mediated OXA-type carbapenemases. Multiple resistance mechanisms contribute to heterogeneous resistance to polymyxins (8). Nonetheless, polymyxins remain key antibiotics for treating carbapenem-resistant A. baumannii infections, either alone or in combination with other drugs.

For hospital-acquired pneumonia (HAP) and VAP caused by extensively drug-resistant Acinetobacter spp., guidelines recommend systemic intravenous polymyxin E combined with aerosolized administration (9–10). In invasive infections due to carbapenem-resistant A. baumannii, it is recommended to combine polymyxin E with another active agent when possible; if no second active agent is available, polymyxin B or polymyxin E monotherapy may be used. Combination therapy can reduce the risk of resistance, and certain combinations show good synergistic or additive effects in vitro (11). Cefoperazone–sulbactam has demonstrated synergistic activity against Acinetobacter in vitro (12), though clinical evidence remains limited.

In this study, cases treated with polymyxin E plus cefoperazone–sulbactam or tigecycline were grouped as combination therapy and compared with polymyxin E monotherapy. The results showed a trend toward a higher response rate with combination therapy (76.9% vs 61.5%), although this difference did not reach statistical significance (Fisher's exact test, P=0.673). However, combination therapy was associated with significantly greater reductions in WBC, PCT, and CRP, suggesting more rapid resolution of inflammation. These findings align with current therapeutic evidence for multidrug-resistant bacterial infections. In a prospective open-label study, Makris et al. (13) enrolled 39 critically ill patients with VAP caused by multidrug-resistant A. baumannii; 19 received polymyxin E monotherapy and 20 received polymyxin E plus ampicillin–sulbactam. At days 4–5, the early clinical cure rate was significantly higher in the combination group than in the monotherapy group (70% vs 15.8%, P=0.001), and combination therapy also reduced clinical mortality. Another retrospective study of more than 300 adults with VAP due to Acinetobacter spp. found that, compared with monotherapy, combination therapy was independently associated with lower 30-day mortality (14).

Regarding safety, nephrotoxicity is the most serious adverse reaction associated with systemic polymyxin E, with reported incidence as high as 36% (15). However, a meta-analysis showed no clear increase in renal impairment in patients receiving IV polymyxin E compared with those receiving other evaluated agents (16). In our study, one case of coagulation abnormality related to cefoperazone–sulbactam occurred in the combination group and improved with symptomatic treatment. Liver and kidney function remained stable before and after treatment in both groups, with no significant between-group differences. Importantly, no patient met KDIGO criteria for AKI, and no dose adjustments or discontinuations were required. However, the small sample size limits the ability to detect rare but clinically significant renal adverse events.

2. Limitation

This study has several important limitations that should be considered when interpreting the results:

First, the sample size was small (26 patients total, 13 per group), and no a priori sample-size calculation was performed. The post-hoc power analysis revealed a statistical power of only 13.6% for the

response-rate comparison, indicating a high probability of type II error. Approximately 280 patients would be needed to achieve 80% power for the observed effect size. The lack of a statistically significant difference in response rate may therefore reflect insufficient power rather than a true absence of effect.

Second, the study used a retrospective, non-randomized design. Treatment assignment was determined by physicians based on clinical judgment, which introduces potential selection bias and confounding by disease severity, prior antibiotic exposure, or other unmeasured factors. Although baseline characteristics — including APACHE II scores — were broadly comparable, the small sample cannot ensure adequate balance of all relevant confounders. Patients in the combination group may have been more severely ill, which would bias the results toward the null, potentially underestimating the true treatment effect.

Third, the combination-therapy group included two mechanistically different regimens: polymyxin E plus cefoperazone–sulbactam (6 cases) and polymyxin E plus tigecycline (7 cases). These agents have different mechanisms of action and clinical evidence. Pooling them assumes equivalence, which is not justified. The small subgroup sizes preclude meaningful separate statistical analysis. Consequently, the study cannot determine which combination is superior or whether the observed effect is driven primarily by one regimen. This heterogeneity is a major limitation, and the results should not be generalized as "polymyxin E plus cefoperazone–sulbactam or tigecycline" without distinguishing between the two combinations. Future studies with larger samples should analyse these subgroups separately.

Fourth, the efficacy assessment was based solely on clinical and inflammatory parameters. Microbiological outcomes, such as bacterial eradication rates or repeat culture results, were not systematically collected. For infections caused by pandrug-resistant organisms, microbiological clearance is a key endpoint, and its absence represents an important gap in this study.

Fifth, the non-response category in the original analysis included heterogeneous outcomes (treatment failure, voluntary discharge, and death). Although we have now reported these subcategories separately (Table 2), the very small numbers in each cell further limit the statistical robustness of the efficacy comparisons.

Sixth, colistin sulfate was used at a relatively low dose (33–50 mg CBA/day) compared with the internationally recommended dosing for CMS (2.5–5 mg/kg/day). This may have implications for the generalisability of the results to settings where CMS is used at higher doses. Additionally, colistin sulfate was administered without concomitant inhaled polymyxin, which is recommended by guidelines for HAP/VAP due to extensively drug-resistant Acinetobacter spp.

Finally, the study was conducted at a single tertiary hospital, and the findings may not be generalizable to other settings.

In summary, polymyxin E combined with cefoperazone–sulbactam or tigecycline showed greater reductions in inflammatory markers than polymyxin E monotherapy for PDRAB pneumonia, with a favorable safety profile. However, the difference in clinical response rate did not reach statistical significance, and the study was substantially underpowered. These findings are preliminary and hypothesis-generating. Larger, prospective, randomized controlled studies with adequate sample sizes are needed to confirm the efficacy of specific polymyxin E combination regimens for PDRAB pneumonia. Until such data are available, treatment decisions should be individualized based on clinical severity, susceptibility results, and patient-specific factors.

Declarations

1. **Consent to publication**

   All authors agreed to publish the manuscript at this journal based on the signed Copyright

Transfer Agreement, and followed publication ethics.

2. **Ethical approval and consent to participants**
The study was approved by the hospital ethics committee (approval No. LX2023-033-01).
3. **Disclosure of conflict of interests**
We declare that no conflict of interest exists.
4. **Funding**
None.
5. **Availability of data and material**
Our data used to support the findings of this study are all included within the article.
6. **Authors' Contributions**
Authors contributed to this paper with design (RL, SLX), data collection (RL, KMY, CHH, SLX), writing (RL, KMY, CHH, SLX), revision (RL, KMY, CHH, SLX), editing (RL, KMY, CHH, SLX) and final approval (SLX).
7. **Acknowledgement**
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