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Original Article

Colistin alone or combined with sulbactam or carbapenem against *A. baumannii* in ventilator-associated pneumonia

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Abstract

Introduction: Colistin use has increased over the last ten years because of multidrug-resistant microorganisms. The aim of this study was to compare the clinical and microbiological efficacy of colistin alone or in combination with sulbactam or carbapenem in the treatment of ventilator-associated pneumonia (VAP) due to multidrug-resistant (MDR) and extremely drug-resistant (XDR) *A. baumannii*.

Methodology: Cases treated for VAP because of MDR and XDR *A. baumannii* between January 2011 and January 2013 were included in the study. The primary and secondary outcome for colistin alone, colistin with sulbactam, and colistin with carbapenems were evaluated. The primary outcomes were clinical efficacy and microbiological efficacy; the secondary outcomes were nephrotoxicity, length of hospitalization, and mortality.

Results: A total of 70 VAP patients were evaluated. A total of 17 patients (24.3%) were administered colistin alone, 20 patients (28.6%) were administered colistin and sulbactam, and 33 patients (47.1%) were administered colistin and carbapenem. Clinical and microbiological response rates were higher in the carbapenem combination group (63.6% and 63.6% in both) than in the sulbactam combination group, which registered 55.0% and 60.0%, respectively. However, this did not represent a significant difference statistically ($p > 0.05$). There was also no significant difference between colistin alone and the combination groups regarding clinical and microbiological efficacy and mortality.

Conclusions: Neither the administration of colistin alone nor colistin combined with either sulbactam or carbapenem had any noticeable advantage in the treatment of VAP in terms of clinical response, microbiological response, nephrotoxicity, length of hospitalization, and mortality.

Key words: colistin; combined antibiotics; *A. baumannii*; ventilator-associated pneumonia.

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Introduction

The recent increase in the prevalence of antibiotic-resistant *A. baumannii* and the growing problem of resistance to carbapenem has created the need for alternative antibiotics [1]. Polymyxins that were used only briefly in the 1960s because of their high toxicity have taken on a life-saving role for the treatment of multidrug-reistant (MDR) and extremely drug-resistant (XDR) *A. baumannii* infections.

The mortality rate was reported to be between 20% and 70% in ventilator-associated pneumonia (VAP) [2-4]. Treatment often consists of using colistin with another antibiotic belonging to another group without taking the antibiotic resistance pattern into consideration. Antimicrobials used frequently with colistin include imipenem/meropenem, sulbactam, and rifampicin, in order to obtain synergistic effects [1,5]. The main reason for the combination therapy is to prevent the selection of heteroresistant strains [5-7]. There are a limited number of studies about the clinical effect and prognosis of combination therapy. The aim of this study was to investigate the effect of antibiotics combined with colistin for the treatment of patients diagnosed with VAP on clinical response, microbiological response, nephrotoxicity, length of hospitalization, and mortality.

Methodology

Study design and setting

A retrospective observational study was performed using data from Yildirim Beyazit University, Ankara Ataturk Training and Research Hospital, which had 600 beds.

Study population

Patients hospitalized in intensive care units (ICUs) are followed daily by an infectious disease and clinical microbiology assistant and specialist. The data is recorded in a specific file for the infectious disease department and evaluated retrospectively. Patients diagnosed with VAP due to multi-drug resistant (MDR) or extremely drug resistant (XDR) *A. baumanni* and who received colistin treatment between January 2011 and January 2013 were included in the study. Patients who received treatment for less than 48 hours and patients who died within 48 hours were excluded. Demographic specifications, antibiotics, treatment duration, clinical and microbiological response, nephrotoxicity, length of hospitalization, and mortality were recorded. If a patient experienced more than one VAP episode, only the first episode was included. Simplified Acute Physiology Score 2 (SAPS 2) was used to measure illness severity, as it is used routinely in ICUs.

Diagnosis

National Healthcare Safety Network (NHSN) criteria were used in the diagnosis of VAP.

Pneumonia was considered to be ventilator-associated if the onset occurred after the patient was intubated and ventilated for ≥ 48 hours [8-10].

1. X-ray findings

The patient with an underlying disease has two or more serial X-rays to ascertain the existence of any of the following:

a. New or progressive and persistent infiltrate
b. Consolidation
c. Cavitation

and

2. Signs and symptoms

At least one of the following:

a. Body temperature > 38°C or < 35.5°C with no other cause
b. Leukopenia (< 4,000 white blood cells [WBCs]/mm^3) or leukocytosis (> 12,000 WBC/mm^3)

and

At least one of the following:

a. New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
b. New onset or worsening cough, or dyspnea, or tachypnea
c. Rales or bronchial breath sounds
d. Worsening gas exchange (*e.g.*, O_2desats PaO_2/FiO_2> 240, increased O_2 requirement, or increased ventilation demand;

and at least one of the following:

a. Positive blood culture not related to another infection
b. Positive pleural fluid culture
c. Positive quantitative culture from low respiratory tract specimens (*e.g.*, bronchial secretions [≥ 10^5], bronchoalveolar lavage [BAL] [≥ 10^4], or protected specimen brushing [≥10^3])
d. Five or more BAL-obtained cells containing intracellular bacteria on direct microscopic examination
e. Histopathological examination showing either abscess formation, foci of consolidation with intense polymorphonuclear accumulation in bronchioles and alveoli, or evidence of lung parenchyma invasion by fungal hyphae or pseudohyphae

The updated pneumonia criteria were not used because they are not yet used by the Turkey National Nosocomial Infection System. If a patient has pneumonia and a resulting positive blood culture, the diagnosis of the patient is accepted as VAP.

Identification of microorganisms

Routine microbiological methods were used in the identification of *A. baumannii*. Sensitivity tests were performed using the agar disk diffusion test and VITEK automated microbiology system. The recommended susceptibility testing methods and interpretation criteria of the Clinical and Laboratory Standards Institute (CLSI) were used, except for colistin [11]. Colistin susceptibility was performed with 10 µg colistin disks, and isolates were considered susceptible to colistin if inhibition zones were ≥ 11 mm, as recommended by the CLSI for *Pseudomonas aeruginosa*. Intermediate susceptible isolates were included in the resistant group. Resistant isolates were confirmed with the E-test method. The minimum inhibitory concentration of colistin was interpreted according to CLSI breakpoints [11].

Microorganisms were defined as MDR if they were non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial categories, and as XDR if they were resistant to carbapenems and to all other antimicrobial drug classes, except colistin [12,13].

Treatment with colistin and other antibiotics

Colistincolistimethate sodium (100 mg colistin base, colomycine) was administered either 75 mg three times per day or 150 mg IV twice per day. The dose was adjusted for patients with renal impairment. Other antibiotics that were used together with colistin were imipenem 500 mg IV four times per day, meropenem 1 g IV three times per day, and sulbactam 1 g IV three times per day. Meropenem was applied as prolonged infusion to obtain optimal efficacy. Dosages were adjusted for patients with renal impairment according to the Sanford Guide.

Primary and secondary outcomes

Clinical and microbiological responses were evaluated as primary outcomes. Nephrotoxicity, length of hospitalization, and crude mortality were evaluated as secondary outcomes. Normalization of body temperature, leukocytosis/leukopenia returning to normal, a decrease in secretions, and improvement or no deterioration in chest X-ray findings were all defined as clinical response [14]. Patients whose signs and symptoms continued or worsened were considered non-responders. Patients whose fever and leukocytosis levels decreased, but whose other signs and symptoms continued, were also included in the non-responder group. Clinical response was evaluated at the end of the therapy. Microbiological response was defined as no bacterial growth from site-specific cultures at the end of the colistin therapy. Because of the speculations that colistin has no effect on lung infection, surveillance cultures were routinely recommended by the infectious diseases consultant during his daily visit to the intensive care unit (ICU). Mortality was recorded on the 28th day of colistin therapy.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) version 11.5 software program. The Chi-square test was performed to compare categorical variables. Continuous variables were analyzed using Student's *t*-test or the Mann-Whitney U test. The statistical significance was set as $p < 0.05$. Multivariate analysis was performed for the variables that were found to have significant differences for mortality in univariate analysis. Survival analysis was also performed by log-rank test of Kaplan Meier analysis.

Results

Of 70 patients diagnosed with VAP, 41 were due to MDR and 29 were due to XDR *A. baumannii.*A total of 70 *A. baumannii* isolates were resistant to imipenem and meropenem. Only five isolates were evaluated for doripenem susceptibility, and all of them were resistant. Only two isolates were susceptible to sulbactam, and all the isolates were susceptible to colistin. The antimicrobial susceptibility profiles of *A. baumannii* according to treatment groups are shown in Table 1.

All these patients were receiving colistin treatment. In addition to colistin, 33 out of 70 cases (47.1%) received imipenem or meropenem, and 20 cases received sulbactam (28.6%). Colistin was used alone in 17 cases (24.3%). When all the groups were compared, there was no statistical difference in demographic specifications, primary diagnosis, presence of a comorbid condition, resistance profile, SAPS 2, duration of stay in hospital, or treatment duration (Table 2).

Table 1. Antimicrobial susceptibility profiles of *A. baumannii* isolates according to treatment groups

	None (n = 17) (%)	Carbapenem (n = 33) (%)	Sulbactam (n = 20) (%)
Imipenem (n = 70)	0	0	0
Meropenem (n = 67)	0	0	0
Colistin (n = 70)	100	100	100
Sulbactam (n = 66)	1/15 (6.7%)	1/15 (6.7%)	1/15 (6.7%)
Gentamicin (n = 70)	5/17 (29.4%)	2/33 (6.1%)	4/20 (20.0%)
Amikacin (n = 69)	2/16 (12.5%)	2/33 (6.1%)	3/20 (15.0%)
Tobramycin (n = 67)	5/15 (33.3%)	8/32 (47.8%)	9/20 (29.9%)
Netilmicin (n = 56)	5/13 (38.5%)	9/26 (34.6%)	9/12 (52.9%)
Trimethoprim/sulfamethoxazole (n = 67)	5/16 (31.2%)	9/31 (29.0%)	3/20 (15.0%)

Table 2. Demographic characteristics, admission diagnosis, comorbidity, and other characteristics of the patients receiving colistin therapy

Characteristics	None (n = 17) (%)	Carbapenem (n = 33) (%)	Sulbactam (n = 20) (%)	P
Gender				**> 0.05**
Male	7 (41.2)	16 (48.5)	10 (50)	
Female	10 (58.8)	17 (51.5)	10 (50)	
Admission diagnosis[1]				> 0.05
Cerebral infarct or hemorrhage and other CNS pathologies	4 (23.6)	10 (30.3)	7 (3.5)	> 0.05
Trauma	7 (41.2)	8 (24.2)	1 (5.0)	> 0.05
COPD	0 (0)	2 (6.1)	1 (5.0)	> 0.05
Malignancy	0 (0)	1 (2.3)	1 (5.0)	> 0.05
Pneumonia	2 (11.8)	1 (3.0)	2 (10.0)	> 0.05
GIS disorder	0 (0)	2 (6.1)	0 (0.0)	> 0.05
Prosthetic joint infection	0 (0)	1 (3.0)	2 (10.0)	> 0.05
Acute renal failure	2 (11.8)	2 (6.1)	2 (10.0)	> 0.05
Others[2]	2 (11.8)	6 (18.2)	3 (15.0)	> 0.05
Comorbidity[3]				> 0.05
Diabetes mellitus	6 (35.3)	5 (15.2)	8 (40)	> 0.05
Chronic renal failure	2 (11.8)	5 (15.2)	5 (25.0)	> 0.05
COPD	3 (17.6)	7 (21.2)	5 (25.0)	> 0.05
Malignancy	2 (11.8)	2 (6.1)	2 (10.0)	> 0.05
Heart failure	2 (11.8)	4 (12.1)	4 (20.0)	> 0.05
Immunosupression	0 (0)	2 (6.1)	1 (5.0)	> 0.05
Treatment change	2 (11.8)	4 (12.1)	0 (0.0)	> 0.05
Colistin dosage				> 0.05
3 × 75	10 (58.8)	16 (48.5)	9 (45.0)	
2 ×150	3 (17.6)	6 (18.2)	2 (10.0)	
Resistance profiles				
XDR	6 (35.3)	17 (51.5)	6 (30.0)	> 0.05
MDR	11 (64.7)	16 (48.5)	14 (70)	> 0.05
SAPS2 (mean)	43.8 ± 12.1	50.7 ± 12.9	51.0 ± 9.8	0.22
Age (mean)	59.8 ± 21.5	59.6 ± 20.5	70.6 ± 14.7	0.14
Duration of hospital stay before VAP (median, minimum-maximum)	16 (4–143)	16 (5–61)	19 (7–95)	0.60
Duration of treatment (mean)	12.3 ± 3.2	11.7 ± 5.6	10.8 ± 4.2	0.64
Time from diagnosis to antibiotic initiation	2.6 ± 1.5	3.3 ± 2.1	3.2 ± 2.6	> 0.05

[1]Each admission diagnosis was compared against other treatment groups; [2]Other admission diagnosis were myocardial infarction, anemia, coronary artery disorder, postpartum cardiopulmonary arrest, status epilepticus, hypertansion, electric schock, femur fracture, non-Hodgkin lenfoma, mesenteric ischemia (2 patients); [3]Each comorbidity group was compared against other comorbidity groups; COPD: chronic obstructive pulmonary disease; XDR: extensively drug resistant; MDR: multidrug resistant

Table 3. Clinical and microbiological response and mortality according to the combined antimicrobial agent

	None (n = 17) (%)	Carbapenem (n = 33) (%)	Sulbactam (n = 20) (%)	P[1]
Clinical response	13 (76.5)	21 (63.6)	11 (55.0)	0.35; 0.53
Microbiological Response	9 (52.9)	21 (63.6)	12 (60.0)	0.23; 0.16
General mortality on 28th day	7 (41.2)	16 (48.5)	14 (70.0)	0.53; 0.21
Nephrotoxicity	3/17 (17.6)	4/33 (12.1)	2/20 (10.0)	0.37; 0.08

[1]The first p value represents colistin alone compared with colistin carbapenem combination and colistin sulbactam combination, and the second p value represents a colistin and carbapenem combination compared with a colistin and sulbactam combination.

Table 4. Risk factors for mortality in univariate analysis

Factor	Survived (n = 33) (%)	Died (n = 37) (%)	P
Gender			0.48
Male	17 (51.5)	16 (43.2)	
Female	16 (48.5)	21 (56.8)	
Comorbidity			
Diabetes mellitus	4 (12.1)	15 (40.5)	0.016
Chronic renal failure	4 (12.1)	8 (21.6)	0.28
COPD	3 (9.1)	12 (32.4)	0.037
Malignancy	2 (6.1)	4 (10.8)	0.47
Heart failure	3 (9.1)	7 (18.9)	0.24
Immunosupression	0 (0)	3 (8.1)	0.09
Colistin alone	10 (30.3)	7 (18.9)	0.41[1]
Combined with carbapenem	17 (51.5)	16 (43.2)	0,48[1]
Combined with sulbactam	6 (18.2)	14 (37.8)	0.06[1]
Clinical response	32 (97.0)	13 (35.1)	0.000
Microbiological response	24 (72.7)	18 (48.6)	0.062
SAPS2 (mean)	43.2 ± 9.8	54.3 ± 11.7	0.000
Age (mean)	54.0 ± 21.8	70.6 ± 13.6	0.000
Duration of hospital stay before VAP (mean)	21.6 ± 10.6	28.7 ± 24.9	0.29
Duration of treatment (mean)	13.9 ± 4.9	9.5 ± 3.6	0.000

[1]Each treatment group was compared against other treatment groups; COPD: chronic obstructive pulmonary disease

Table 5. Risk factors for mortality in multivariate analysis

Factor	P	OR	95% CI
Diabetes mellitus	0.008	7.1	0.017–0.63
COPD	0.043	4.0	0.02–1.05
Clinical response	0.000	20.3	5.7–852.9

COPD: chronicobstructive pulmonary disease

It was found that clinical and microbiological response was better in the groups that received colistin alone and a combination of carbapenem and colistin when compared with the group that received sulbactam and colistin. Mortality rates were also found to be lower in these groups. However, there was no statistical difference between each group (Table 3).

There was no difference between the two groups according to the colistin dosage as 3 × 75 mg IV and 2 × 150 mg IV in terms of clinical response and microbiological response (62.9% vs. 81.8%, p = 0.22; 50% vs. 50%, p = 0.73, respectively).

There was no difference in clinical response between the patients infected with MDR vs. XDR (58.5% vs. 71.4%, respectively; p = 0.40). Survival rates and mean survival times were not significantly different statistically for the three treatment groups (Table 3 and Figure 1).

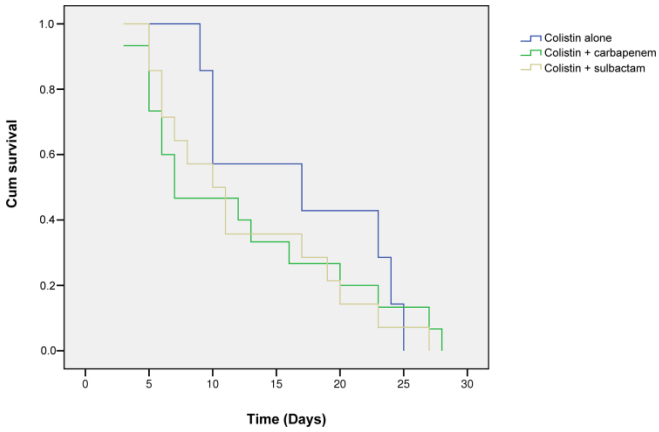
Mortality risk factors were also evaluated by univariate and multivariate analysis (Tables 4 and 5). Diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and clinical response were found to be independent risk factors for mortality in multivariate analysis (Table 5).

No resistance to colistin was registered in patients receiving combined treatments using colistin with sulbactam or carbapenem. In the case of one patient receiving treatment with colistin alone, *A. baumannii* became resistant to colistin.

Discussion

Greatly increased rates of resistance to carbapenem have been reported worldwide, including in Turkey. A multicenter study, including 43 centers in North America, 30 centers in 14 different European countries including Israel and Turkey, 10 centers in 4 different countries in Latin America, and 74 centers in 12 different countries in Asia-Pacific region, has been recently published. Rates of resistance to imipenem and colistin were reported to be 40.3% and 0.9%, respectively in this study, which included 4,686 *Acinetobacter* spp. that were isolated between 2006 and 2009. When the regions were evaluated separately, resistance to imipenem increased to 54.9% in 2011 from 35.3% in 2006 for the 14 European countries, including Israel and Turkey [15]. In a study performed in Turkey by Guven *et al*., the imipenem-resistance rate was detected to be 54% in 2008 and 98.9% in 2011 for *A. baumannii*. The meropenem-resistance rate was detected to be 78.5% and 98.5% in the same years [16].

Figure 1. Kaplan-Meier survival analysis for death at 28 days after colistin therapy.Comparison between treatment regimens by log-rank test: 1) Colistin alone vs. colistin-carbapenem, p = 0.44; 2) Colistin alone vs. colistin-sulbactam, p = 0.27; 3) Colistin-sulbactam vs. colistin-carbapenem, p = 0.84.



Over the last 15 years, colistin has been used for the treatment of VAP caused by resistant *A. baumannii*. The clinical cure rate of VAP patients receiving colistin alone or combined with other antibiotics has been reported to be highly variable, between 15% and 85.7% [17-22]. In our study, the rate was found to be 64.2%.

It is now known that colistin heteroresistant strains are present among *Acinetobacter* isolates [6,7]. The rate of heteroresistance has been reported to be statistically significant among patients who had received colistin treatment. The primary reason for combining colistin with other antibiotics is to prevent the selection and prevalence of colistin-heteroresistant strains. Another reason is to provide a synergistic effect for the salvage therapy because of the debate about low penetration of the colistin into the lungs. According to other studies, imipenem, meropenem, sulbactam, rifampicin, and tigecycline were found to have synergistic effects with colistin [2,23-26]. Clinical studies researching the effect of combination therapy with respect to clinical response, microbiological response, and mortality have been limited, and there is no consensus. In our study, we investigated the effect of colistin alone and also colistin combined with other antibiotics, and the effect of the various antibiotics that were used in combination. One of the limitations of our study was the inability to perform *in vitro* synergy tests.

According to experimental studies, sulbactam is one of the recommended antibiotics for carbapenem-resistant *A. baumannii* infections [27-29]. Since the penetration of sulbactam into the lung tissue is good,

sulbactam is used either alone or with ampicillin for the treatment of resistant *Acinetobacter* species infections. Sulbactam was used successfully for the treatment of infections including bacteremia and VAP caused by *A. baumannii* [3,5,24,29-31]. In a study performed by Kempf*et al*., the *in vitro* synergistic effect of the colistin-sulbactam combination therapy was demonstrated, and as a result, the researchers recommended adding sulbactam to colistin to prevent the emergence of resistant strains [23].

We could find only two publications evaluating the effect of colistin and sulbactam combination therapy on VAP and hospital-acquired pneumonia. In the first manuscript, 89 patients diagnosed with VAP were examined. Colistin was given to 52 of them (58.4%), while colistin combined with sulbactam was given to 37 patients (41.6%). On the fifth day of treatment, the clinical response rate was 40.4% in the colistin group and 43.2% in the combined treatment group. At the end of the treatment, the clinical response rate was 29.8% and 40%, and the bacteriological response rate was 72.3% and 85.7%, respectively. It was reported that the clinical response and bacteriological cure rates were better in the sulbactam-colistin group, but the difference was not statistically significant [2]. The second study, performed by Khawcharoenporn*et al*., used high-dose sulbactam in 93 patients who had XDR *A. baumannii* pneumonia. The survival rate on day 28 was 65%. They compared three combination therapies: colistin-sulbactam, colistin-tygecycline, and colistin-carbapenem. They did not find any differences in survival rates or length of hospital stay between these combinations [32]. In our study, the survival rate was 30%. When we evaluated risk factors of mortality, the colistin-sulbactam combination was not found to be a risk factor ($p = 0.06$). In a meta-analysis comparing sulbactam treatment with other combinations in *A. baumannii* infections, it was shown that treatments including sulbactam were not superior to other treatments [33]. The authors concluded that a high quality randomized controlled study would be required to secure more enhanced evidence. We found no statistically significant difference between treatment with sulbactam-colistin and colistin alone with respect to clinical and microbiological responses. The microbiological eradication rate was better in the colistin-sulbactam combination, but the mortality rate was higher, which may have been the result of confounding factors affecting mortality.

The synergistic effect of colistin and imipenem and colistin and meropenem combinations were shown in *in vitro* studies and in animal studies [34,35]. Pongpech*et al*. studied the synergistic antibacterial effect of the following four combinations of treatment against carbapenem-resistant MDR *A. baumanni*: imipenem and colistin; meropenem and colistin; imipenem, colistin and sulbactam; and meropenem, colistin, and sulbactam.The antibacterial effect was found to be highest with the imipenem-colistin combination [35]. In a study performed by Falagas *et al*., various infections caused by MDR Gram-negative microorganisms were evaluated. In this study, colistin monotherapy and various combinations were compared in *A. baumannii* infections, and the clinical cure with colistin monotherapy was found to be 87%, with colistin and meropenem 83.9%, with colistin and piperacillin-tazobactam 67.7%, and with colistin and aminoglycoside, imipenem, cephalosporin, aztreonam, and ciprofloxacin combinations 58.3% [36]. In the multivariate analysis, the clinical cure rate was three times higher in patients using colistin alone or a colistin-meropenem combination. In the same study, colistin alone and a colistin-meropenem combination were compared in terms of clinical cure, and the difference was not found to be significant [36]. As demonstrated in *in vitro* studies, heteroresistance may develop when colistin is used alone. Therefore, it was emphasized that one needs to be cautious with monotherapy. According to our findings, combining colistin with carbapenem contributed to the microbiological response rate, but the difference was not statistically significant.

The widespread use of carbapenems has been reported to cause increased selection of carbapenem-resistant *A.baumannii* [37]. Carbapenem-sparing combinations may be preferable in the treatment of *Acinetobacter* infections to prevent collateral damage (particularly resistance selection) and to decrease the prevalence of *Acinetobacter* infections [37-39]. Because the outcomes of the combination treatment groups did not differ significantly, colistin-sulbactam may be an advisable and economical combination.

It has been reported that the *in vitro* activity of colistin increases significantly with the presence of rifampicin, and therefore colistin-rifampicin combination therapy has been recommended [40,41]. In a study published recently in Italy, 210 patients with serious infections caused by XDR *A. baumannii* were randomized into two groups. Patients in the first group were administered colistin alone, and patients in the second group were administered colistin plus 600 mg IV rifampicin twice per day. It was found that the mortality rate was not significantly different by the thirtieth day. The microbiological eradication rate was

found to be significantly higher in the combination group. There was no significant difference between the two groups regarding death due to infection and length of hospitalization [13]. Since IV rifampicin is not available in Turkey, it has not been possible to investigate the effect of this combination.

A multicenter study from Turkey evaluating the benefits of combination therapy in patients who had bloodstream infections due to XDR *A. baumannii* was published recently. The study found that rates of complete response (cure) and 14-day survival were relatively higher, the microbiological eradication rate was significantly higher, and the in-hospital mortality rate was significantly lower in the combination therapy group [38]. We could not find the same results. This may be due to the different site-specific infections (bloodstream vs. VAP) of the two studies and perhaps also due to confounding factors affecting mortality.

In our study, predictors of mortality were found to be DM, COPD, and clinical response in multivariate analysis. The APACHE II score, duration of infection onset to receipt of active regimen, underlying malignancy and chronic kidney diseases were all found to be independent risk factors for mortality in the study performed by Khawcharoenporn *et al*. [32]. We believe that we found different risk factors for mortality because of the different patient populations.

In addition to the small sample size and retrospective methodology, we were also unable to identify heteroresistant strains. Because the active substance was not available, the E test method was used to confirm resistance to colistin. These were the main limitations of our study. It should be noted that other limitations, such as pharmacokinetics or pharmacodynamics of the colistin and other combined antibiotics, could not be evaluated, and a loading dose was not used.

Conclusions

Colistin alone seems to be as effective as colistin combined with either carbapenem or sulbactam. However, colistin monotherapy cannot be recommended because heteroresistant strains could not be evaluated in our study. Similar to Khawcharoenporn *et al*.'s study [32], there was no difference in clinical and microbiological response and mortality between colistin-sulbactam and colistin-carbapenem combinations in our study. Both of these drugs may be used with colistin, but further evaluation is required.

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