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ORIGINAL RESEARCH

Comparison of Two Different Doses of Ampicillin-Sulbactam as Part of Combination Therapy in the Treatment of Multidrug Resistant *Acinetobacter baumannii* Ventilator Associated Pneumonia: A Randomized Clinical Trial

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Purpose: Ventilator-associated pneumonia (VAP) caused by multidrug-resistant (MDR) *Acinetobacter baumannii* is associated with high morbidity and mortality, and optimal antimicrobial dosing strategies remain uncertain. Although ampicillin-sulbactam is increasingly used for MDR *Acinetobacter baumannii* infections, limited clinical data exist regarding the efficacy and safety of different dosing regimens when used as part of combination therapy. This study aimed to compare the clinical outcomes of low- versus high-dose ampicillin-sulbactam in combination of meropenem and colistin in patients with MDR *Acinetobacter baumannii* associated VAP.

Patients and Methods: In this randomized clinical trial, patients with MDR *Acinetobacter baumannii* associated VAP admitted to the intensive care unit were allocated to receive either low-dose ampicillin-sulbactam (6 g IV every 6 h; total 24 g/day) or high-dose ampicillin-sulbactam (9 g IV every 6 h; total 36 g/day). Meropenem and colistin were administered concomitantly in both groups, as they remain commonly used standard therapies for severe MDR infections despite increasing resistance and toxicity concerns. Clinical outcomes, including fever duration, pulmonary secretions, Clinical Pulmonary Infection Score (CPIS), duration of mechanical ventilation, length of ICU and hospital stay, mortality, and adverse drug reactions, were assessed over a 10-day follow-up period.

Results: A total of 77 patients were enrolled (39 in the low-dose group and 38 in the high-dose group). The high-dose group demonstrated significantly shorter hospital stay (15.34 ± 4.99 vs 19.46 ± 6.91 days; P = 0.007), ICU length of stay (11.66 ± 6.11 vs 17.08 ± 7.40 days; P < 0.001), and duration of mechanical ventilation (6.39 ± 2.14 vs 7.74 ± 2.60 days; P = 0.003).

Conclusion: Among patients receiving combination therapy for MDR *Acinetobacter baumannii* associated VAP, higher-dose ampicillin-sulbactam was associated with improved clinical outcomes without increased toxicity. However, the small sample size, short follow-up period, and use of concomitant antibiotics limit attribution of outcomes solely to ampicillin-sulbactam dosing. Larger, well-controlled studies are needed to define the optimal dosing strategy.

Keywords: *Acinetobacter baumannii*, ampicillin, pneumonia, ventilator-associated, sulbactam

Introduction

Ventilator-associated pneumonia (VAP) is a life-threatening condition in intensive care units that leads to high mortality rates among patients.[1] This problem worsens with the presence of resistant microorganisms, which often do not respond to standard antibiotic treatments, further increasing the risk of death.[2] Notably, *Pseudomonas aeruginosa, Acinetobacter baumannii*, and

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Klebsiella pneumoniae are responsible for approximately 80% of the VAP cases. Of these, *Acinetobacter baumannii* poses a particularly serious therapeutic challenge due to its rapid acquisition of multidrug resistance and limited treatment options. *Acinetobacter baumannii*, a non-fermenting Gram-negative bacterium, is especially known for quickly developing antibiotic resistance. Studies have shown that 41–93% of *Acinetobacter baumannii* strains can become resistant to infection, making treatment more challenging.[3,4] Several antibiotics such as penicillin, quinolones, and carbapenems have largely become ineffective against this *Acinetobacter baumannii*, which makes them multidrug resistance (MDR).[5] Antibiotic resistance occurs when bacteria evolve mechanisms to avoid the adverse effects of drugs. The overuse and misuse of antibiotics in medicine and agriculture drives this process, leading to the rise of MDR pathogens.[6]

Sulbactam, a synthetic beta-lactamase inhibitor, has direct antimicrobial effects against *Acinetobacter* species and is effectively used both alone and alongside ampicillin or imipenem to treat severe *Acinetobacter* infections specially when the isolate remains susceptible to sulbactam, particularly when administered at optimized or high doses in severe infections such as VAP.[7] Previous studies have suggested that combination regimens including ampicillin-sulbactam, carbapenems, and colistin may reduce mortality in infections caused by highly resistant *Acinetobacter*, including colistin-resistant strains. However, in these regimens, the specific contribution of sulbactam dosing to clinical outcomes remains unclear.[8] The pharmacodynamics of high-dose ampicillin-sulbactam, whether used alone or in combination with other treatments, is not well understood. From a pharmacokinetic/pharmacodynamic (PK/PD) perspective, achieving adequate sulbactam exposure is critical for therapeutic success. Sulbactam exhibits time-dependent bactericidal activity, and higher doses or prolonged infusions may be required to maintain plasma and epithelial lining fluid concentrations above the minimum inhibitory concentration (MIC) for MDR isolates. In critically ill patients with VAP, altered PK, including increased volume of distribution and augmented renal clearance, may further compromise target attainment with standard dosing regimens. These PK/PD challenges have prompted increasing interest in high-dose ampicillin-sulbactam strategies as a means of optimizing pulmonary drug exposure and improving clinical outcomes.[9] In cases of resistance to all available antibiotics, various approaches have been investigated, such as longer infusion times, higher doses, and alternative delivery methods such as nebulized therapy for lung infections.[10] The effects of the antibiotic dose on overcoming resistance are complex and significant in the context of microbial treatment. Higher antibiotic doses can enhance drug efficacy by achieving more effective bacterial killing, potentially reducing the likelihood of resistance development. However, prolonged or excessive use of high doses can inadvertently exert selective pressure on microorganisms, favoring survival and proliferation of resistant strains.[11] This phenomenon occurs when bacteria exposed to suboptimal drug concentrations are not fully eradicated, thereby allowing the proliferation of resistant mutations. Additionally, the PK and PD of antibiotics, including factors such as drug concentration at the site of infection and the duration of exposure, play critical roles in determining the balance between therapeutic effectiveness and the risk of resistance. Optimizing antibiotic dosing is crucial for preventing resistance and ensuring eradication of the infection, highlighting the need for precision medicine and stewardship programs to guide appropriate dosage regimens.[11,12]

Despite growing clinical use of high-dose ampicillin-sulbactam for MDR *Acinetobacter baumannii* associated VAP, robust clinical evidence guiding optimal dosing remains limited. In particular, comparative studies evaluating different ampicillin-sulbactam dosing regimens within a standardized combination therapy framework are scarce. This lack of evidence represents a critical knowledge gap, as dose optimization may significantly influence outcomes in this high-risk population.

Accordingly, this study aimed to evaluate the efficacy and safety of two different ampicillin-sulbactam dosing regimens administered as part of combination therapy for the treatment of VAP caused by MDR *Acinetobacter baumannii*.

Materials and Methods

Design

This study was a randomized clinical trial conducted at Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Patients admitted to the intensive care unit of the hospital from September 2023 to November 2024 were included in this trial.

Study Registration

This study was approved by the Research Ethics Committee of the School of Pharmacy, Shahid Beheshti University of Medical Sciences (IR.SBMU.PHARMACY.REC.1402.094) and this study complies with the Declaration of Helsinki. This trial was registered with the Iranian Registry of Clinical Trials (IRCT20180802040665N2).

Patients

The cohort examined in this study included all patients with VAP. According to the IDSA definition, VAP is characterized by the emergence of new or worsening infiltrates on a patient's radiographic imaging, observable at least 48 hours after the initiation of mechanical ventilation. In addition, diagnosis requires the presence of at least two of the following clinical indicators: 1. Fever exceeding 38 °C, 2. Either leukocytosis or leukopenia (WBC < 4000/μL or WBC > 12000/μL) and 3. Presence of purulent pulmonary secretions. The Clinical Pulmonary Infection Score (CPIS) is recommended.[13] This scoring system integrates clinical, radiographic, physiological, and microbiological information to estimate the likelihood of VAP, with a score exceeding six indicating a higher probability of the VAP.

Notably, recent updates have suggested that routine lung radiography is not advisable for follow up. Eligible patients were evaluated based on the inclusion, non-inclusion, and exclusion criteria (Table 1).

The sample size of this study was estimated based on a study by Ungthammakhun et al. The alpha and power values were considered as 0.05 and 80%, respectively. In addition, a 20% dropout rate was considered in the final calculations. P1 was considered as 0.41, which represents the survival rate, and P2 was considered 0.8.[14]

Table 1 The Inclusion, Not-Inclusion, and Exclusion Criteria of the Study

Inclusion criteria	Individuals who are 18 years of age or older
	Diagnosed with VAP in accordance with the IDSA criteria, characterized by the emergence of pneumonia (evidenced by new pulmonary infiltrates alongside clinical manifestations such as fever, purulent sputum, leukocytosis, and reduced oxygenation) occurring after 48 hours of initiation of mechanical ventilation.
	Patients who received empiric antibiotic regimen consist of meropenem (at dose of 1000 mg IV q8h) and vancomycin (at dose of 15 mg/kg IV q12h) for the first 48 hours until the results of the culture are determined.
	Culture results which reported after first 48 hours indicating the presence of pulmonary secretions with *Acinetobacter baumannii* exhibiting resistance to aminoglycosides, fluoroquinolones, cephalosporins, penicillin, and carbapenem simultaneously.
	Must provide signed informed consent
Not-inclusion criteria	Individuals who are either lactating or pregnant.
	Patients diagnosed with infections distinct from VAP.
	Obese individuals with a BMI exceeding 35.
	Patients possessing a documented history of allergic reactions to medications included in the treatment protocol.
	Patients with underlying lung diseases, immunocompromised patients, and those with recurrent lung infection.
	Patients presenting with sepsis at the commencement of the study, according to the 2021 sepsis campaign guidelines.
	Individuals with pre-existing pulmonary conditions, such as COPD, lung cancer, or pulmonary PTE.
Exclusion criteria	Patients whose antibiotic treatment may be altered in terms of dosage and administration schedule.
	Patients experiencing a hypersensitivity reaction during the course of the medication.
	Patients who have ceased medication for a duration of less than 10 days.

Abbreviations: BMI, Body mass index; COPD, Chronic obstructive pulmonary diseases; IDSA, Infectious diseases society of America; VAP, Ventilator-associated pneumonia; PTE, pulmonary thromboembolism.

$$\text{Effect Size(d)} = \frac{|p1 - p2|}{\sqrt{\frac{(p1+p2)}{2} * \left(1 - \frac{(p1+p2)}{2}\right)}} = 0.79$$

$$n = \frac{2 \times \left(\left(z_{1-\frac{\alpha}{2}}\right) + \left(z_{1-\beta}\right)\right)^2}{d^2} = 25$$

Consequently, a sample size of 50 patients was determined with 25 patients allocated to each group. However, considering the anticipated dropout rate of approximately 20%, the final selection consisted of 30 patients per group.

The patients selected for this study were enrolled using a block randomization method. Fifteen blocks, each containing four patients, were created using an online platform. Within each block, two patients were assigned to group A, while the remaining two patients were allocated to group B. This study was not blinded due to practical and safety considerations. Administration of high-dose ampicillin-sulbactam required dose-specific preparation and monitoring, and blinding was considered potentially unsafe given the risk of dosing errors in critically ill patients. In addition, blinding was not feasible because identical vial appearance and preparation could not be ensured, particularly in the absence of validated procedures for sterile repackaging and standardization of study medications.

Interventions

After allocating patients to group A and group B, the antibiotic regimen of patients in group A includes meropenem (Daana pharmaceutical company, Tabriz, Iran) 2000 mg IV every eight hours plus colistin (Exir pharmaceutical company, Borujerd, Lorestan, Iran) 4.5 million units IV every 12 hours plus ampicillin-sulbactam (Daana Pharmaceutical Company, Tabriz, Iran) 6 g IV (4 grams ampicillin + 2 grams sulbactam) every six hours (24 grams daily). This meropenem and colistin combination regimen was similar in both groups, and it was considered as a combination therapy. The subsequent cohort, referred to as the group B or high-dose group, was administered an identical antibiotic regimen; however, the key distinction was that ampicillin-sulbactam was prescribed at an elevated dose of 9 g IV (6 g ampicillin + 3 g sulbactam) every six hours (36 g daily). The duration of antibiotic infusion was comparable between the groups. The adherence to the therapy protocol was evaluated by the master nurse of study team.

Outcomes

The primary outcome of this study was clinical improvement, defined as the proportion of patients who demonstrated resolution of key clinical symptoms without any changes to their antibiotic regimen throughout the study period. Clinical improvement was objectively assessed by resolution of fever, reduction in purulent pulmonary secretions, absence of vasopressor support for at least 48 hours.

CPIS score and mortality were analyzed as secondary outcomes, along with other objective measures of disease severity. Other secondary outcomes included, successful weaning from mechanical ventilation or tolerance of spontaneous breathing, duration of stay in the ICU and hospital, occurrence of adverse drug reactions. Safety was actively monitored through daily assessment of vital signs, clinical parameters, and paraclinical tests. Any suspected drug-related events were recorded according to predefined criteria.

Patients were evaluated daily during hospitalization. Clinical parameters assessed included fever, pulmonary secretions, oxygenation levels, ventilator dependency, blood pressure, and the need for norepinephrine as a marker of septic shock-related end-organ dysfunction. Paraclinical parameters, including CBC, BUN, creatinine, lactate, ESR, CRP, ABG, AST, ALT, and ALP, were measured every two days. Severity scores, including SOFA, APACHE II, and CPIS, were calculated at baseline and at the end of the study.

All clinical outcomes were recorded by a trained nurse independent of the study team to reduce subjectivity and ensure consistent data collection. Microbiological assessments included evaluation of MICs for meropenem, colistin, and ampicillin-sulbactam.

Statistical Analysis

Fisher's exact test was used for all categorical data, and the Student's *t*-test was used for all continuous data comparisons. SPSS (version 21.0; IBM Corp., Armonk, NY, United States) was used for the statistical analyses. Statistical significance ($P < 0.05$) was set as significant level.

Results

In this randomized clinical trial, 288 patients were evaluated, 194 of whom did not meet the inclusion criteria (Table 2). Infections other than VAP were the most common cause of exclusion followed by non-CRAB cultures, and underlying lung diseases were the most common cause of non-inclusion. The remaining 94 patients were enrolled in the study, of which 45 were assigned to the low-dose group and 49 to the high-dose ampicillin-sulbactam group. During the study, six patients in the low-dose group and 11 patients in the high-dose group were excluded because of antibiotic regimen changes and cessation of the study after 10 days. Finally, 39 patients in the low-dose group and 38 patients in the high-dose group completed the study. Although the initial sample size calculation estimated 50 patients per group, enrollment was increased to compensate for anticipated dropout, early death, and overlapping eligibility. The final number of patients included in the analysis was determined after these exclusions. The Consolidated Standards of Reporting Trails (CONSORT) flowchart of this study is shown in Figure 1.

Demographic data showed that 23 patients (59.0%) in the low-dose group and 24 patients (63.2%) in the high-dose group were male ($P = 0.443$). Pneumonia was the most common reason for admission in both groups (six patients in each group). Diabetes (12.8% of patients in the low-dose group and 18.42% of patients in the high-dose group), hypertension (20.51% of patients in the low-dose group and 18.42% patients in the high-dose group), and ischemic heart diseases (7.69% patients in the

Table 2 The Demographic Data of Participants

Parameter		Low Dose Group (n= 39)	High Dose Group (n= 38)	P value
Gender	Male	23 (59.0%)	24 (63.2%)	0.443
Admission reason	Trauma	6 (15.40%)	8 (21.10%)	0.338
	Pneumonia	6 (15.40%)	6 (15.80%)	
	Brain tumor	5 (12.80%)	4 (10.50%)	
	Toxicity	4 (10.30%)	4 (10.50%)	
	CVA	5 (12.80%)	2 (5.30%)	
Past medical history	None	10 (25.6%)	13 (33.3%)	0.740
	Diabetes	9 (23.1%)	7 (17.9%)	
	Hypertension	8 (20.5%)	8 (20.5%)	
	IHD	6 (15.4%)	6 (15.4%)	
	Cancer	5 (12.8%)	3 (7.7%)	
	Addiction	3 (7.7%)	3 (7.7%)	
	BPH	2 (5.1%)	2 (5.1%)	
	Dementia	2 (5.1%)	3 (7.7%)	
	Dyslipidemia	2 (5.1%)	1 (2.6%)	
	Hypothyroidism	2 (5.1%)	2 (5.1%)	
	Parkinson	2 (5.1%)	1 (2.6%)	

Abbreviations: IHD, Ischemic heart disease; BPH, Benign prostatic hyperplasia; CVA, Cerebrovascular accident.

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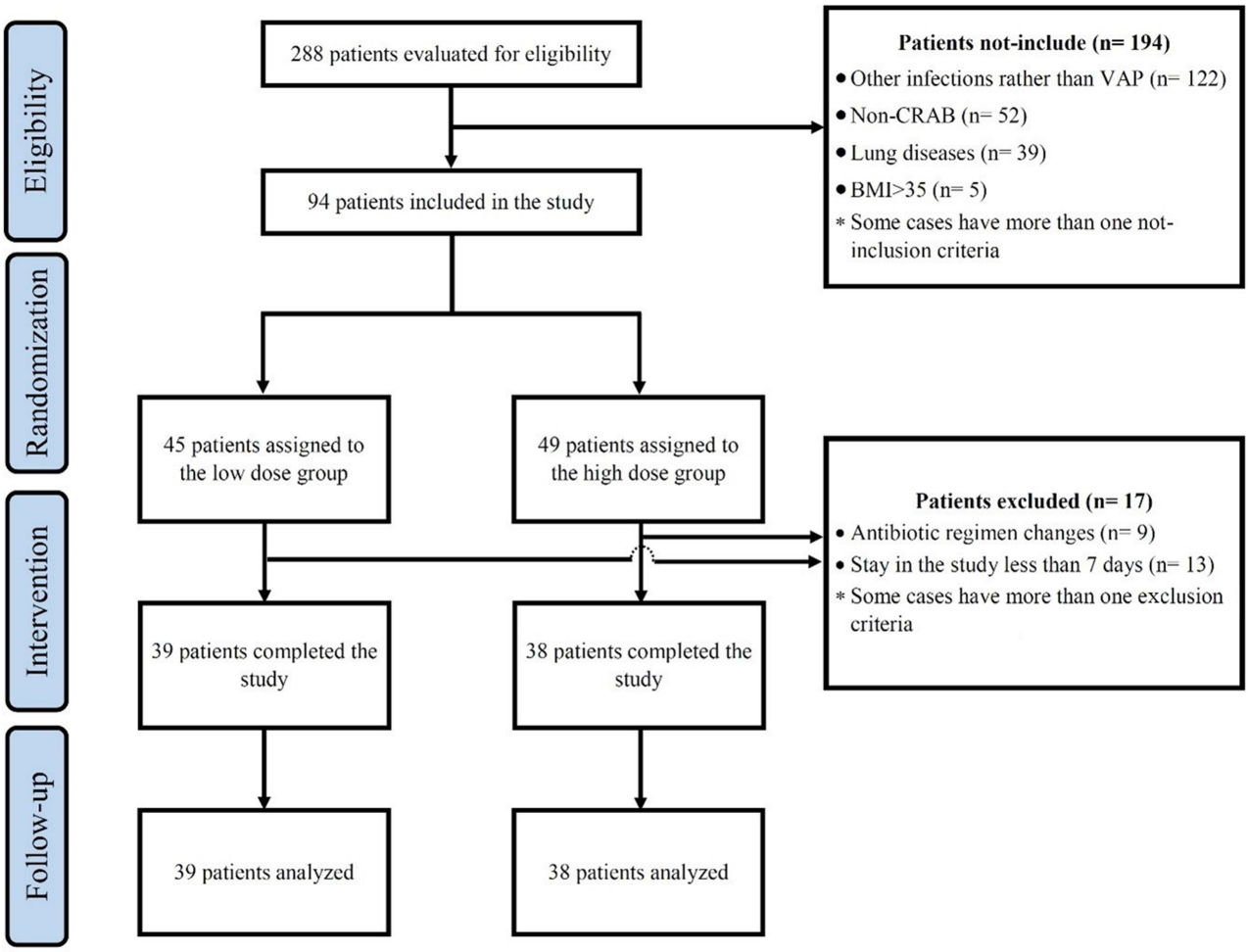

Figure 1 The Consolidated Standards of Reporting Trails (CONSORT) flowchart of study.

low-dose group and 10.52% of patients in the high-dose group) were the most prevalent underlying diseases in both groups (P = 0.740). The age of patients (mean ± SD) in the low-dose groups was 55.21 ± 20.14 years old and 55.00 ± 19.82 years old in high dose group (P = 0.980). The demographic data of the participants are shown in Table 2.

Microbiological studies were conducted to evaluate the MICs of meropenem, colistin, and ampicillin-sulbactam. The results are presented in Table 3. Higher MIC values indicate reduced bacterial susceptibility and support the rationale for dose escalation of ampicillin-sulbactam in critically ill patients.

Laboratory parameters were evaluated at the beginning and end of the study. There were no statistically significant differences between the two groups in terms of laboratory parameters (P > 0.05 for all parameters) (Table 4).

Table 3 The Minimum Inhibitory Concentration (MIC) Results

Drug	MIC (μg/mL)	Low Dose Group (n= 39)	High Dose Group (n= 38)
Meropenem	4	1 (2.60%)	0 (0%)
	8	2 (5.10%)	0 (0%)
	16	0 (0%)	1 (2.60%)
	≥64	36 (92.30%)	37 (97.40%)

(*Continued*)

Table 3 (Continued).

Drug	MIC (µg/mL)	Low Dose Group (n= 39)	High Dose Group (n= 38)
Colistin	4	16 (41.0%)	8 (21.10%)
	8	10 (25.60%)	15 (39.5%)
	16	13 (33.30%)	15 (39.5%)
Ampicillin-sulbactam	4	1 (2.60%)	1 (2.60%)
	8	2 (5.10%)	0 (0%)
	16	25 (64.10%)	16 (41.0%)
	32	11 (28.20%)	21 (55.30%)

Abbreviation: MIC, Minimum inhibitory concentration.

Table 4 The Laboratory Parameters at the Base of the Study and at the End of the Study

Parameter	Low Dose Group (n= 39)	High Dose Group (n= 38)	P value
Creatinine at day 0 (mg/dL)	0.96 ± 0.32	1.11 ± 0.35	0.560
Creatinine at day 10 (mg/dL)	1.14 ± 0.31	1.13 ± 0.30	0.922
WBC at day 0 ($\times 10^9$/L)	11.36 ± 5.18	13.33 ± 4.77	0.062
WBC at day 10 ($\times 10^9$/L)	11.88 ± 4.61	10.63 ± 3.77	0.256
Platelet at day 0 ($\times 10^3$/µL)	285.69 ± 150.78	248.53 ± 142.02	0.313
Platelet at day 10 ($\times 10^3$/µL)	284.64 ± 138.32	218.74 ± 137.98	0.064
Lactate at day 0 (mg/dL)	29.82 ± 9.28	26.76 ± 8.12	0.106
Lactate at day 10 (mg/dL)	17.69 ± 6.52	20.24 ± 6.72	0.105

Abbreviation: WBC, White blood cells.

Clinical parameters including fever duration and secretion trends were also evaluated. The results showed that seven patients (18%) in the low-dose group had fever for more than two days. However, only two patients (5.26%) in the high-dose group had fever for more than two days (P = 0.155). Pulmonary secretions of 23 (59.0%) patients in the low-dose group diminished until day 10. In contrast, 33 (86.8%) patients in the high-dose group showed fewer secretions on day 10. This decrease in pulmonary secretion was statistically significant (P = 0.023). The CPIS score was evaluated on Days 0 and 10. The results showed that on the first day of the study, 30 (76.90%) patients in the low-dose group had a CPIS score more than six and in the high-dose group, 31 (81.70%) patients had a CPIS score more than six (P = 0.872). At the end of the study, 16 (41.0%) patients in the low-dose group had CPIS score more than six and seven patients (18.42%) in the high-dose group had CPIS score more than six (P = 0.027). The hospitalization/ICU length of stay was significantly lower in the high-dose group than in the low-dose group. The mean ± SD of hospitalization length of stay in low- and high-dose group were 19.46 ± 6.91 and 15.34 ± 4.99 days (P = 0.007), respectively. The mean ± SD of ICU length of stay in low and high-dose group were 17.08 ± 7.40 and 11.66 ± 6.11days (P < 0.001), respectively. The length of intubation was also evaluated in both groups. The results showed that the lengths of intubation in the low- and high-dose groups were 7.74 ± 2.60 and 6.39 ± 2.14 days, respectively (P = 0.003). In summary, changes in CPIS scores, hospital length of stay, ICU length of stay, and duration of intubation were significantly better in the high-dose group compared with the low-dose group. At the end of the study which was on the day 10, nine patients (23.10%) in the low dose group and six patients in high-dose group (15.80%) expired. This difference was not statistically significant (P = 0.302). No adverse drug reactions based on the clinical and paraclinical parameters were observed during the study. Clinical outcomes are shown in Table 5.

Table 5 The Clinical Outcomes of Study

Outcomes		Low Dose Group (n= 39)	High Dose Group (n= 38)	P value
Fever more than two days		7 (17.90%)	2 (5.30%)	0.155
Pulmonary secretion	Decreased	23 (59.00%)	33 (86.80%)	0.023
	No changes	13 (33.30%)	4 (10.50%)	
	Increased	3 (7.70%)	1 (2.60%)	
CPIS >6 at day 0		33 (76.90%)	3 (81.70%)	0.872
CPIS >6 at day 10		16 (41.1%)	7 (18.42%)	0.027
Hospitalization length of stay (days)		19.46 ± 6.91	15.34 ± 4.99	0.007
ICU length of stay (days)		17.08 ± 7.4	11.66 ± 6.11	< 0.001
Intubation period (days)		7.74 ± 2.6	6.39 ± 2.14	0.003
SOFA score at the 0		7.62 ± 3.09	8.00 ± 3.15	0.580
SOFA score at day 10		8.05 ± 3.14	7.87 ± 3.31	0.866
APACHE score at day 0		20.74 ± 5.50	19.55 ± 6.11	0.432
APACHE score at day 10		21.23 ± 5.03	20.13 ± 5.76	0.405
Outcome	Survived	30 (76.90%)	32 (84.20%)	0.302
	Expired	9 (23.10%)	6 (15.80%)	

Abbreviations: APACHE, Acute physiology and chronic health evaluation; CPIS, Clinical pulmonary infection score; ICU, Intensive care unit; SOFA, Sequential organ failure assessment.

Discussion

This study evaluated the management of VAP caused by MDR *Acinetobacter baumannii* using ampicillin-sulbactam at two dosing regimens (24 g/day vs 36 g/day), in combination with standardized meropenem and colistin co-administration. Standardizing the backbone therapy minimized confounding and allowed focused assessment of the impact of varying ampicillin-sulbactam doses. The rationale for including meropenem and colistin is supported by their known synergistic mechanisms with sulbactam, including enhanced bacterial membrane disruption and complementary inhibition of cell wall synthesis, which have been demonstrated in vitro and in hollow-fiber infection models.[15]

Administration of high-dose ampicillin-sulbactam was associated with improved short-term clinical outcomes, particularly a more pronounced reduction in CPIS. PK/PD principles emphasize the importance of achieving a higher percentage of free drug time above the minimum inhibitory concentration (%fT > MIC) to optimize bacterial killing, particularly in critically ill patients. Higher sulbactam dosing facilitates attainment of these targets and may enhance clinical efficacy.[15]

Despite improvements in CPIS and other short-term clinical parameters, there was no statistically significant difference in mortality between dosing groups. However, the mortality should be interpreted cautiously due to low sample size. As all patients received similar doses of meropenem and colistin, these agents may have substantially contributed to clinical outcomes, suggesting that the independent effect of high-dose ampicillin-sulbactam should be interpreted cautiously.

Previous studies provide important context but differ in key aspects. Randomized trials assessing high-dose meropenem in MDR-VAP did not demonstrate significant differences in clinical recovery, though higher doses were associated with improved SOFA scores, highlighting that outcome vary by antibiotic class and combination strategy. Similarly, extended meropenem infusion has limited efficacy when MIC exceeds 4 μg/mL, reinforcing the rationale for dose escalation rather than prolonged infusion.[16]

MIC analysis in the present study indicated widespread resistance to meropenem (≥16 µg/mL) across both groups. Colistin resistance was more pronounced in the low-dose group (MIC 8 µg/mL: 41.0% vs 21.1%). For ampicillin-sulbactam, resistance was observed in both groups (low-dose: 64.1% at MIC 16 µg/mL; high-dose: 55.3% at MIC 32 µg/mL), yet the high-dose group achieved better clinical outcomes, including shorter ICU stays and reduced intubation duration. These findings support the utility of high-dose therapy in overcoming elevated MICs.

Prior research further contextualizes these findings. Betrosian et al compared high-dose ampicillin-sulbactam with colistin monotherapy, reporting comparable efficacy and safety at lower doses than those employed in this study.[17] This controversy may be due to different resistance pattern. McMillian et al demonstrated that standard-dose ampicillin-sulbactam monotherapy is largely ineffective for VAP due to MDR *Acinetobacter baumannii* in trauma patients, emphasizing the necessity of higher dosing. In the McMillian's study, ampicillin–sulbactam showed poor empiric activity for early-onset VAP, with resistance rates of 40% by day 3 that progressively increased to 60% after eight days of hospitalization, substantially exceeding the predefined 15% threshold for empiric failure. Gram-negative pathogens accounted for 71% of isolates, and ampicillin–sulbactam resistance was significantly associated with established MDR pathogen risk factors, prolonged hospital length of stay, prior antibiotic exposure within 90 days, and hospitalization longer than four days. Collectively, these findings demonstrate that ampicillin–sulbactam is not an effective empiric option for early-onset VAP in this trauma population.[18] Our results are different with McMillian's study probably due to different administrated doses and also different resistance pattern. Additionally, trauma patients may exhibit augmented renal clearance, which can lead to PK failure. Combination therapy with colistin and ampicillin-sulbactam has been associated with improved clinical recovery, as shown in a study by Makris et al.[6] Current results support the superior efficacy of combination therapy over colistin monotherapy for MDR *Acinetobacter baumannii* associated VAP. A recent prospective, randomized study demonstrated that early clinical cure was significantly higher in patients receiving colistin plus high-dose ampicillin-sulbactam compared to colistin alone. Multivariate analysis identified combination therapy and lower SOFA scores as independent predictors of favorable clinical response, while lower APACHE II scores and early treatment response were associated with ICU survival. These findings underscore the potential benefit of adding high-dose ampicillin-sulbactam to colistin, likely improving bacterial eradication in the context of limited pulmonary penetration of colistin.

Ungthammakhun et al evaluated ampicillin-sulbactam at 9 g/day versus 12 g/day in combination with colistin, noting trends toward reduced mortality and increased microbiological success with higher doses, though statistical significance was limited.[14] Collectively, these studies indicate that higher doses of ampicillin-sulbactam in combination regimens improve outcomes in MDR *Acinetobacter baumannii* infections, and the present study extends this evidence by evaluating an even higher dose (36 g/day).

Mechanistically, increasing antibiotic dose and employing combination therapy are complementary strategies to overcome resistance. Higher local concentrations enhance bacterial killing, while combination therapy targets multiple bacterial pathways simultaneously, potentially mitigating the emergence of resistance. However, careful consideration of toxicity and resistance selection is necessary, highlighting the importance of individualized regimens guided by PK/PD principles and MIC data.

The findings are aligned with current guideline recommendations. The 2024 Infectious Diseases Society of America (IDSA) guidance for carbapenem-resistant *Acinetobacter baumannii* supports the use of high-dose ampicillin-sulbactam in combination therapy when newer agents such as sulbactam-durlobactam are unavailable, recommending co-administration with at least one additional active agent.[19] The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines similarly endorse combination therapy, including ampicillin-sulbactam, for severe carbapenem-resistant *Acinetobacter baumannii* infections when the isolate is susceptible.[20]

The present triple therapy regimen, comprising high-dose ampicillin-sulbactam with meropenem and colistin, reflects these principles, despite meropenem not typically being preferred for CRAB; institutional use is based on potential synergy and empirical coverage as stated before.

Several limitations of this study should be considered. The open-label design was necessitated by the need for dose-specific preparation, as identical vial appearance could not be ensured and blinding could have introduced a risk of dosing errors. The relatively small sample size may have limited the ability to detect differences in mortality, and the 10-

day follow-up primarily captures short-term clinical outcomes rather than long-term effects. Additionally, while the study provides a strong PK/PD rationale for high-dose ampicillin-sulbactam, findings may not generalize to other patient populations, healthcare settings, or alternative dosing regimens.

Despite these limitations, this study provides valuable insights into the efficacy and safety of high-dose ampicillin-sulbactam in the management of MDR *Acinetobacter baumannii* associated VAP. The findings suggest that higher dosing may enhance short-term clinical recovery while maintaining an acceptable safety profile. Future research should investigate optimal dosing strategies, long-term outcomes, resistance patterns, and patient-centered endpoints such as ventilator-free days and mortality. Larger, multicenter, prospective studies are warranted to confirm these findings and guide evidence-based recommendations for the management of severe MDR *Acinetobacter baumannii* infections.

Conclusion

The study demonstrated that a high dose of ampicillin-sulbactam in combination of meropenem and colistin significantly reduced hospitalization and ICU length of stay, as well as the duration of intubation, compared to a low dose. These findings suggest that higher doses may improve short-term clinical outcomes in patients with MDR *Acinetobacter baumannii* associated VAP, particularly in the context of high MIC values, which support dose escalation. Further randomized studies with larger sample sizes and longer follow-up are warranted to confirm these findings and assess their impact on survival outcomes.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to institutional policies but are available from the corresponding author upon reasonable request.

Ethics Approval

This study was approved by the Research Ethics Committee of the School of Pharmacy, Shahid Beheshti University of Medical Sciences (IR.SBMU.PHARMACY.REC.1402.094) and this study complies with the Declaration of Helsinki. This trial was registered with the Iranian Registry of Clinical Trials (IRCT20180802040665N2).

Consent to Participate

Informed consent was obtained from all individual participants (or their legal parents) included in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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