ORIGINAL ARTICLE

Comparison Between the Combination Therapy in Terms of Therapeutic Effectiveness and Anti-Microbial Efficacy in Extensive Drug-Resistant Acinetobacter Baumannii Infections

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ABSTRACT

Objective: To compare the clinical and antimicrobial efficacy of a triple-antibiotic regimen (Colistin, Cefoperazone/Sulbactam, and Tigecycline) with a double-antibiotic regimen (Colistin and Minocycline) for treating drug-resistant *Acinetobacter baumannii* infections in critically ill patients.

Study Design: A comparative cross-sectional study design.

Place and Duration of Study: The study was conducted at the Medical Intensive Care Unit (ICU) of Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan from April 2022 to October 2022.

Materials and Methods: A total of 38 patients aged 18-70 years admitted to the Medical Intensive Care Unit (ICU) of the Pakistan Institute of Medical Sciences, Islamabad gave consent to participate in the study. Any patient having a culture-proven polymicrobial infection was excluded. A total of 20 patients were allocated to Group A (triple-antibiotic regimen) and 18 patients to Group B (double-antibiotic regimen). Vital statistics were recorded daily, while laboratory-based biochemical markers (leucocyte count, CRP, lactate, procalcitonin) were recorded every 48 hours for ten days. Antimicrobial efficacy was assessed by a culture analysis on the 10th day.

Results: There were 20 patients in Group A and 18 in Group B. There were 32 patients with Ventilator-Associated Pneumonia (VAP), and six with bloodstream infection. No significant difference in the vitals and lab markers were found between the two groups. The only exception was serum lactate levels, which were significantly higher Group A (34.03 + 28.37 mg/dL), compared to Group B (16.11 $\pm$ 15.63 mg/dL; p = 0.024). Group A therapy was also found to have significantly improved antimicrobial efficacy in terms of positive-culture results (n=4, 20%) compared to Group B (n=10, 55.6%; p = 0.023).

Conclusion: The triple-antibiotic regimen had better antimicrobial efficacy than the double-antibiotic regimen for treating *Acinetobacter baumannii*-related infections.

Keywords: *Acinetobacter Baumannii, Ventilator Associated Pneumonia, Carbapenems, Multi Drug Resistant organisms.*

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Introduction

Antimicrobial-resistant infections have grown as a serious threat in recent times.[1] The more resistant microbes are identified as difficult-to-treat ESKAPE pathogens, including *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species.[2,3] Among these, *Acinetobacter baumannii* is now realized as a global threat, especially in intensive care units (ICUs), owing to a high morbidity and mortality rate.[4]

According to the latest guidelines regarding multidrug-resistant organisms (MDRO), novel β-lactam/β-lactamase inhibitors, especially ceftazidime–avibactam, are currently the treatment of choices for CRE and CRPA.[5-7] However, clinical isolates with resistance to novel β-lactam/β-lactamase inhibitors are emerging.[8] Carbapenem has been administered as an antibiotic for treating nosocomial infections. However, the high use of antimicrobials has led to carbapenem *resistant Acinetobacter baumannii* (CRAB) becoming common around the world.[9] The occurrence of CRAB has been reported to vary from 15 to 50% across Europe, and rates of more than 50% have been reported in the United States.[10,11] In South Korea, CRAB rates of about 90% have been reported.[12] There are no reported studies related to CRAB in Pakistan.

Ventilator-associated-pneumonia (VAP) is the most common health condition associated with *Acinetobacter baumannii*.[13] Colistin has been reported to show promising results for treating CRAB VAP.[14] However, with the widespread use of the drug, resistance has been developed to Colistin as well. A recent European multi-center trial investigated the antimicrobial susceptibility of *Acinetobacter baumannii* isolates collected from VAP affected patients. A 47.7% resistance to Colistin was reported in the study.[15] Evidence suggests that antibiotics are prescribed at a higher frequency in low and middle-income countries such as Pakistan compared to high-income countries.[16] This could have significant implications on the efficacy of the prescribed antibiotics in different populations. Different combinations of antibiotics have been used for managing CRAB-caused infections. However, the evidence regarding the efficacy of different antibiotic regimens is inconclusive.[17] Therefore, the efficacy of multi-drug regimens against *Acinetobacter baumannii* needs to be further explored. The current study assessed the clinical and antimicrobial efficacy of a triple regiment (Colistin, Cefoperazone/ Sulbactam, and Tigecycline) as compared to a double regimen (Colistin and Minocycline) in treating drug resistant *Acinetobacter baumannii* infections in patients admitted in the ICU in a hospital in Pakistan.

Materials and Methods

A comparative cross-sectional study design was conducted among patients admitted to the Medical Intensive Care Unit (ICU) of Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan, with proven XDR *A.* baumannii by culture and sensitivity. The study compared the outcomes of the combination therapy of antibiotics for XDR A baumannii. After approval of the ethical committee vide IERB certificate No.FMTI ERRB/07/02, this cross-sectional study was conducted from 30th April 2022 to 30 October 2022.Patients above 18 years of age, admitted to the ICU with any ailment, diagnosed with hospital-acquired XDR *A.* baumannii in the absence of a mixed bacterial infection with the targeted bacteria at the site of infection were included in the study. Any patient with severe liver cirrhosis (Child-Pugh class C), having a recent partial hepatic donation, or currently undergoing or with a history of liver transplantation was excluded from the study. Written, informed consent was taken from all patients. Patients were allotted code numbers. Patients with odd code numbers were placed in Group A, while those with even code numbers were placed in Group B. Patients in Group A were treated with an intravenous Colistin (9 million IU) loading dose; after 12 hours, maintenance of 3 million IU was administered every eight hours. In addition, a high-dose intravenous Tigecycline (200 mg) loading dose was given. After 12 hours, a maintenance dose of 100 mg was given. Also, 8 g Cefoperazone/ Sulbactam (2 + 2) was given every six hours. Patients in Group B with an intravenous loading dose of Colistin (9 million IU), followed after 12 hours by a maintenance dose of 3 million IU every eight hours. Moreover, a 200 mg oral, loading dose of Minocycline was given, followed after 12 hours by 100 mg every 12 hours.

In addition, the patient's name, gender, and diagnosis was recorded. Vital signs were measured to record vasopressor requirements. The vital signs were recorded daily. The biochemical parameters recorded were white blood cell counts, CRP levels, serum procalcitonin levels, and serum lactate levels. These parameters were recorded every 48 hours till the 10th day. A successful clinical outcome was described as the resolution of signs and symptoms and improvement in the laboratory-based biochemical indicators. Microbial success was determined on a day-10 negative culture. If there was no improvement or the symptoms worsened

after 4-7 days of starting treatment, the case was considered therapeutic failure.

Data was entered and analyzed on SPSS v 26.0. Frequencies and percentages were described for categorical variables, such as gender and diagnosis. Mean and standard deviation were calculated for quantitative variables, such as the levels of the biochemical markers, age, and vital levels. Chi-squared test was applied to compare the microbial success. A p value of less than 0.05 was considered to be significant.

Results

A total of 38 patients were included in the study with 20 patients in Group A (triple-antibiotic regimen treatment group) and 18 in Group B (double-antibiotic regimen group). The mean age of the patients was 42.49 ± 19.60 years. There were 16 males and 21 females in the study. Age and gender were not reported for one patient. The age and gender of both groups has been shown in Table 1.

Table 1: Age and Gender of Both Groups (n = 37)

		Group A	Group B	Total	*P* Value
Age (Years)		44.10 ± 21.16	40.59 ± 18.06	42.49 ± 19.60	0.589
Gender	Male	9 (47.4%)	7 (38.9%)	16 (43.2%)	0.603
	Female	10 (52.6%)	11 (61.1%)	21 (56.8%)	

Table 2: Vitals and Laboratory-Based Biochemical Markers for Both Groups (n = 38; BP = Blood Pressure ; CRP = C-Reactive Protein)

	Group A	Group B	Total	*P* Value
Systolic BP (mm Hg)	105.40 ± 5.76	105.05 ± 9.74	105.23 ± 7.79	0.896
Diastolic BP (mm Hg)	59.37 ± 7.84	58.82 ± 6.71	59.11 ± 7.23	0.819
Heart Rate (/min)	114.23 ± 10.30	111.48 ± 15.88	112.89 ± 13.19	0.535
Temperature (°C)	37.35 ± 0.77	37.64 ± 0.38	37.49 ± 0.63	0.152
Vasopressor (Days)	7.5 ± 5.15	6.56 ± 5.04	7.05 ± 5.05	0.572
White Blood Cells (/μl)	15976.57 ± 7214.82	16174 ± 5421.46	16070.37 ± 6343.88	0.924
CRP (mg/L)	95.87 ± 74.48	98.61 ± 54.74	97.17 ± 65.02	0.897
Lactate (mg/dL)	34.03 ± 28.37	16.11 ± 15.63	25.31 ± 24.50	0.024
Procalcitonin (mg/mL)	61.33 ± 231.60	121.54 ± 331.93	89.85 ± 281.23	0.517
Positive Culture	4 (20%)	10 (55.6%)	24 (63.2%)	0.023

The vitals and biochemical markers for both groups have been illustrated in Table 2.

There was no significant difference in the vital indicators between the two groups. Similarly, no significant difference was observed for the lab-based biochemical markers between the two groups, except for serum lactate levels which were significantly greater for patients in Group A (p = 0.024). A significantly greater number of positive culture samples were found for Group B (n = 10, 55.6%), compared to Group A (n = 4, 20%; p = 0.023), suggesting improved antimicrobial efficacy of the triple regimen antibiotics.

A total of 32 (84.2%) patients were diagnosed with VAP, while six (15.8%) had bloodstream infections. There was no difference in the diagnosis distribution between the two groups (p = 0.184), as shown in Figure 1.

Discussion

The present study found that *Acinetobacter baumannii-caused* bacteremia was still present in 63.2% (n = 24) of patients in both groups after ten days of therapy (Table 2). The triple-antibiotic regimen (positive culture cases after 10 days = 4, 20%) was found to have significantly better antimicrobial efficacy in comparison to the double-antibiotic regimen (positive culture cases after 10 days = 10, 55.6%; p = 0.023). However, no difference

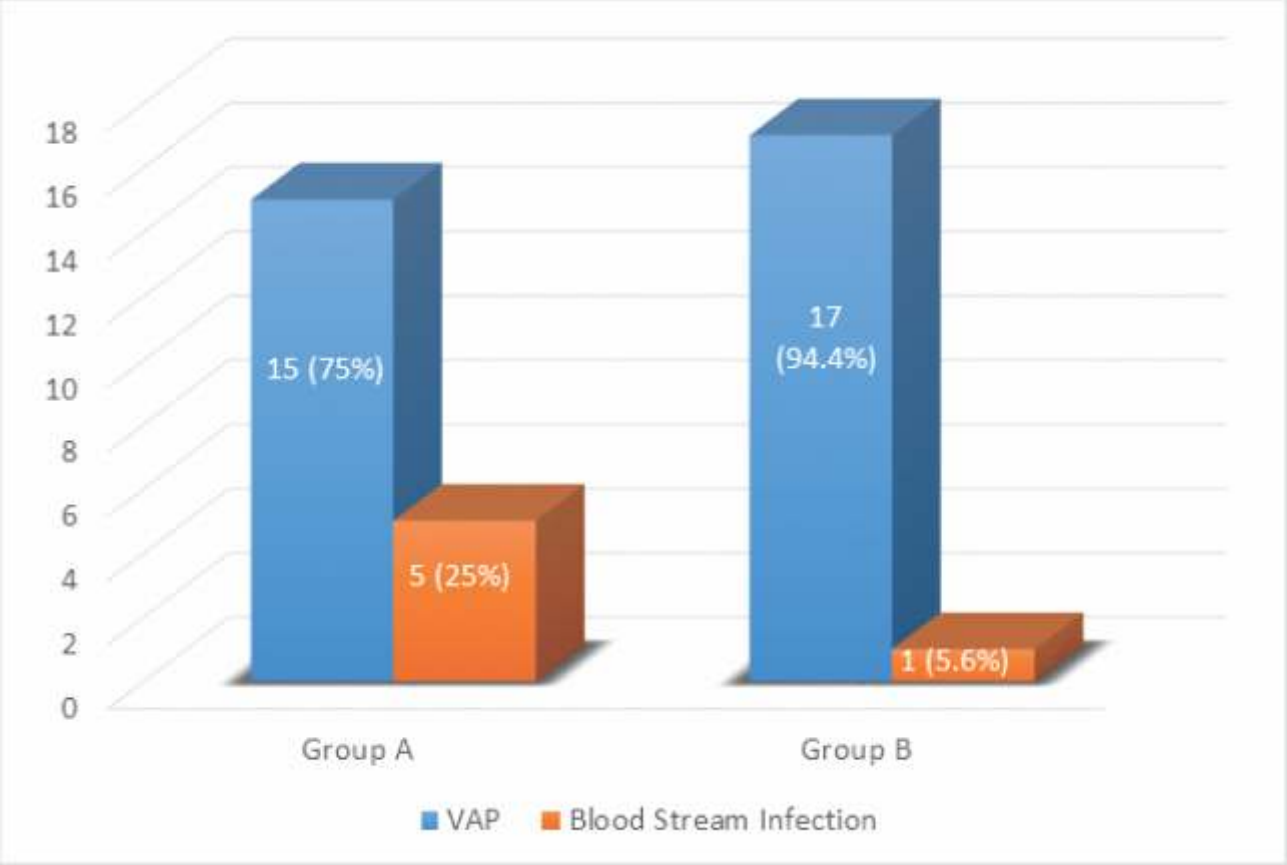

Fig 1: Frequency of VAP and Blood Stream Infections in Both Groups (n = 38)

in the clinical vital signs was found between the two groups. Paul et al. compared the efficacy of Colistin and Meropenem against Colistin alone in CRAB infections. A total of 406 patients were included in this randomized controlled trial (RCT). The study reported no difference in the efficacy of the two regimens.[18] Regimens using varying dosages have also been attempted in such cases. In a retrospective analysis, De Pascale et al. compared the efficacy of different dosages of Tigecycline in 100 treating CRAB-infected patients. Patients receiving high dosages of Tigecycline (200 mg loading loss, and 100 mg every 12 hours thereafter) were found to have better clinical efficacy against CRAB infections.[19] Jung et al. conducted a meta-analysis of 23 trials investigating the effectiveness of antibiotic regimens for treating severely ill pneumonia caused by CRAB. A total of 15 different regimens were compared in this analysis. The study found that Sulbactam had the highest efficacy in terms of reducing mortality. Fosfomycin and Colistin, high-dose Tigecycline, and Colistin have had the highest antimicrobial efficacy.[20]

In a multi-center trial investigating different regimens for treating CRAB-caused pneumonia, regimens including Minocycline were found to have the highest efficacy. Moreover, it was suggested that Colistin monotherapy does not have promising results in such cases.[17] ICU patients with Acinobacter colistin resistant infections have excessive mortality, and they often develop a fulminant form of sepsis that rapidly progresses to shock and eventually death.[21]

CRAB related infections have become an emerging problem at a global level. New antimicrobials such as Tazobactam have not been found to have significantly efficacious in managing these infections.[22] As a result, combination regimens are recommended in CRAB related infections.[23,24] Since the results of studies investigating the efficacy of CRAB infections are contradictory, this study set out to compare the efficacy of two different regimens.

Another notable feature in the patient population was the age of the selected participants.

A limitation of this study was the quasi-experimental

design. Also, a small sample of 38 was included due to limited resources. Also, age-wise comparisons were not made in this study. Future studies should adopt an RCT design, recruiting a larger sample size.

Conclusion

The triple-antibiotic regimen (Colistin, Cefoperazone /Sulbactam, and Tigecycline) was found to have significantly improved antimicrobial efficacy in comparison to the double-antibiotic regimen (Colistin and Minocycline). The triple-antibiotic regimen is recommended to be used in CRAB related pneumonia and bacteremia in intensive care patients.

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