Research Article

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Meropenem/colistin versus meropenem/ampicillin–sulbactam in the treatment of carbapenem-resistant pneumonia

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Aim: Efficacy of colistin and ampicillin–sulbactam have not been compared in treatment of ventilator-associated pneumonia due to *A. baumannii*. Efficacy of colistin and ampicillin–sulbactam in combination with meropenem were compared in treatment of ventilator-associated pneumonia due to carbapenem-resistant *A. baumannii*. **Method:** 47 patients with ventilator-associated pneumonia due to carbapenem-resistant *A. baumannii* were randomized to receive meropenem/colistin or meropenem/ampicillin–sulbactam for 14 days. Clinical and microbiological responses and 28-day mortality were considered as outcomes. **Results:** Clinical response (75 vs 69.6%; p = 0.75) and microbial eradication (87.50 vs 91.3%; p = 0.59) were comparable between meropenem/colistin and meropenem/ampicillin–sulbactam groups, respectively. **Conclusion:** In this study, clinical and microbiological response were comparable between the meropenem/colistin and meropenem/ampicillin–sulbactam groups.

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Keywords: *Acinetobacter* • ampicillin–sulbactam • colistin • pneumonia

Lower respiratory tract infection is among the leading causes of mortality among infectious diseases. Unfortunately, its incidence has been increasing significantly since 1984 [1,2]. Ventilator-associated pneumonia (VAP) is one of the lower respiratory tract infections that is associated with prolonged mechanical ventilation, hospitalization, increased mortality and cost [3]. Each VAP episode leads to an increase in additional hospital costs by more than USD$10,000 [2,4]. Based on Magill's study, more than 39% of healthcare-associated pneumonias are VAPs [5]. At least 50% of these cases emerge as a result of antibiotic-resistant isolates [6]. Incidence of VAP caused by multidrug-resistant (MDR) *A. baumannii* was reported to be between 1.9 and 18.3% per 1000 ventilator days. Considering geographical area, population, assessment tools, diagnostic criteria and history of previous antibiotic exposure are factors that influenced the incidence of VAP. The incidence of VAP was reported in 20–30% of critically ill Iranian patients [7,8].

Acinetobacter species are aerobic Gram-negative coccobacilli and one of the common causes of VAP (17%) [9]. According the National Health Safety Network report, *Acinetobacter* species are considered as the fifth pathogen known in creating VAP [10]. Based on the recent Centers for Disease Control and Prevention report, 2% of all healthcare-associated infections were related to *the Acinetobacter spp* [11].

Significant changes in the antimicrobial susceptibility pattern of these isolates have been detected during the last four decades. *Acinetobacter* isolates were described for first time in 1911. Antimicrobial resistance rate of these isolates are increasing [12]. At present, *Acinetobacter spp.* are resistant to the most broad spectrum of antibacterial

agents, even carbapenems [13]. The resistance rate to carbapenems increased from 9% in 1995 to 40% in 2004, and MDR isolates have been rapidly spreading in recent decades [9,14]. Approximately 63% of the *Acinetobacter* isolates are MDR pathogens [11].

Treatment of VAP due to resistant *Acinetobacter* species is a challenging issue as limited therapeutic options are available. Carbapenems, sulbactam, polymixins, aminoglycosides, tetracyclines and tigecycline were examined in some previous studies [9,15–17].

Following the introduction of new antibiotics and safety concerns, especially nephrotoxicity and neurotoxicity, systemic administration of polymixins was restricted for more than 60 years. However, colistin, as a member of polymixins group, is the only available option for the treatment of carbapenem-resistant *A. baumannii* [17].

Sulbactam is an irreversible inhibitor of β-lactamase, which has an intrinsic activity against *A. baumannii*. Sulbactam efficacy for the treatment of VAP was investigated in some studies [17–20].

The synergistic effects of carbapenems with other effective antibiotics have been reported in some studies for the treatment of carbapenem-resistanct *A. baumannii* infections [21]. The efficacy of colistin and ampicillin–sulbactam has not been compared in a head-to-head analysis in the treatment of VAP caused by *A. baumannii*. Therefore, the purpose of this study was to compare efficacy of colistin and ampicillin–sulbactam, in combination with meropenem in the treatment of VAP caused by carbapenem-resistant *A. baumannii* among critically ill patients.

Methods

Design

This open-label, randomized, clinical trial was conducted from October 2015 to October 2017 on critically patients admitted to the general intensive care unit (ICU) of Imam Khomeini hospital complex, Tehran, Iran. This study was registered in the Iranian Registry of Clinical Trials; a primary registry in the WHO registry network (registered code number: IRCT201509213449N19).

Ethical committee of Tehran University of Medical Sciences approved the study protocol (ethical code number: IR.TUMS.REC.1394.867).

Change in procalcitonin level following VAP treatment was considered for sample size calculation. Including $\alpha = 0.05$ and $\beta = 0.80$, 23 patients were recruited in each group.

Study variables

Adult patients (18–75 years old) diagnosed with VAP (pneumonic following at least 48 h of mechanical ventilation) were screened. Clinical status, laboratory parameters and radiographic results were used for the diagnosis of pneumonia. The presence of at least two of the following parameters was main criteria: fever (T >38°C) or hypothermia (T <35.5°C), leukocytosis (WBC >12000 cells/ml) or leukopenia (WBC <4000 cells/ml) and positive tracheal culture or new or progressive infiltration in chest x-ray [22].

Patients with a history of hypersensitivity reactions to ampicillin–sulbactam, colistin, meropenem and tracheal aspiration isolates other than *A. baumannii* were excluded from the study.

Microbiology laboratory procedure

Endotracheal aspirates were collected in aseptic conditions from the patients with suspected VAP for further microbiological evaluation based on the recommendations by the Clinical and Laboratory Standard Institute [23].

Antimicrobial disks, such as ampicillin/sulbactam (10/10 μg), piperacillin/tazobactam (100/10 μg), ceftriaxone (30 μg), meropenem (10 μg), gentamicin (10 μg), ciprofloxacin (5 μg) and trimethoprim-sulfamethoxazole (1.25/23.75 μg) were tested against *A. baumannii* isolates. Zone diameters that were considered to be resistant are: ≤11 mm for ampicillin sulbactam, ≤17 mm for piperacillin tazobactam, ≤8 mm for ceftriaxone, ≤14 mm for meropenem, ≤12 mm for gentamicin, ≤15 mm for ciprofloxacin and ≤10 mm for trimethoprim sulfamethoxazole [23].

Meropenem and colistin Minimum Inhibitory Concentration (MICs) were determined using the E-test method for *A. baumannii* isolates. E-test strips were obtained from the Liofilchem Company, Roseto Dgli Abruzzi, Italy. MIC ≥ 8 μg/dl and MIC ≥ 2 μg/dl were considered as the breakpoints, based on Clinical and Laboratory Standard Institute and European Committee on Antimicrobial Susceptibility Testing for meropenem and colistin resistance, respectively [23,24].

Therapeutic regimens

Using the simple randomization method via random number generator, 47 patients with VAP caused by carbapenem-resistant *A. baumannii* were assigned to receive either meropenem/colistin or meropenem/ampicillin–sulbactam. ampicillin–sulbactam and colistin were administered with a daily dose of 12/6 g (divided in 6 equal doses during a 1-h intravenous [iv.] infusion) and 9 million international units as loading dose and then daily (divided in 2 equal doses, during 1-h iv. infusion) respectively [25,26]. Both the groups also received meropenem 2 g three-times a day and each dose was administered during 4 h iv. infusion [27]. Doses of the antibiotics were adjusted according to the patients' renal function.

Demographic data

Demographic (sex, age and weight) and primary characteristics (baseline diseases, cause of hospital and ICU admission, history of antibiotic use and concomitant medications) were collected from each patient's medical chart. Clinical status, oxygenation and hemodynamic parameters of the patients were assessed daily during the 14 days of antibiotic therapy. To assess the response to these treatment regimens, clinical data, such as sequential organ failure assessment (SOFA) and Clinical pulmonary infection score, laboratory variables such as complete blood count, erythrocyte sedimentation rate, C-reactive protein, and serum procalcitonin and microbiological findings were used.

The culture of endotracheal samples for each patient were repeated at days 7 and 14. Follow-up of the patients was carried out for 28 days. Clinical and microbiological responses were considered as the primary outcome. Clinical response at the end of treatment course was classified either as a success or a failure. Complete resolution of the signs of VAP was defined as clinical success. The patient was categorized as a partial responder when at least two signs of VAP were resolved. Persistence or worsening of VAP signs was considered as clinical failure [28]. Microbiological response was categorized as eradication or persistent. Absence or presence of the pretreatment pathogen 1 or 2 weeks after VAP treatment was defined as eradication and persistence, respectively [16].

Incidence of acute kidney injury (AKI) was detected based on the KDIGO definition [29]. An increase of $\geq$0.3 mg/dl in serum creatinine within 48 h of therapy or 1.5-times increase in the baseline within 7 days or urine volume of less than 0.5 ml/kg/h for 6 h were all considered as AKI definitions.

The duration of hospitalization in the ICU and 28-day mortality were defined as the secondary outcomes of this study.

Statistical analysis

Statistical Package for Social Sciences (SPSS) 21.0 program was used for data analysis. Continuous and categorical variables were reported as mean $\pm$ standard deviation and numbers or percentages, respectively. The Mann–Whitney rank sum test was performed to compare the continuous data between the groups. Fisher's Chi-square tests were used for the assessment of clinical and microbiological responses. The time between treatment initiation to death or ICU discharge was defined as the survival time. Survival analysis was performed for the regimens with the help of the Kaplan–Meier test. A p-value of less than 0.05 was considered to be statistically significant.

Results

Out of the 891 patients who were admitted to the ICU, 125 (14.03%) developed VAP. Among them, 78 (62.4%) patients were not eligible for further evaluation. The consort flow diagram of the study has been depicted in Figure 1. Endotracheal aspirate samples were negative (culture-negative VAP) and positive (culture-positive VAP) in 38/125 (30.4%) and 87/125 (69.6%) of the patients, respectively. *A. baumannii* (47/125), *Klebsiella spp.* (22/125), *P. aueroginosa* (10/125), *Enterobacter spp.* (2/125), *E.coli* (2/125), *Staphylococcus. aureus* (2/125), *Staphylococcus. epidermidis* (1/125) and *Streptococcus spp.* (1/125) were the isolated pathogens in the culture-positive patients. All *A. baumannii* isolates were resistant to third-generation cephalosporins, fluoroqinolones, aminoglycosides, piperacillin-tazobactam and meropenem. According to the antibiotic susceptibility tests, all were carbapenem-resistant isolates. Resistance of the isolates toward meropenem was confirmed through the MIC test. All the isolates had meropenem MIC values $\geq$32 μg/ml. Colistin MIC values of *A. baumannii* isolates were between 0.25 and 2 μg/ml.

Demographic, laboratory and clinical characteristics of the patients have been shown in Table 1. Considering these variables, there was no significant difference between the groups. Also, baseline diseases and concomitant medications were similar between the groups (Table 2). Only baseline cardiovascular diseases were more common

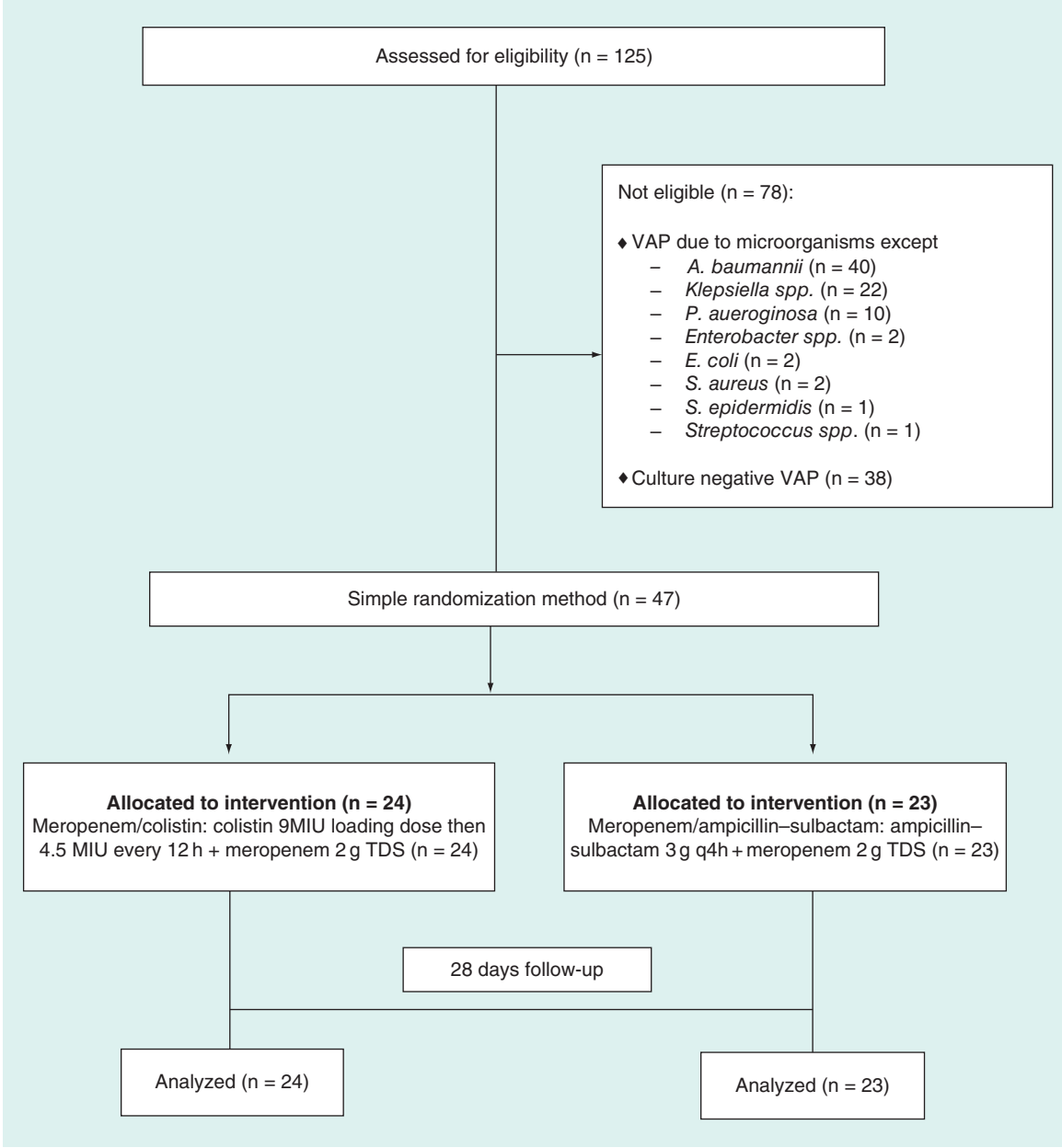

Figure 1. The CONSORT flow diagram of the study.
MIU: Million international units; TDS: Ter die sumendim (three times daily).

in meropenem/colistin as compared with the meropenem/ampicillin–sulbactam groups (p = 0.008). Based on regression analysis, cardiovascular diseases had no effect on primary and secondary outcome.

All the recruited patients had at least one risk factor for developing MDR VAP. Prior antibiotic use (89.36%) and at least 5 days of hospitalization before VAP (95.74%) were identified as risk factors.

Clinical pulmonary infection score and procalcitonin decreased significantly within both the groups at the end of treatment course as compared with the baseline values. However, the change was not very different intergroup. Although SOFA score decreased in both the groups, but the changes were not significant for both intergroup and intragroup. Serum C-reactive protein and erythrocyte sedimentation rate decreased significantly within the meropenem/ampicillin–sulbactam (p = 0.04) and meropenem/colistin groups (0.01), respectively. However, the intergroup changes were comparable (Table 3).

Table 1. Demographic, laboratory and clinical characteristics of patients.

Parameter	Meropenem/colistin group (n = 24)	Meropenem/ampicillin–sulbactam group (n = 23)	p-value
Age (mean ± SD)	60.63 ± 12/97	56.26 ± 11/50	0.44
Gender Male (%) Female (%)	 16/24 (66.7%) 8/24 (33.3%)	 19/23 (82.6%) 4/23 (17.4%)	0.32
Weight (kg)	70.63 ± 9.24	70.87 ± 10.19	0.93
Recent surgery (during past 30 days)	6/24 (25%)	7/23 (30.4%)	0.75
Previous antibiotic therapy (during past 30 days)	22/24 (91.7%)	20/23 (87%)	0.67
Charlson comorbidity score (median/ range)	4 (0–9)	3 (0–10)	0.52
Duration of hospital stay before ICU admission (median/range)	5.5 (0–45)	5 (0–60)	0.71
Duration of ICU stay before VAP diagnosis (median/range)	10 (2–51)	8 (2–27)	0.067
SOFA score (median/range)	5.5 (0–12)	6.5 (0–19)	0.21
Predicted mortality rate (%) (based on SOFA score)	39.13 ± 13.81	48.14 ± 23.68	0.19
CPIS score (median/range)	8.5 (6–11)	8 (5–11)	0.61
Procalcitonin (median/range)	1.22 (0.08–44.74)	0.75 (0.14–90.76)	0.66
CRP [mg/l] (mean ± SD)	72.39 ± 38.04	90.52 ± 43.97	0.16
ESR [mm/h] (mean ± SD)	67 ± 34.52	54.95 ± 35.43	0.27
WBC (mean ± SD)	15.76 ± 5.63	15.34 ± 10.58	0.87
HR [bpm] (median/range)	97 (69–148)	103 (57–135)	0.74
RR [bpm] (median/range)	22 (12–30)	22 (11–42)	0.10
MAP [mmHg] (mean ± SD)	87.75 ± 15.96	95 ± 20.3	0.18
Temperature [°C] (mean ± SD)	38.04 ± 1.17	37.65 ± 0.79	0.058

CPIS: Clinical pulmonary infection assessment; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ICU: Intensive care unit; MAP: Mean arterial pressure; RR: Respiratory rate; SD: Standard deviation; SOFA: Sequential organ failure assessment; VAP: Ventilator-associated pneumonia; WBC: White blood cells.

During the study period, AKI occurred in three and one patients in the meropenem/colistin and meropenem/ampicillin–sulbactam groups, respectively (p = 0.11).

Clinical improvement of pneumonia was achieved in 18/24 (75%) and 16/23 (69.6%) of patients in the meropenem/colistin and meropenem/ampicillin–sulbactam group, respectively (p = 0.75) (Table 4). During the antibiotic treatment course, cultures of endotracheal samples became negative in 5/24 (87.50%) and 5/23 (91.30%) of patients in the meropenem/colistin and meropenem/ampicillin–sulbactam groups, respectively (p = 0.59).

The 28-day mortality (Table 5) was not different between the meropenem/colistin and meropenem/ampicillin–sulbactam groups (10/24 [41.67%] and 9/23 [39.13%], p >0.99). No significant difference in mortality was found between the groups in the survival analysis (p = 0.78) during hospitalization at the ICU (Figure 2).

Discussion

In this pilot, randomized, clinical trial, the meropenem/colistin and meropenem/ampicillin–sulbactam groups showed similar efficacy and renal safety in critically ill patients with VAP caused by carbapenem-resistant *A. baumannii*. Clinical and microbiological responses, episodes of AKI, duration of ICU hospitalization and 28-day mortality were comparable among the groups.

Based on a large multicenter study in VAP patients, *Klebsiella species* was the most common isolate, followed by *P. aeroginosa* or *A. baumannii* pathogens [30,31]. During the years 2003–2008, the incidence rate of carbapenem-resistant *A. baumannii* increased 57% in the USA hospitals. ampicillin–sulbactam also showed same change in its antimicrobial susceptibility pattern [32]. In Iran, more than 70% of *A. baumannii* isolates were carbapenem-resistant [33]. In this study, all of the *A. baumannii* isolates were resistant to carbapenem. In a recent paper with published data from 348 hospitals of diverse geographical areas in USA, the prevalence of MDR *A. bauamnnii* isolates was reported as 36.3%. Most of the MDR *A. baumannii* was detected in midwest (44.4%), followed by west (42.5%), northeast (40.5%) and south (29.5%) [34]. The prevalence of colistin-resistant *A. baumannii* was reported as ranging from 0 to 40.6% over the world. The highest values were attributed to Asian and European

Table 2. Baseline diseases and concurrent medications of patients.

Parameter	Meropenem/colistin group (n = 24)	Meropenem/ampicillin–sulbactam group (n = 23)	p-value
Baseline diseases			
Cardiovascular diseases	15/24 (62.5%)	5/23 (21.7%)	0.008
Respiratory diseases	6/24 (25%)	2/23 (8.7%)	0.24
CVA	4/24 (16.7%)	2/23 (8.7%)	0.67
Neurological diseases	3/24 (12.5%)	2/23 (8.7%)	> 0.99
Solid tumors	2/24 (8.3%)	6/23 (26.1%)	0.14
Genetic disorders	2/24 (8.3%)	1/23 (4.3%)	> 0.99
IV drug user	2/24 (8.3%)	1/23 (4.3%)	> 0.99
Thyroid disorders	1/24 (4.2%)	–	> 0.99
Diabetes mellitus	9/24 (37.5%)	4/23 (17.4%)	0.19
Rheumatologic disorders	–	1/23 (4.3%)	0.49
Hematologic disorders	1/24 (4.2%)	1/23 (4.3%)	> 0.99
Genitourinary problems	2/24 (8.3%)	–	0.49
CKD	1/24 (4.2%)	1/23 (4.3%)	> 0.99
Gasterointestinal diseases	–	1/23 (4.3%)	0.49
Psychiatric problems	1/24 (4.2%)	–	> 0.99
Concurrent medications			
Vancomycin	10/24 (41.7%)	7/23 (30.4%)	0.55
Caspofungin	3/24 (12.5%)	3/23 (13%)	>0.99
Linezolide	1/24 (4.2%)	–	>0.99
Vasopressor	11/24 (45.8%)	9/23 (39.1%)	0.77
NAC	2/24 (8.3%)	2/23 (8.7%)	>0.99
Atorvastatin	8/24 (33.3%)	5/23 (21.7%)	0.52
Corticosteroid	5/24 (20.8%)	3/23 (13%)	0.7
Immunosuppresants	1/24 (4.2%)	–	>0.99

CKD: Chronic kidney disease; CVA: Cerebrovascular accident; IV: Intravenous; NAC: N-acetyl-L-cysteine.

Table 3. Mean difference in sequential organ failure assessment and clinical pulmonary infection scores, inflammatory biomarkers at baseline and the end of treatment within either colistin or ampicillin–sulbactam group and also between the groups.

Parameter	Baseline vs week 4
SOFA score	
Mean (95% CI) difference value within meropenem/colistin group [p-value]	0.15 (-0.18 to 1.11) [0.74]
Mean (95% CI) difference value within meropenem/ampicillin–sulbactam group [p-value]	0.83 (-1.31 to 2.98) [0.41]
Mean (95% CI) difference value between meropenem/colistin and Meropenem/ampicillin–sulbactam groups [p-value]	1.51 (-4.15 to 1.12) [0.24]
CPIS	
Mean (95% CI) difference value within meropenem/colistin group [p-value]	3.76 (3.07 to 4.45) [<0.001]
Mean (95% CI) difference value within meropenem/ampicillin–sulbactam group [p-value]	3.68 (2.59 to 4.78) [<0.001]
Mean (95% CI) difference value between meropenem/colistin and meropenem/ampicillin–sulbactam groups [p-value]	0.26 (-0.72 to 1.25) [0.59]
Procalcitonin	
Mean (95% CI) difference value within meropenem/colistin group [p-value]	3.72 (-5.06 to 12.46) [0.008]
Mean (95% CI) difference value within meropenem/ampicillin–sulbactam group [p-value]	7.29 (-4.27 to 18.86) [0.03]
Mean (95% CI) difference value between meropenem/colistin and meropenem/ampicillin–sulbactam groups [p-value]	-1.55 (-11.35 to 8.23) [0.74]
ESR	
Mean (95% CI) difference value within meropenem/colistin group [p-value]	23.13 (5.20 to 41.07) [0.01]
Mean (95% CI) difference value within meropenem/ampicillin–sulbactam group [p-value]	3.80 (-9.84 to 17.44) [0.56]
Mean (95% CI) difference value between meropenem/colistin and meropenem/ampicillin–sulbactam groups [p-value]	7.42 (-13.33 to 27.81) [0.47]
CRP	
Mean (95% CI) difference value within meropenem/colistin group [p-value]	2.21 (-21.99 to 26.43) [0.85]
Mean (95% CI) difference value within meropenem/ampicillin–sulbactam group [p-value]	33.20 (2.13 to 64.27) [0.04]
Mean (95% CI) difference value between meropenem/colistin and meropenem/ampicillin–sulbactam groups [p-value]	-4.55 (-22.52 to 13.41) [0.61]

CI: Confidence interval; CPIS: Clinical pulmonary infection score; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SOFA: Sequential organ failure assessment.

Table 4. Clinical response and 28-day mortality of recruited patients.

Type of regimen	Clinical response			28-day mortality		
	Improvement	Failure	p-value	Yes	No	p-value
Meropenem/colistin (n = 24)	18/24 (75%)	6/24 (25%)	0.75	10/24 (41.67%)	14/24 (58.33%)	0.99
Meropenem/ampicillin–sulbactam (n = 23)	16/23 (69.6%)	7/23 (30.4%)		9/23 (39.13%)	14/23 (60.87%)	

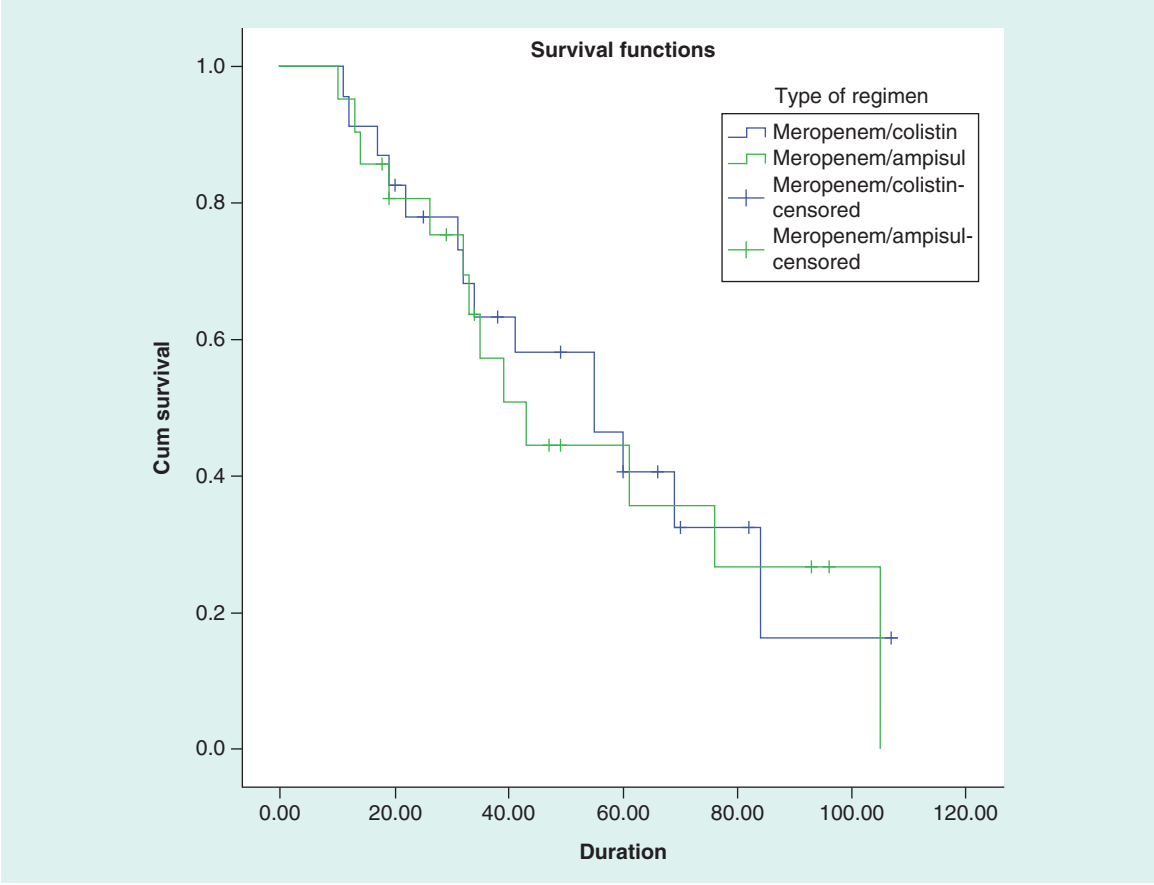

Figure 2. Kaplan–Meier curve for survival analysis of patients in both meropenem/colistin and meropenem ampicillin–sulbactam regimens during of ICU stay (log Rank [Mantel–Cox]: 0.78).

countries [35–37]. According to the results of the E-test method in this study, the rate of colistin resistance in *A. baumannii* isolates was about 2%.

There are limited therapeutic options for the treatment of VAP caused by carbapenem-resistant *A. baumannii*. Although carbapenem-resistant isolates are increasing, however carbapenem-heteroresistant should be considered. Heteroresistant isolates are genetically homogenous microorganisms but have different antimicrobial susceptibility pattern. Synergistic effects of a carbapenem with other antimicrobial agents are proposed for carbapenem-resistant isolates [38–40].

In a prospective cohort study in Greece, the efficacy and safety of sulbactam and colistin as monotherapy were found to be comparable for the treatment of MDR *A. baumannii*-associated VAP in a population of debilitated patients. The clinical response rate of sulbactam and colistin was similar in our study with others [41].

Colistin caused renal injury was detected in 0–57% of the recipients [42]. Patient features, such as age, obesity, comorbidities, concomitant nephrotoxic medications, serum concentration and dose of colistin, were defined as important risk factors for the development of colistin-induced nephrotoxicity [43]. In this study, all the patients with AKI during the colistin therapy were old-age individuals and received vancomycin concomitantly with colistin.

Unfortunately, colistin-resistant Gram-negative pathogens have emerged following the overuse of this antibiotic during the recent years. The increasing resistance to colistin is a serious threat around the word. In an era of colistin resistance, inhaled antibiotics may be the last viable option for the treatment of severe pneumonia. The efficacy of different antimicrobial agents, such as colistin and aminoglycosides, as inhalation therapy was assessed for the treatment of VAP. Combination regimens consisting of a systemic or nebulized aminoglycosides were reviewed. Nebulized aminoglycoside is recommended due to its better penetration and lesser toxicity [44].

Increased rate of treatment failure and mortality due to MDR infections is a global issue. The estimation of the directly attributed mortality of these infections is difficult. Patient comorbidities (malignancies, renal and liver disorders, genetic and neurological problems), delay in start of effective antibiotic regimens, inappropriate selection of antimicrobial regimens, septic shock, resistant pathogens, concurrent infections, previous antibiotic and corticosteroid therapies, high APACHEII and SOFA scores were significant risk factors of mortality in patients with MDR *A. baumannii*-associated VAP [7,45–47].

In this study, the 28-day all-cause mortality was similar to previous studies. Global mortality related to VAP was reported in the range of 20–50% of critically ill patients. However, in a large meta-analysis, the direct attributable mortality of VAP was reported as 13% [48].

The mortality rates of MDR *A. baumannii*-associated pneumonia were estimated as 7.8–23 and 10–43% in patients who were hospitalized in the wards and the ICU, respectively [18,48].

The efficacy and the safety of colistin and high-dose ampicillin/sulbactam were comparable in the treatment of VAP caused by MDR *A. baumannii* in critically ill patients [41]. However, in a retrospective comparison study, higher microbiological failure and mortality were detected in the colistin group in comparison with the ampicillin–sulbactam group [49].

Ampicillin–sulbactam may be as a suitable alternative for colistin in the treatment of VAP caused by carbapenem-resistant *A. baumannii* in critically ill patients. However, the limitations of this study should also be considered. This was a pilot, single-center, randomized, clinical trial without a considerable sample size. Sulbactam is not commercially available in Iran and, therefore, ampicillin–sulbactam was used instead of sulbactam. The main activity of ampicillin–sulbactam against *A. baumannii* is attributed to the sulbactam component. The ampicillin moiety of this compound may restrict the dose of ampicillin–sulbactam in clinical practice. Efficacy and safety of different doses of sulbactam may be examined in well-designed, randomized, clinical trials for the treatment of VAP, resulting from carbapenem-resistant pathogens. Increasing incidence rate of infections due to MDR producing carbapenemase Gram-negative pathogens especially *A. baumannii* should be in mind when an empirical antibiotic regimen for empiric therapy of VAP is selected. Availability and cost are other deterring factors in selecting an appropriate antibiotic especially in developing countries. As discussed earlier, colistin is not an ideal antibiotic due to its limitations.

Conclusion

In this study clinical and microbiological response, duration of intensive care unit stay and 28-day mortality were compared between the meropenem/colistin and meropenem/ampicillin–sulbactam in critically ill patients with pneumonia due to *A. baumannii*. Sulbabtam (or ampicillin–sulbactam) may be a potential option for treatment of infections due to carbapenem-resistant *A. baumannii*. Therefore, further clinical trials are needed for the conclusion.

Future perspective

Treatment of infections due to Gram-negative pathogens especially *A. baumannii* is a challenging issue. Introducing appropriate antibiotic regimens for treatment of these infections should be considered in future well-designed multicenter studies with adequate sample sizes.

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Summary points

Aim

- Sulbactam efficacy for the treatment of ventilator-associated pneumonia (VAP) was investigated in some studies.
- The efficacy of colistin and ampicillin–sulbactam has not been compared in the treatment of VAP caused by *A. baumannii*.

Methods

- 47 patients with VAP caused by carbapenem-resistant *A. baumannii* were assigned to receive either meropenem/colistin or meropenem/ampicillin–sulbactam. Clinical response at the end of treatment course was classified either as a success or a failure. Microbiological response was categorized as eradication or persistent.

Results

- Clinical improvement of pneumonia was achieved in 75 and 69.6% of patients in the meropenem/colistin and meropenem/ampicillin–sulbactam group, respectively. During the antibiotic treatment course, cultures of endotracheal samples became negative in 87.50 and 91.30% of patients in the meropenem/colistin and meropenem/ampicillin–sulbactam groups, respectively.

Conclusion

- Sulbabtam (or ampicillin–sulbactam) may be a potential option for treatment of infections due to carbapenem-resistant *A. baumannii*.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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