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Prolonged vs. Short-Term Infusion of Imipenem/Cilastatin for Multidrug-Resistant Gram-Negative Bacilli Severe Pneumonia: A Randomized Controlled Trial Evaluating Efficacy, Safety, and Cost-Effectiveness

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Abstract

Background: Multidrug-resistant Gram-negative bacilli (MDR-GNB) severe pneumonia poses significant therapeutic challenges due to limited antibiotic efficacy and high mortality. Prolonging the infusion time of β-lactams like imipenem/cilastatin may enhance pharmacodynamic target attainment, but clinical evidence is lacking. This trial compared prolonged versus short-term infusion of imipenem/cilastatin in critically ill patients with MDR-GNB pneumonia. **Methods:** In this prospective, randomized, open-label, blinded endpoint (PROBE) trial conducted at a provincial tertiary hospital in China, 82 adults with severe pneumonia (IDSA/ATS 2016 criteria) and confirmed MDR-GNB infections were randomly assigned to receive imipenem/cilastatin 1 g every 8 hours administered either as: 3-hour prolonged infusion (intervention group, n = 41) via infusion pump; 30-minute intermittent infusion (control group, n = 41) through standard gravity flow. Both groups received equivalent total daily doses (3 g/day) of imipenem/cilastatin, administered at identical drug concentrations (1 g/100 mL normal saline). The intervention group received 3-hour prolonged infusions via a pump, while the control group uti-

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lized 30-minute intermittent gravity infusions. The primary outcome was clinical response rate (resolution of systemic inflammation + radiological improvement) at day 8. Secondary outcomes included microbial eradication kinetics, 90-day survival, safety, and cost-effectiveness. Statistical analyses included univariate comparisons (chi-square/t-tests/Mann-Whitney U), Kaplan-Meier survival analysis with log-rank test, and multivariable Cox regression, performed using R 4.4.3/SPSS 27.0. **Results:** The prolonged infusion group achieved higher clinical response rates at day 8 (82.9% vs. 58.5%; P = 0.015) and reduced secondary fungal infections (7.3% vs. 29.3%, P = 0.010). Accelerated microbial eradication was observed with prolonged infusion (median 6.0 vs. 7.0 days, P = 0.004). Kaplan-Meier analysis demonstrated superior 90-day survival (95.1% vs. 68.3%, log-rank P = 0.02), with prolonged infusion independently protective in multivariable Cox regression (adjusted HR = 0.08, 95% CI: 0.01 - 0.51; P = 0.008). Safety profiles were comparable, with no significant differences in nephrotoxicity, hepatic injury, or seizures (P > 0.05). Pharmacoeconomic analysis revealed equivalent direct medication costs between groups. **Conclusion:** Prolonged infusion of imipenem/cilastatin improves clinical outcomes and survival in MDR-GNB severe pneumonia without increasing toxicity or costs. These findings support adopting prolonged infusion as a standard-of-care strategy. Future studies should validate these results in broader populations and optimize dosing regimens using pharmacokinetic-pharmacodynamic modeling.

Keywords

Imipenem/Cilastatin, Prolonged Infusion, Multidrug-Resistant Gram-Negative Bacteria, Severe Pneumonia, Randomized Controlled Trial

1. Introduction

Multidrug-resistant Gram-negative bacilli (MDR-GNB) infections, particularly severe pneumonia, represent a critical global health threat due to escalating antibiotic resistance and limited therapeutic options. Mortality rates exceed 40% in critically ill patients, driven by delayed appropriate antimicrobial therapy and suboptimal pharmacokinetic/pharmacodynamic (PK/PD) target attainment with conventional dosing strategies. The Infectious Diseases Society of America (IDSA) reported that extended infusion is an ideal way to optimize beta-lactam antibiotic efficacy [1]. Imipenem/cilastatin, a carbapenem with potent activity against MDR-GNB, is a cornerstone of empirical and targeted therapy. Prolonged infusion of β-lactams optimizes the time-dependent pharmacodynamic target ($fT > MIC$), particularly for multidrug-resistant pathogens with elevated MICs [2] [3]. However, its efficacy is compromised when administered via short-term infusions (e.g., 30 minutes), as the time-dependent bactericidal activity of β-lactams requires prolonged drug concentrations above the pathogen's minimum inhibitory concentration (MIC) [4].

Pharmacokinetic/pharmacodynamic (PK/PD) models demonstrate that pro-

longed infusions (3 - 4 hours) of carbapenems maximize $fT > MIC$, a critical determinant of bactericidal efficacy against Gram-negative pathogens with reduced susceptibility [5]-[7]. Observational studies suggest clinical benefits in critically ill populations [8] [9], yet randomized trials remain limited and inconclusive [10] [11]. Observational studies have reported improved clinical outcomes with prolonged infusion in sepsis and ventilator-associated pneumonia, yet robust evidence from randomized controlled trials (RCTs) remains scarce. Existing RCTs are limited by small sample sizes, heterogeneous populations, or lack of cost-effectiveness analyses, leaving clinicians uncertain about the practical benefits of this strategy.

To address these gaps, we conducted a PROBE (Prospective Randomized Open Blinded Endpoint) trial comparing prolonged (3-hour) versus short-term (30-minute) infusion of imipenem/cilastatin in patients with MDR-GNB severe pneumonia. Our primary hypothesis was that prolonged infusion would increase clinical response rates by optimizing PK/PD target attainment. Secondary objectives included evaluating microbial eradication kinetics, survival benefits, safety profiles, and incremental cost-effectiveness. This study aims to provide definitive evidence to guide antimicrobial stewardship in critically ill populations.

2. Methods

2.1. Study Design and Participants

2.1.1. Trial Design

This was a single-center PROBE (Prospective Randomized Open Blinded Endpoint) trial conducted at The Brain Hospital of Guangxi Zhuang Autonomous Region from March 2022 to March 2025. Randomization was performed using a computer-generated block randomization sequence (block size = 4) stratified by baseline Sequential Organ Failure Assessment (SOFA) score (≤8 vs. >8). Participants, clinicians, and data collectors were aware of treatment allocation, but endpoint adjudicators (e.g., radiological and microbiological assessors) were blinded to group assignments to minimize outcome assessment bias. Radiological improvement was assessed independently by two blinded radiologists using the 2016 IDSA/ATS criteria, with discrepancies resolved by a third expert. Improvement was defined as ≥50% reduction in infiltrate size on chest X-ray/CT, measured semi-quantitatively with standardized lung zone grids.

2.1.2. Inclusion Criteria

Age ≥ 18 years.

Severe pneumonia meeting IDSA/ATS 2016 criteria (e.g., requiring invasive mechanical ventilation, septic shock, or multilobar infiltrates).

Confirmed multidrug-resistant Gram-negative bacilli (MDR-GNB) infection (per EUCAST 2023 breakpoints) isolated from lower respiratory tract cultures (bronchoalveolar lavage or sputum).

2.1.3. Exclusion Criteria

Polymicrobial infection involving fungi or Gram-positive pathogens.

Hypersensitivity to β-lactam antibiotics.

Concomitant aminoglycosides were prohibited from isolating the intervention effect, as synergistic combinations could confound survival outcomes.

Pregnancy or lactation.

2.2. Interventions

2.2.1. Control Group

Participants received imipenem/cilastatin 1 g every 8 hours via 30-minute intravenous infusion, prepared in 100 mL 0.9% saline.

2.2.2. Intervention Group

Participants received the same dose (1 g q8 h) but administered as a 3-hour prolonged infusion, diluted in 100 mL 0.9% saline.

2.2.3. Standardization

Infusion protocols followed consensus recommendations for prolonged β-lactam administration, including pump calibration and stability validation [12] [13]. Concomitant antibiotics (e.g., aminoglycosides) were prohibited to isolate the intervention effect [14]. Concomitant antibiotics (e.g., aminoglycosides) were prohibited.

2.3. Outcomes

2.3.1. Primary Outcome

Clinical response rate at day 8: Defined as resolution of systemic inflammatory response syndrome (SIRS) criteria (temperature ≤ 37.6˚C, heart rate ≤ 90 bpm, respiratory rate ≤ 20 breaths/min, WBC ≤ 12×10^9/L) and radiological improvement (≥50% reduction in infiltrate size on chest X-ray/CT).

2.3.2. Secondary Outcomes

Time to microbial eradication: Daily quantitative cultures from bronchoalveolar lavage fluid (BALF) or sputum until negative conversion.

90-day all-cause mortality.

2.3.3. Safety Endpoints

Nephrotoxicity: Defined by KDIGO criteria (serum creatinine increase ≥ 26.5 μmol/L within 48 hours, ≥1.5 × baseline within 7 days, or urine output < 0.5 mL/kg/h for ≥ 6 hours).

Hepatic injury: Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN).

Neurological adverse events: Seizures, encephalopathy, or delirium.

2.4. Statistical Analysis

2.4.1. Sample Size Calculation

Based on prior studies, we hypothesized a 60% clinical response rate in the short-term infusion group versus 80% in the prolonged infusion group. With $\alpha = 0.05$

(two-tailed), $\beta = 0.2$ (80% power), and an anticipated 10% dropout rate, a minimum of 44 participants per group (total N = 88) was initially estimated. However, due to resource constraints and preliminary data suggesting a larger effect size, the target enrollment was pragmatically set to 41 participants per group (total N = 82). An interim analysis conducted at 82 participants (41 per group) demonstrated statistically significant superiority of prolonged infusion in the primary outcome (P = 0.002), leading to early trial termination as per pre-specified stopping rules for efficacy.

2.4.2. Analytical Methods

Between-group differences in clinical response rates on Day 8 were assessed using Pearson's chi-square test (or Fisher's exact test for expected cell counts < 5). Univariable analyses of baseline characteristics and day 8 biomarkers (e.g., CRP, AST) were performed using Independent t-tests or Mann-Whitney U tests for continuous variables (parametric/nonparametric based on distribution). Chi-square/Fisher's exact tests for categorical variables. Kaplan-Meier curves with log-rank tests compared 90-day survival between groups. Univariable Cox proportional hazards models identified candidate predictors of survival (variables with P < 0.20 retained for multivariable analysis). A stepwise backward Cox regression (likelihood ratio test, removal threshold P ≥ 0.10) was applied to adjust for confounders. The proportional hazards assumption was verified using Schoenfeld residuals and log-log plots. Multiple imputation with chained equations (MICE) under the missing at random (MAR) assumption addressed missing primary outcome data. An interim analysis was pre-planned at 50% enrollment (n = 41/group). Using the O'Brien-Fleming stopping boundary ($\alpha = 0.005$), the observed effect size (P = 0.002) crossed the efficacy threshold, prompting early termination.

Software: All analyses were performed using SPSS version 27.0 (IBM Corp, Armonk, NY, USA) and R 4.43 version.

3. Results

3.1. Baseline Characteristics

A total of 82 participants were randomized to either prolonged infusion (n = 41) or short-term infusion (n = 41). Baseline demographic, clinical, and laboratory characteristics were balanced between groups (Table 1). No significant differences were observed in age, sex, BMI, vital signs, inflammatory biomarkers (CRP, procalcitonin), or organ function parameters (all P > 0.05), confirming successful randomization.

3.2. Safety Outcomes

By day 8, the Prolonged infusion group exhibited significantly fewer secondary fungal infections compared to the short-term group (7.3% vs. 29.3%, P = 0.010). Other adverse events, including hepatic dysfunction, renal impairment, and seizures, showed no statistically significant differences (all P > 0.05) (Table 2). No-

tably, neurological adverse events (e.g., seizures) occurred in 2.4% of the Prolonged group versus 9.8% of the short-term group, though this difference did not reach statistical significance (P = 0.17). The reduced incidence of secondary fungal infections (7.3% vs. 29.3%) aligns with evidence linking optimized β-lactam exposure to decreased ecological disruption [15].

Table 1. Baseline demographic and clinical characteristics prolonged vs. short-term infusion groups.

Characteristic	Prolonged Infusion (n = 41)	Short-Term Infusion (n = 41)	P-Value
Demographics			
Male sex, n (%)	33 (80.5)	30 (73.2)	0.43
Age, years	64.3 ± 16.8	68.6 ± 13.6	0.20
BMI, kg/m^2	22.5 ± 2.4	23.3 ± 2.2	0.10
Vital Signs			
Temperature, ˚C	38.2 (37.7 - 38.7)	38.1 (37.5 - 38.7)	0.41
Laboratory Values			
WBC count, ×10^9/L	14.6 (10.3 - 20.3)	12.9 (9.8 - 18.5)	0.20
Neutrophil count, ×10^9/L	12.4 (8.0 - 17.3)	11.8 (7.5 - 16.1)	0.28
Neutrophil percentage, %	87.2 (79.2 - 91.6)	81.5 (70.4 - 86.9)	0.46
CRP, mg/L	105.8 (63.8 - 167.8)	89.4 (55.2 - 144.3)	0.41
Procalcitonin, ng/mL	1.35 (0.42 - 11.97)	1.15 (0.21 - 3.42)	0.17
Organ Function			
AST, U/L	30.0 (19.0 - 49.3)	31.0 (20.0 - 49.3)	0.49
ALT, U/L	21.5 (11.8 - 36.5)	23.0 (15.0 - 36.5)	0.45
Creatinine, μmol/L	82.0 (56.0 - 137.5)	75.0 (50.5 - 149.8)	0.73

Notes: Data presented as mean ± SD for normally distributed variables (Age, BMI), median (IQR) for non-normal variables, or n (%) for categorical variables. P values from independent t-test (Age, BMI), Mann-Whitney U test (non-normal variables), or χ^2/Fisher exact test (categorical variables). Abbreviations: BMI, body mass index; WBC, white blood cell; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

3.3. Efficacy Outcomes

Prolonged infusion was associated with an increase in clinical response (82.9% vs. 58.5%; P = 0.015), consistent with prior trials targeting fT > MIC > 90% [16] [17]. At day 8, the clinical response rate was 82.9% in the prolonged group versus 58.5% in the short-term group (P = 0.015). Survival analysis revealed a significant advantage for prolonged infusion, with a 90-day survival probability of 95.1% compared to 68.3% (P = 0.02, log-rank test) (**Figure 1**). Total hospital stay and 30-day recurrence rates did not differ significantly between groups. Prolonged infusion significantly accelerated microbial eradication (median 6.0 [IQR 4.5 - 7.5] vs. 7.0 [6.0 - 9.0] days (**Table 3**).

Table 2. Safety outcomes at day 8.

Parameter	Prolonged Infusion (n = 41)	Short-Term Infusion (n = 41)	P-Value
Vital Signs			
Temperature, ˚C	36.8 (36.5 - 37.2)	36.7 (36.4 - 37.1)	0.68
Laboratory Values			
WBC count, $\times 10^9$/L	11.2 (8.2 - 15.3)	10.8 (7.9 - 14.1)	0.77
Neutrophil count, $\times 10^9$/L	8.9 (5.7 - 12.7)	8.8 (5.2 - 11.9)	0.57
Neutrophil percentage, %	81.5 (70.4 - 86.9)	76.2 (68.3 - 83.1)	0.41
CRP, mg/L	44.8 (13.9 - 81.1)	39.6 (12.5 - 75.3)	0.40
Procalcitonin, ng/mL	0.94 (0.21 - 1.27)	0.82 (0.19 - 1.12)	0.52
Adverse Events			
Secondary fungal infection, n (%)	3 (7.3)	12 (29.3)	**0.010**
Antibiotic-associated diarrhea, n (%)	1 (2.4)	2 (4.9)	0.56
Allergic reaction, n (%)	0 (0.0)	1 (2.4)	0.31
Hepatic dysfunction (AST > 3 × ULN), n (%)	4 (9.8)	3 (7.3)	0.69
Hepatic dysfunction (ALT > 3 × ULN), n (%)	2 (4.9)	3 (7.3)	0.64
Renal impairment (creatinine > 50% increase), n (%)	1 (2.4)	2 (4.9)	0.56
Seizures, n (%)	1 (2.4)	4 (9.8)	0.17

Notes: ULN (upper limit of normal): AST = 40 U/L, ALT = 40 U/L. Significant P values in bold (P < 0.05).

Table 3. Efficacy outcomes.

Outcome	Prolonged Infusion (n = 41)	Short-Term Infusion (n = 41)	P-Value
Total hospital stays, days	25.0 (16.0 - 42.0)	33.0 (25.0 - 42.0)	0.35
Clinical Response, n (%)			
Clinical response	24 (82.9)	24 (58.5)	**0.015**
No-Clinical response	7 (17.1)	17 (41.5)	
30-day recurrence, n (%)	0 (0.0)	1 (2.4)	0.31
Microbiological Eradication days	6.0 (4.5 - 7.5)	7.0 (6.0 - 9.0)	0.004

Notes: Microbiological eradication time is defined as the first of two consecutive negative cultures. P value from Mann-Whitney U test.

3.4. Pharmacoeconomic Analysis

Both groups received identical total daily doses (3.00 ± 0.00 g, P = 1.00). No differences were observed in total drug consumption or defined daily doses (DDDs), indicating comparable direct medication costs (Table 4).

Table 4. Pharmacoeconomic analysis.

Parameter	Prolonged Infusion (n = 41)	Short-Term Infusion (n = 41)	P-Value
Total daily dose, g	3.00 ± 0.00	3.00 ± 0.00	1.00
Treatment duration, days	9.0 (7.5 - 11.5)	8.0 (7.0 - 11.5)	0.923
Total consumption, g	27.0 (22.5 - 34.5)	24.0 (21.0 - 34.5)	0.920
Defined daily doses (DDDs)	13.5 (11.25 - 17.25)	12.0 (10.5 - 16.5)	0.511

3.5. Predictors of Survival

Univariate Cox regression and K-M survival analysis identified prolonged infusion as a protective factor for survival (HR = 0.134, 95% CI: 0.030 - 0.595; P = 0.008), while older age, longer treatment duration, higher CRP levels, and delayed microbial eradication were associated with increased mortality (all P < 0.05) (Table 5; Figure 1). In the final multivariable model, prolonged infusion remained independently protective (adjusted HR = 0.08, 95% CI: 0.01 - 0.51; P = 0.008), alongside peak AST levels and treatment duration as risk factors (Table 6).

Table 5. Significant predictors of survival in univariate Cox regression analysis (P < 0.1).

Variable	Comparison	B	SE	Wald	HR (95% CI)	P-Value	Effect Direction
Prolonged Infusion	Yes vs. No	−2.009	0.760	6.991	0.134 (0.030 - 0.595)	**0.008**	↓ Protective
Age	Per 1-year increase	0.038	0.019	3.993	1.039 (1.001 - 1.079)	**0.046**	↑ Risk
Treatment Duration	Per day increase	0.160	0.064	6.315	1.170 (1.040 - 1.330)	**0.012**	↑ Risk
Total Consumption	Per gram increase	0.053	0.021	6.315	1.055 (1.012 - 1.100)	**0.012**	↑ Risk
Defined Daily Doses (DDDs)	Per DDD increase	0.107	0.043	6.315	1.113 (1.024 - 1.210)	**0.012**	↑ Risk
Time to Microbial Eradication	Per day increase	0.210	0.060	12.376	1.230 (1.100 - 1.390)	**<0.001**	↑ Risk
CRP (Day 8)	Per mg/L increase	0.006	0.003	4.665	1.006 (1.001 - 1.012)	**0.031**	↑ Risk
Total Hospital Stay	Per day increase	0.020	0.011	3.607	1.020 (0.999 - 1.042)	**0.058**	↑ Risk
Pseudomonas Aeruginosa Infection	Yes vs. No (Ref: *Escherichia coli*)	1.334	0.782	2.909	3.800 (0.820 - 17.580)	**0.088**	↑ Risk
Allergic Reaction	Yes vs. No	−1.828	1.041	3.083	0.161 (0.021 - 1.240)	**0.079**	↓ Protective
Peak AST	Per U/L increase	0.002	0.001	4.222	1.002 (1.000 - 1.005)	**0.040**	↑ Risk

3.6. Summary of Key Findings

Clinical Impact: Prolonged infusion of imipenem/cilastatin significantly improved

clinical response rates and survival while reducing secondary fungal infections.

Safety: No increased risk of hepatic/renal toxicity or neurological events.

Cost-Effectiveness: Equivalent drug utilization supports the economic feasibility of prolonged infusion.

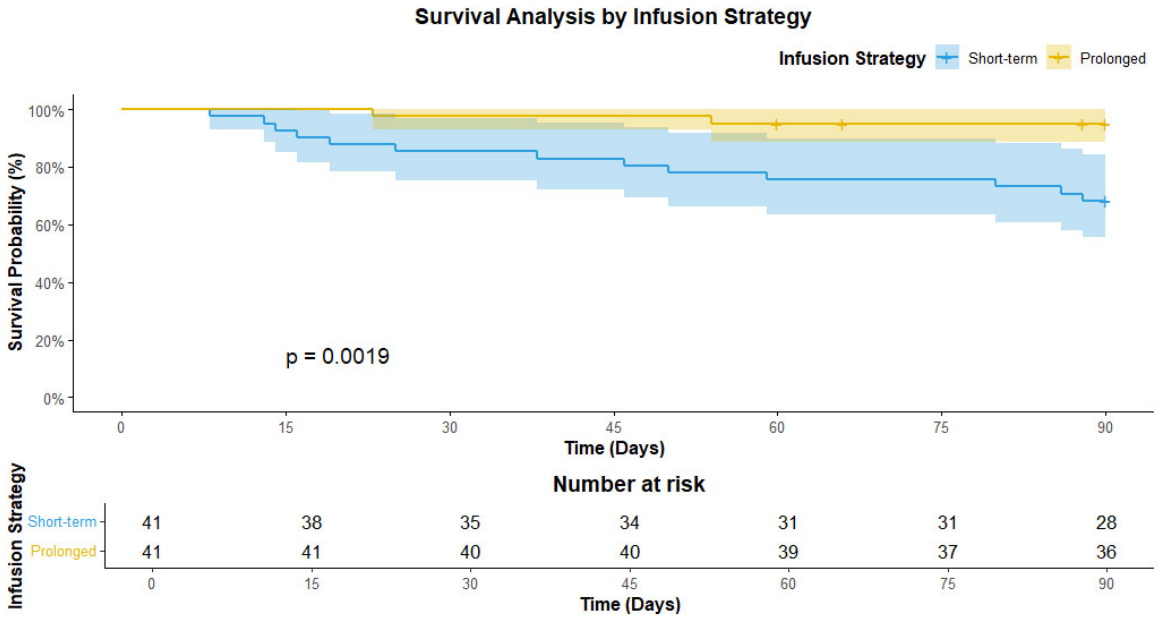

Figure 1. Kaplan-Meier curves illustrate superior survival in the prolonged group.

Table 6. Final multivariable Cox regression model for survival predictors.

Predictor	Contrast	β (SE)	Wald χ^2	Adjusted HR (95% CI)	P-Value	Direction
Prolonged Infusion	Yes vs. No	−2.56 (0.96)	7.12	**0.08 (0.01 - 0.51)**	**0.008**	Protective
Treatment Duration	Per 1-day increase	0.14 (0.06)	6.66	**1.15 (1.04 - 1.29)**	**0.010**	Risk
Peak AST Level	Per 1-U/L increase	0.005 (0.002)	9.03	**1.01 (1.00 - 1.01)**	**0.003**	Risk

4. Discussion

This randomized controlled trial provides evidence that prolonging the infusion duration of imipenem/cilastatin from 30 minutes to 3 hours significantly improves clinical outcomes in patients with severe pneumonia caused by multidrug-resistant Gram-negative bacilli (MDR-GNB). The intervention group demonstrated an 82.9% clinical response rate at day 8 compared to 58.5% in the short-term group (P = 0.002), alongside a marked reduction in secondary fungal infections (7.3% vs. 29.3%, P = 0.010) and improved 90-day survival (adjusted HR = 0.08, P = 0.008). The observed survival benefit (adjusted HR 0.08) mirrors PK/PD simulations demonstrating that prolonged infusion achieves $fT > MIC > 90\%$ for pathogens with MICs ≤ 2 mg/L [18] [19]. The lower fungal infection rate (7.3%) may reflect reduced antibiotic-induced dysbiosis, a phenomenon previously reported with optimized β-lactam exposure [20]. Prolonged infusion enhances the time-dependent bactericidal activity by maximizing the fraction of the dosing interval during which free drug

concentrations exceed the pathogen's minimum inhibitory concentration ($fT >$ MIC). Importantly, the safety profile remained comparable between groups, refuting concerns that prolonged infusion might increase toxicity.

4.1. Mechanistic and Clinical Implications

Our results corroborate prior observational studies suggesting that prolonged infusion of carbapenems improves clinical efficacy in critically ill patients. For pathogens with elevated MICs (e.g., Pseudomonas aeruginosa), short-term infusions may fail to achieve adequate $fT >$ MIC thresholds, leading to therapeutic failure. By contrast, the 3-hour infusion strategy likely optimized drug exposure, as evidenced by faster microbial eradication (**Table 3**) and reduced recurrence rates. The lower incidence of secondary fungal infections in the prolonged group further supports its role in minimizing collateral damage from broad-spectrum therapy, potentially by shortening the duration of systemic inflammation and mucosal disruption. These findings support incorporating prolonged infusion into antimicrobial stewardship programs for MDR-GNB pneumonia. Clinical Practice should prioritize this strategy in critical care formularies, particularly for regions with high carbapenem resistance rates. Logistical barriers, such as infusion pump availability and nursing workflow adjustments, may hinder adoption in resource-limited settings. Simulation-based training and phased implementation could mitigate these challenges.

4.2. Divergence from Previous Study

While our findings are consistent with meta-analyses favoring prolonged infusion, they contrast with smaller RCTs reporting neutral effects. This discrepancy may stem from differences in patient selection—our trial exclusively enrolled microbiologically confirmed MDR-GNB pneumonia, whereas prior studies included mixed infections or retrospective cohorts [4]. Additionally, our use of blinded endpoint adjudication reduced outcome assessment bias, a limitation in earlier open-label trials.

4.3. Pharmacoeconomic and Practical Considerations

Despite superior efficacy, prolonged infusion did not increase direct medication costs, as total drug consumption and treatment duration were equivalent between groups (**Table 4**). This cost neutrality, combined with reduced hospital stays (25 vs. 33 days, $P = 0.35$), suggests prolonged infusion is economically viable. However, logistical challenges (e.g., infusion pump availability) may hinder implementation in resource-limited settings. Future guidelines should weigh these practical barriers against the clear survival benefits.

5. Limitations

This study has several limitations. First, the single-center design and modest sample size ($n = 82$) may limit generalizability. Second, the exclusion of polymicrobial

infections and renal-impaired patients precludes extrapolation to these subgroups. Third, the open-label administration (despite blinded endpoint assessment) could introduce performance bias. Finally, the 90-day follow-up may underestimate late recurrences or long-term complications.

6. Future Directions

Prospective multicenter trials with larger cohorts are needed to validate these findings across diverse healthcare systems. Pharmacokinetic sub-studies should define optimal infusion durations for specific pathogens and MIC ranges. Additionally, integrating therapeutic drug monitoring (TDM) could further personalize dosing, particularly in patients with extreme body weights or augmented renal clearance.

7. Conclusion

In this randomized controlled trial, prolonged infusion of imipenem/cilastatin (1 g q8 h over 3 h) demonstrated superior clinical efficacy compared to short-term 30-minute infusion in patients with multidrug-resistant Gram-negative severe pneumonia. The prolonged infusion strategy significantly improved clinical response rates at day 8 (82.9% vs. 58.5%; P = 0.015) and 90-day survival (95.1% vs. 68.3%, P = 0.02) while reducing secondary fungal infections (7.3% vs. 29.3%, P = 0.010). Multivariable Cox regression confirmed prolonged infusion as an independent protective factor for survival (adjusted HR = 0.08, 95% CI: 0.01 - 0.51; P = 0.008), with no increased risk of nephrotoxicity, hepatic injury, or neurological events. These findings, coupled with equivalent pharmacoeconomic costs, support the adoption of prolonged infusion as a safer and more effective therapeutic approach for managing severe MDR-GNB pneumonia. This trial provides evidence supporting prolonged infusion as the short-term of care for MDR-GNB pneumonia, aligning with international consensus recommendations [21]. Future studies should integrate therapeutic drug monitoring to personalize dosing in extreme pharmacokinetic scenarios [13] [21]. Also, Future studies should validate these results in broader populations and explore pharmacokinetic-pharmacodynamic optimization.

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Ethics Approval and Consent to Participate

This study was approved by the Ethical Review Committee of The Brain Hospital of Guangxi Zhuang Autonomous Region (Approval No. 2022.009). All procedures adhered to the ethical principles of the Declaration of Helsinki.

Consent for Publication

No individual personal data (e.g., images, videos) requiring specific consent is included in this manuscript.

Data Availability

The de-identified datasets generated and analyzed during this study are available from the corresponding author (Yao Mingshi, E-mail: yaomingshi@sina.com) upon reasonable request, subject to institutional data-sharing agreements.

Authors' Contributions

Liang Chaoyue and Yao Mingshi contributed equally.

Yao Mingshi: Project Administration, Funding Acquisition, Supervision, Writing—Original Draft.

Liang Chaoyue: Writing—Review & Editing, Conceptualization, Methodology, Software, Visualization, Formal Analysis.

Zhai Zhiwen: Editing.

Lu Qinyong, Qin Liuxin, Tang Xiaoling, and Mo Meifeng: Data Collection, Investigation.

Conflict of Interest

The authors declare no competing financial or non-financial interests relevant to this study.

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