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Retrospective Study

Risk factors and clinical responses of pneumonia patients with colistin-resistant *Acinetobacter baumannii-calcoaceticus*

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Patients were not required to give informed consent statement for this study due to the suggestion of ethical committee of our hospital. We did not use any personal data. The data which was used for this study is available from our hospital's computer system. But written informed consent forms were taken for the agreement to treatment of pan-drug resistant *Acinetobacter baumannii* infections from patients or legal representatives.

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Abstract

BACKGROUND

Nosocomial infections with carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (ABC) strains are great problem for intensive care units. ABC strains can develop resistance to all the antibiotics available. Carbapenem resistance is common and colistin resistance is rare in our country. Knowing the risk factors for colistin resistance is important since colistin seems to be the only remaining therapeutic option for the patients with pneumonia due to extensively drug resistant ABC for our country.

AIM

To investigate the comparison of clinical responses and outcomes between pneumonia patients with colistin-susceptible and -resistant *Acinetobacter sp.* Strains.

METHODS

During the study period, 108 patients with pneumonia due to colistin-susceptible strains and 16 patients with colistin-resistant strains were included retrospectively. Continuous variables were compared with the Mann-Whitney U test, and categorical variables were compared using Pearson's chi-square test or Fisher's Exact chi-square test for two groups. A binary logistic regression model was developed to identify the potential independent factors associated with colistin resistance in patients with colistin-resistant strains.

the corresponding author on reasonable request.

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RESULTS

High Acute Physiology and Chronic Health Evaluation II scores (OR = 1.9, 95%CI: 1.4-2.7; $P < 0.001$) and prior receipt of teicoplanin (OR = 8.1, 95%CI: 1.0-63.3; $P = 0.045$) were found to be independent risk factors for infection with colistin-resistant *Acinetobacter* sp. Different combinations of antibiotics including colistin, meropenem, ampicillin/sulbactam, amikacin and trimethoprim/sulfamethoxazole were used for the treatment of patients with colistin-resistant strains. Although the median duration of microbiological cure ($P < 0.001$) was longer in the colistin-resistant group, clinical ($P = 0.703$), laboratory ($P = 0.277$), radiological ($P = 0.551$), microbiological response ($P = 1.000$) and infection related mortality rates ($P = 0.603$) did not differ between the two groups. Among the patients with infections due to colistin-resistant strains, seven were treated with antibiotic combinations that included sulbactam. Clinical (6/7) and microbiological (5/7) response rates were quite high in these patients.

CONCLUSION

The optimal therapy regimen is unclear for colistin-resistant *Acinetobacter* sp. infections. Although combinations with sulbactam seems to be more effective in our study patients, data supporting the usefulness of combinations with sulbactam is very limited.

Key words: *Acinetobacter baumannii*; Colistin; Ventilator-associated pneumonia

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Core tip: *Acinetobacter baumannii-calcoaceticus* complex (ABC) may cause serious infections. As *Acinetobacter* species are resistant to many antimicrobials, treatment options for them are extremely limited. Knowing risk factors is important for colistin resistance since colistin seems to be the only remaining therapeutic option for the patients with pneumonia due to extensively drug resistant ABC. We aimed to investigate the risk factors for colistin resistance in ABC strains isolated from the patients with ventilator associated pneumonia (VAP). We also compared clinical response and the outcome between VAP patients due to colistin susceptible and resistant *Acinetobacter* sp. strains. Furthermore, different treatment combinations were evaluated.

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INTRODUCTION

Acinetobacter baumannii-calcoaceticus complex (ABC) consists of Gram-negative round, rod-shaped bacteria that may cause serious hospital acquired infections. As *Acinetobacter* species (sp.) are simultaneously resistant to many antimicrobial agents, treatment options are extremely limited. Colistin is known as the most active therapeutic agent against extensively drug resistant (XDR) *Acinetobacter* sp. infections. Currently, besides its toxicities, the use of this agent is limited by the resistance of *Acinetobacter* sp. strains^[1,2]. As shown in the literature, colistin-resistance has been reported worldwide^[2]. The first colistin-resistant *Acinetobacter* sp. isolate was notified from the Czech Republic in 1999 by Vincent *et al*^[3]. The highest rate of colistin-resistance was reported from Asia followed by Europe and other regions of the world^[2]. Furthermore, in a surveillance study conducted in United States hospitals, it was reported that 5.3% of all *Acinetobacter* sp. strains were resistant to colistin^[4]. Per the limited reported data, colistin resistance in ABC strains is rare in our country^[5,6], with most of our isolates resistant to carbapenems but susceptible to colistin^[7,8]. Knowledge of the risk factors is important for colistin resistance, since colistin appears to be the only remaining therapeutic option for patients with pneumonia due to XDR ABC. Combination therapy is a common strategy because of the in vitro synergistic

effect of antimicrobials against XDR ABC infections^[9]. Although a few researches have studied the *in-vitro* activity of antimicrobial combinations against colistin-resistant *Acinetobacter* sp. isolates^[10,11], these studies were not supported by clinical trials. Limited reported data are available about the clinical response and outcome of nosocomial pneumonia caused by colistin-resistant ABC (CRABC)^[12,13]. In this study, we aimed to investigate the risk factors for colistin resistance in ABC strains isolated from patients with ventilator-associated pneumonia (VAP). We also compared clinical response and outcome between VAP patients due to colistin susceptible and resistant *Acinetobacter* sp. strains. Furthermore, different treatment combinations were evaluated in patients with VAP caused by CRABC.

MATERIALS AND METHODS

This comparative, retrospective, single-center study was conducted between January 2015 and April 2018 in the Zonguldak Bülent Ecevit University Hospital, a 416 bed adult tertiary care center with 49 adult intensive care unit beds. This study was approved by the ethics committee of the hospital. The following were included: patients aged ≥ 18 years who were diagnosed with VAP and whose culture and antimicrobial susceptibility results indicated infection with CRABC or colistin-susceptible ABC (CSABC), and patients who were within 48 h of the onset of VAP. Exclusion criteria included the following: (1) Patients who had polymicrobial cultures; (2) Patients who acquired different infection with another microorganism; (3) Patients who were transferred from different center under antibiotic treatment; (4) Patients who died within 3 d of antimicrobial therapy; and (5) Patients who were colonized with ABC without symptoms and signs of an infection. Resistance to imipenem and meropenem was defined as carbapenem resistance^[14].

VAP diagnoses were made when the onset of the signs, and symptoms of pneumonia occurred 48 h after the initiation of mechanical ventilation^[15]. These signs and symptoms included new or increased infiltrate on chest X-ray and two or more of the following: hyperthermia or hypothermia ($> 38^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$), white blood cell count > 12000 cells/ mm^3 or < 4000 cells/ mm^3 , and purulent bronchial secretion. ABC strains were isolated from cultures of tracheal aspirates (TA) and/or bronchoalveolar lavages. ABC was considered to be the causative agent if the TA culture yielded $> 10^6$ colony forming units (cfu)/mL of the organism^[15,16]. TA specimens having > 25 polymorphonuclear leucocytes and ≤ 10 epithelial cells on the Gram stain were cultured. Blood cultures were taken routinely from patients who were diagnosed with VAP. The infectious disease (ID) specialist followed-up daily and evaluated patients to determine treatment durations. Patients were treated with broad-spectrum antimicrobials when the diagnosis of pneumonia was established. The initial antimicrobial regimens were modified within 2 d as soon as the susceptibilities of ABC strains became available. The total length of ICU stay was defined as the number of days hospitalized in this unit until death, discharge or transfer to another unit. Patients who fulfilled the following criteria were considered to have a clinical response: (1) Resolution of high fever or hypothermia with fever between $36\text{--}38^{\circ}\text{C}$; (2) Reduction of tracheal secretion or the absence of purulence, with polymorphonuclear neutrophil counts < 25 cells/ mm^3 in Wright stain smears of the tracheal secretion; (3) Improvement of hypoxemia, a $\text{PaO}_2/\text{FiO}_2$ ratio (the ratio of partial pressure of arterial O_2 to the fraction of inspired O_2) > 240 , or elimination of the need for mechanical ventilation; and (4) Partial or complete resolution of respiratory crackles was observed^[15,16,17]. The study patients were followed by the ID specialist until death or discharge. Bronchial secretion cultures were taken at the time of VAP diagnosis, before initial antibiotic therapy and after 3rd, 5th–7th and 10th d of treatment and when the treatment duration was completed.

If subsequent cultures (blood and TA) were negative for ABC, then patients were considered to have a microbiological response to antibiotic treatment. If a clinical response was achieved but the microorganism could not be eradicated from the cultures, the antibiotic regimen was stopped and the patient was thought to be colonized. The normalization of white blood cell counts ($4000\text{--}10000$ cells/ mm^3), a decrease in the sedimentation rate, or a 40% decrease of the beginning CRP levels were defined as laboratory response. Disappearance of consolidation and absence of parapneumonic effusion on chest radiography were considered to be a radiological response to antibiotic treatment^[17]. Death under the antibiotic treatment of infection or death occurring when the signs and symptoms of pneumonia were present, or death due to septic shock was considered as VAP-related mortality^[15].

Isolation and identification of *Acinetobacter* sp. from cultures

Isolation and identification of ABC were performed by conventional techniques and confirmed by the BBL Crystal enteric/nonfermenter identification system (Becton Dickinson, United States). Susceptibility to antibiotics was determined by the standard disk diffusion method and interpreted according to the Clinical Laboratory Standards Institute (CLSI)^[18]. Resistance to imipenem and meropenem was verified by determination of the minimal inhibitory concentrations (MICs) with E-tests (AB Biodisk, Sweden)^[18]. The MICs of colistin were determined using the broth microdilution method according to CLSI recommendations. Standard powder form colistin sulphate (Sigma Chemical Co.) was stored at 2-8 °C until use. The stock solutions and serial twofold dilutions (to at least double the MIC) were prepared according to CLSI recommendations and in-house prepared panels of concentrations of 0.125–512 mg/mL were used. The breakpoints for colistin resistance were defined by CLSI recommendations (≤ 2 mg/mL for susceptible and ≥ 4 mg/mL for resistant)^[18].

Molecular typing

Molecular typing was performed on 16 colistin-resistant isolates by the arbitrary primer polymerase chain reaction (AP-PCR) typing method.

Isolation of genomic DNA

Strains were grown overnight on MacConkey agar plates at 37 °C, and the growth from approximately one-quarter of a plate was resuspended in 180 μ L of distilled water. Following this, 200 μ L buffer solution (0.01 mol Tris-Cl, pH 7.8, 0.005 mol EDTA, and 0.5% SDS) and 20 μ L proteinase K (1 mg/mL) was added. The mixture was incubated for 2 h at 55 °C followed by conventional phenol-chloroform extraction^[19]. The DNA concentration was measured by UV absorbance at A_{260} .

AP-PCR

AP-PCR was performed using M13 and DAF4 primers^[20]. Amplification products were electrophoresed on 2% agarose gel with ethidium bromide and were visualized under UV illumination. Strains belonging to the same clones showed identical DNA profiles.

Statistical analysis

The statistical review of the study was performed by a biomedical statistician. Statistical analysis was performed with SPSS 19.0 software (SPSS Inc., United States). The distribution of data was determined by the Shapiro-Wilk test. Continuous variables were expressed as the median (min-max); categorical variables were expressed as frequency and percent. Continuous variables were compared with the Mann-Whitney *U* test, and categorical variables were compared using Pearson's chi-square test or Fisher's exact chi-square test for two groups. A binary logistic regression model was developed to identify the potential independent factors associated with colistin resistance in patients with VAP due to ABC strains. Statistically significant and/or clinically relevant variables [APACHE II scores (Acute Physiology and Chronic Health Evaluation), duration of mechanical ventilation before diagnosis, prior use of colistin, prior receipt of carbapenems, prior receipt of ampicillin/sulbactam, prior receipt of piperacillin/tazobactam, prior receipt of fluoroquinolones, prior receipt of teicoplanin, and total parenteral nutrition (TPN)] were entered into the multivariate logistic regression model with 95% confidence intervals (CIs) calculated as estimators. When *P* values were < 0.05 , they were accepted to be statistically significant.

RESULTS

During the study period, 124 patients with VAP due to CRABC and CSABC met the inclusion criteria. Patients' underlying medical conditions, previous antimicrobial usage and clinical characteristics were summarized in Table 1. The median age of patients infected with CSABC (74.0 ± 18 -91) was significantly older than the patients with CRABC (59.5 ± 18 -86) ($P = 0.022$). The ratio of male patients with VAP due to CRABC (81.3%) was significantly higher than male patients with CSABC (46.3%) ($P = 0.019$). Prior colistin ($P = 0.001$) and TPN ($P = 0.030$) usages were more common in the CRABC group than CSABC group. Although there was no statistically significant difference between the SOFA (Sequential Organ Failure Assessment) scores ($P = 0.546$) of the two groups on the day of VAP diagnosis, the difference in the APACHE II scores ($P < 0.001$) at time of ICU admission was statistically significant. The median APACHE II scores were higher in the CRABC group (22.5 ± 17 -28) than in the CSABC group (12.0 ± 5 -22). Although the median duration of microbiological cure ($P < 0.001$)

was longer in CRABC group, clinical ($P = 0.703$), laboratory ($P = 0.277$), radiological ($P = 0.551$) and microbiological response ($P = 1.000$) rates did not differ between the two groups. Although the crude in-hospital mortality (71/108, 65.7%, $P = 0.058$) and VAP-related mortality (45/108, 41.7%, $P = 0.603$) rates were higher in the CSABC group, the differences were not statistically significant. Using multivariate analysis, prior receipt of teicoplanin (OR = 8.1, 95%CI: 1.0-63.3; $P = 0.045$) and high APACHE II scores (OR = 1.9; 95%CI: 1.4-2.7; $P < 0.001$) were found to be independent risk factors for resistance to colistin. Clinical characteristics, antibiotic treatments and responses to treatment of the patients with VAP due to CRABC are shown in Table 2 and Table 3.

In the CSABC group, antibiotic combinations of 106 patients (98.1%) included colistin. Nephrotoxicity occurred in 38 (35.8%), and antibiotic dosage was adjusted in 32 (30.2%) cases. In the CRABC group, 12 of 16 patients (75%) were treated with colistin. Four patients (33.3%) developed nephrotoxicity during colistin treatment, and dosage was adjusted in these cases.

Sixteen of 124 (12.9%) isolated *Acinetobacter* sp. strains were resistant to colistin, and 108 of these isolates were susceptible to colistin. Only 7 of 108 (6.5%) colistin-susceptible strains were also susceptible to carbapenems (imipenem and/or meropenem). Ten (62.5%) of the colistin-resistant strains were resistant to all antibiotics tested, and all of them were resistant to carbapenems. The phenotypes of the CRABC isolates are shown in Table 4. Four different phenotypes were detected in these strains. Phenotype 1 isolates were resistant to all tested antibiotics. Phenotype 2 isolates were susceptible to tobramycin which is not available in our country; and while phenotype 3 isolates were susceptible to gentamicin, phenotype 4 isolates were susceptible to trimethoprim/sulfamethoxazole. Six isolates showed elevated colistin MICs (256 µg/mL to ≥ 512 µg/mL). AP-PCR analysis was performed on 16 CRABC isolates. AP-PCR fingerprinting yielded two types. Type 1 included 13 isolates, while type 2 included 3 isolates. Genotypes were not correlated to the phenotypes.

DISCUSSION

In recent years, carbapenem resistance seemed to be the primary barrier to treating infections with *Acinetobacter* sp. strains. Although colistin was a longstanding antimicrobial agent and not preferred due to side effects, it was reintroduced to clinical practice as a treatment of last resort because of the emergence of carbapenem-resistant Gram-negative pathogens including *Acinetobacter* sp. strains^[1]. Clinicians have begun to use colistin more commonly due to an increase in carbapenem resistance in multidrug-resistant microorganisms, including *Acinetobacter* sp. Today, the emergence of colistin resistance and salvage therapies in *Acinetobacter* sp. infections are widely-studied topics in many countries^[2,10,21,22]. *Acinetobacter* sp. strains are one of the most common pathogens in ICUs in our country^[6]. The dissemination of resistance to carbapenems and recent resistance to colistin are major problems for our country and the world. In the literature, mechanical ventilation, hemodialysis^[23], prior receipt of carbapenems and fluoroquinolones^[24] and high SOFA score^[25] were found to be independent risk factors for carbapenem resistant *Acinetobacter* infections. However, limited data is available about the risk factors for colistin-resistant *Acinetobacter* sp. infections. In a recently published study, prior use of colistin (OR = 155.95, 95%CI: 8.00-3041.98), carbapenems (OR = 12.84, 95%CI: 1.60-103.20) and a high Simplified Acute Physiology Score (OR = 1.10, 95%CI: 1.01-1.22) were found to be risk factors for VAP due to pan-drug resistant *A. baumannii*^[25]. In our study, high APACHE II scores and prior teicoplanin receipt were found to be independent risk factors for colistin resistance. In another recently published multicenter study conducted in our country, prior carbapenem and fluoroquinolone usage was found to increase the risk of infection with colistin-resistant Gram-negative microorganisms. Their study population included not only colistin-resistant *A. baumannii* but also *Klebsiella pneumonia* and *Pseudomonas aeruginosa*^[12]. In our study, finding that prior receipt of teicoplanin was an independent risk factor for colistin resistance may be worth exploring further, as a recent study found that teicoplanin appeared to enhance the activity of colistin in a mouse model. Although the authors suggested that the combination of colistin and teicoplanin may improve the therapy of multiresistant *A. baumannii* infection, this may lead to further infection due to colistin-resistant strains^[26].

The mortality rate was higher in patients with multidrug resistant *Acinetobacter* strains. A systematic review of observational studies that included over 2500 patients with infection due to either carbapenem susceptible or resistant *Acinetobacter* strains found that the overall mortality rate was 33%, and, in this study, carbapenem resistance was found to increase mortality (pooled odds ratio 2.22, 95%CI: 1.66-2.98).

Table 1 Demographic data and clinical characteristics of patients with ventilator-associated pneumonia due to colistin-resistant and colistin-susceptible *Acinetobacter baumannii-calcoaceticus* complex

Variable	Total, n = 124	CRABC group, n = 16	CSABC group, n = 108	P-value
Male sex (%)	63 (50.8)	13 (81.3)	50 (46.3)	0.019
Age, med ± (min-max)	73.0 ± (18-91)	59.5 ± (18-86)	74.0 ± (18-91)	0.022
Comorbidity				
Diabetes mellitus (%)	35 (28.2)	5 (31.5)	30 (27.8)	0.771
Chronic renal failure (%)	11 (8.9)	0 (0.0)	11 (10.2)	0.356
Chronic obstructive lung disease (%)	33 (26.6)	4 (25.0)	29 (26.9)	1.000
Hypertension (%)	57 (46.0)	8 (50.0)	49 (45.4)	0.938
Congestive heart failure (%)	25 (20.2)	4 (25.0)	21 (19.4)	0.738
Malignity (%)	30 (24.2)	2 (12.5)	28 (25.9)	0.353
Cerebrovascular disease (%)	24 (19.4)	1 (6.3)	23 (21.3)	0.305
Trauma (%)	8 (6.5)	3 (18.8)	5 (4.6)	0.066
Operation (%)	24 (19.4)	2 (12.5)	22 (20.4)	0.735
Immunosuppression (%)	9 (7.3)	1 (6.3)	8 (7.4)	1.000
Obesity (%)	12 (9.7)	3 (18.8)	9 (8.3)	0.186
Duration of mechanical ventilation before diagnosis, med ± min-max	11 ± (2-450)	12 ± (4-50)	11 ± (2-450)	0.872
Total length of ICU stays, med ± min-max	45.5 ± (5-540)	49.0 ± (11-305)	43.0 ± (5-540)	0.685
Central venous catheterization (%)	67 (54.0)	9 (56.3)	58 (53.7)	1.000
Urethral catheterization (%)	114 (91.9)	14 (87.5)	100 (92.6)	0.616
Total parenteral nutrition (%)	21 (16.9)	6 (37.5)	15 (13.9)	0.030
Prior receipt of colistin (%)	11 (8.9)	6 (37.5)	5 (4.6)	0.001
Prior receipt of carbapenems (%)	68 (54.8)	10 (62.5)	58 (53.7)	0.696
Prior receipt of linezolid (%)	6 (4.8)	1 (6.3)	5 (4.6)	0.571
Prior receipt of ampicillin/sulbactam (%)	19 (15.3)	1 (6.3)	18 (16.7)	0.462
Prior receipt of flouroquinolones (%)	51 (41.1)	5 (31.3)	46 (42.6)	0.556
Prior receipt of teicoplanin (%)	25 (20.2)	6 (37.5)	19 (17.6)	0.091
Prior receipt of piperacillin/tazobactam (%)	19 (15.3)	1 (6.3)	18 (16.7)	0.462
Prior receipt of ceftriaxone (%)	9 (7.3)	0 (0.0)	9 (8.3)	0.603
Presence of bacteremia (%)	3 (2.4)	2 (12.5)	1 (0.9)	0.044
APACHE II scores, med ± min-max	14.0 ± (5-28)	22.5 ± (17-28)	12.0 ± (5-22)	< 0.001
SOFA scores, med ± min-max	9.0 ± (3-20)	9 ± (7-18)	9 ± (3-20)	0.546
Clinical response (%)	71 (61.3)	11 (68.8)	65 (60.2)	0.703
Laboratory response (%)	82 (66.1)	13 (81.3)	69 (63.9)	0.277
Radiological response (%)	65 (52.4)	10 (62.5)	55 (52.9)	0.551
Microbiological response (%)	67 (54.0)	9 (56.3)	58 (53.7)	1.000
Duration of microbiological cure, med ± (min-max)	4 ± (2-10)	6 ± (3-10)	3 ± (2-7)	<0.001
In-hospital mortality (%)	77 (62.1)	6 (37.5)	71 (65.7)	0.058
VAP-related mortality (%)	50 (40.3)	5 (31.3)	45 (41.7)	0.603

VAP: Ventilator associated pneumonia; CRABC: Colistin resistant *Acinetobacter baumannii-calcoaceticus* complex; CSABC: Colistin susceptible *Acinetobacter baumannii-calcoaceticus* complex; APACHE: High Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

Since the patients with carbapenem-resistant infection were more likely to have severe comorbid diseases, or to receive inappropriate empiric antibiotic therapy, these were likely confounding variables that lead to an increased mortality^[27].

In our study, our strains were mostly carbapenem resistant (only seven isolates were susceptible to carbapenems). The median duration of microbiological cure was longer in patients with VAP due to CRABC. Although VAP-related mortality and in-hospital mortality rates were lower in the CRABC group, the differences were not statistically significant. We also did not find statistically significant differences in clinical, laboratory, radiological or microbiological responses between the two groups. In a recently published clinical trial, data from 266 patient isolates were evaluated (214 CSABC and 52 CRABC). Patients with colistin-resistant isolates had lower rates of mechanical ventilation. After adjusting for variables associated with mortality, they found a significantly lower mortality rate among patients with CRABC^[28]. In our

Table 2 Clinical characteristics and antibiotic treatment combinations of patients with ventilator-associated pneumonia due to colistin-resistant *Acinetobacter baumannii* - *calcoaceticus* complex (part 1)

Patients' number with ventilator associated pneumonia due to colistin-resistant <i>Acinetobacter baumannii</i> - <i>calcoaceticus</i> complex								
Isolate number of patients	1	2	3	4	5	6	7	8
Culture location	TA	BAL	TA	TA	TA	BAL	TA	BAL
Phenotype of isolate	1	1	1	1	1	1	1	2
MIC of isolate	8	> 256	4	6	4	> 256	> 256	> 256
Treatment	1	1	1	1	2	3	2	2
Clinical response	Yes	Yes	No	No	Yes	Yes	No	Yes
Laboratory response	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Radiological response	Yes	Yes	No	No	Yes	Yes	No	Yes
Microbiological response	Yes	Yes	No	No	Yes	Yes	Yes	Yes
VAP-related mortality	No	No	Yes	No	No	No	Yes	No

Treatment 1: meropenem + colistin, Treatment 2: meropenem + ampicillin/sulbactam, Treatment 3: colistin + amikacin. MIC: Minimum inhibitory concentration; VAP: Ventilator-associated pneumonia; BAL: Bronchoalveolar lavage; TA: Tracheal aspirate.

study, although the mortality rate did not statistically differ between the patients with CSABC and CRABC, the VAP-related mortality rate for all study patients was quite high.

In clinical trials, a combination of antimicrobials is frequently preferred for treatment of *Acinetobacter* sp. infections. Although it seems that an appropriate approach is to cover resistant strains before antimicrobial susceptibility testing is available, there are no clear clinical data supporting this strategy. However, some studies suggest combination therapy may improve the outcome of infections with resistant *Acinetobacter* sp. strains^[29-31]. Treatment of patients with pan-drug-resistant strains is a major emerging problem for clinicians. Combination therapies including ampicillin/sulbactam, carbapenems, minocycline, tigecycline, rifampicin and vancomycin might be administered to patients with pan-drug-resistant strains as a salvage therapy^[2,10]. In our study, different combinations of colistin, meropenem, sulbactam, amikacin and trimethoprim/sulfamethoxazole were used for treatment of patients with CRABC as salvage therapies. The combination of meropenem and colistin, and the combination of meropenem and ampicillin/sulbactam, were the most commonly used regimens. Seven patients were treated with meropenem and colistin. Microbiological (2/7) and clinical (3/7) response rates were very low with this treatment. The meropenem and ampicillin/sulbactam combination was administered to four patients. Microbiological eradication and clinical response were obtained from three of them. Among the VAP patients with CRABC, seven were treated with antibiotic combinations including sulbactam. Clinical (6/7) and microbiological (5/7) response rates were quite high in these patients. Although it is difficult to draw a firm conclusion about the optimal antibiotic treatment due to the small sample size of our CRABC group, combinations including sulbactam seem to yield better clinical response and microbiological eradication.

Limitations

Our study has some limitations including that it was a retrospective study with a small sample size for the colistin-resistant group and the difficulty in the diagnosis of VAP and in the evaluation of the outcomes in critically ill patients with comorbidities.

Conclusions

We found a high APACHE II score and usage of teicoplanin to be risk factors for colistin resistance. No data are available for the optimal therapy regimen for resistant strains. Various antibiotic combinations might be given to patients with infections due to CRABC as salvage therapies. Among colistin-resistant group, the clinical responses were better with antibiotic combinations including sulbactam. As very limited data to support the usefulness of combination therapies with sulbactam is available, management in these patients should be individualized, and further comparative clinical studies are needed to identify optimal treatment regimens.

Table 3 Clinical Characteristics and Antibiotic treatment combinations of patients with ventilator-associated pneumonia due to colistin-resistant *Acinetobacter baumannii* - *calcoaceticus* complex (part 2)

Variables	Patients' number with ventilator associated pneumonia due to colistin-resistant <i>Acinetobacter baumannii</i> - <i>calcoaceticus</i> complex							
Isolate number of patients	9	10	11	12	13	14	15	16
Culture location	TA	TA	TA	TA	TA	TA	BAL	TA
Phenotype of isolate	3	4	3	1	1	4	4	1
MIC of isolate	> 256	32	> 256	16	6	8	24	4
Treatment	4	5	1	1	2	7	6	1
Clinical response	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Laboratory response	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Radiological response	Yes	Yes	No	Yes	No	Yes	Yes	No
Microbiological response	Yes	Yes	No	No	No	No	Yes	No
VAP related mortality	No	No	Yes	No	Yes	No	No	Yes

Treatment 1: meropenem + colistin, Treatment 2: meropenem + ampicillin/sulbactam, Treatment 4: colistin + ampicillin/sulbactam + trimethoprim/sulfamethoxazole, Treatment 5: colistin + ampicillin/sulbactam, Treatment 6: meropenem + trimethoprim/sulfamethoxazole, Treatment 7: meropenem + sulbactam + trimethoprim/sulfamethoxazole. MIC: Minimum inhibitory concentration; VAP: Ventilator-associated pneumonia; BAL: Bronchoalveolar lavage; TA: Tracheal aspirate.

Table 4 Phenotypes of colistin-resistant *Acinetobacter* sp. isolates

Isolate number of patients	AN	CN	TOB	SAM	STX	IPM	MEM	CAZ	CIP	TZP
1	R	R	R	R	R	R	R	R	R	R
2	R	R	R	R	R	R	R	R	R	R
3	R	R	R	R	R	R	R	R	R	R
4	R	R	R	R	R	R	R	R	R	R
5	R	R	R	R	R	R	R	R	R	R
6	R	R	R	R	R	R	R	R	R	R
7	R	R	R	R	R	R	R	R	R	R
8	R	R	S	R	R	R	R	R	R	R
9	R	S	R	R	R	R	R	R	R	R
10	R	R	R	R	S	R	R	R	R	R
11	R	S	R	R	R	R	R	R	R	R
12	R	R	R	R	R	R	R	R	R	R
13	R	R	R	R	R	R	R	R	R	R
14	R	R	R	R	S	R	R	R	R	R
15	R	R	R	R	S	R	R	R	R	R
16	R	R	R	R	R	R	R	R	R	R

CO: Colistin; AN: Amikacin; CN: Gentamicin; TOB: Tobramycin; TE: Tetracycline; IPM: Imipenem; LEV: Levofloxacin; SXT: Trimethoprim-sulfamethoxazole; CIP: Ciprofloxacin; MEM: Meropenem; PIP: Piperacillin; TZP: Piperacillin-tazobactam; FEP: Sefepim; CAZ: Ceftazidim; SAM: Sulbactam-ampicillin; R: Resistant; S: Susceptible.

ARTICLE HIGHLIGHTS

Research background

Acinetobacter species are simultaneously resistant to many antimicrobial agents, and treatment options are extremely limited. Although colistin appears to be the only remaining therapeutic option for extensively-resistant *Acinetobacter* infections, colistin resistance in *Acinetobacter* strains has been reported worldwide. Knowledge of the risk factors is important for colistin resistance. This study highlights risk factors of colistin resistance and salvage therapies in *Acinetobacter* sp. Infections.

Research motivation

Infections with resistant *Acinetobacter* strains were found to be associated with high mortality

rates. Combination therapies were commonly recommended since resistance could develop during therapies. The main goals for control of multidrug-resistant *Acinetobacter* should be early recognition, knowing risk factors, aggressive control of spread of the resistant strains. The problem for treatment of nosocomial infections with extensively- or pandrug-resistant *Acinetobacter* strains may be solved in future with development of new antimicrobial agents targeting these resistant strains.

Research objectives

In our study we evaluated the clinical responses and the outcomes of ventilator-associated pneumonia (VAP) patients with resistant *Acinetobacter* strains. The risk factors for colistin resistance were also investigated.

Research methods

Between January 2015 and April 2018, 108 patients with VAP due to colistin-susceptible strains and 16 patients with colistin-resistant strains were included in this study retrospectively. These two groups were compared for the age, sex, comorbidities, prior receipt of antibiotics, mortality rates, APACHE II and SOFA scores, duration of microbiological cure and the clinical, laboratory, radiological, and microbiological responses. Mann-Whitney *U* test was used to compare continuous variables whereas Pearson's χ^2 test or Fisher's Exact χ^2 test was used to compare the categorical variables. The potential independent risk factors for infection with colistin resistant strains were identified by using a binary logistic regression model.

Research results

The median duration of microbiological cure ($P < 0.001$) was longer in colistin-resistant group. Clinical ($P = 0.703$), laboratory ($P = 0.277$), radiological ($P = 0.551$), microbiological response ($P = 1.000$) and infection related mortality rates ($P = 0.603$) did not differ between patients with pneumonia due to colistin-resistant and colistin-susceptible strains. Independent risk factors for pneumonia with colistin-resistant *Acinetobacter* strains were found to be high APACHE II scores (OR = 1.9, 95%CI: 1.4-2.7; $P < 0.001$) and prior receipt of teicoplanin (OR = 8.1, 95%CI: 1.0-63.3; $P = 0.045$). Different combination of antibiotic regimens included colistin, meropenem, ampicillin/sulbactam, amikacin and trimetoprim/sulfamethoxazole were given to patients with colistin-resistant strains. Among patients with infection due to colistin-resistant strains, seven of them were treated with antibiotic combinations included sulbactam. Clinical (6/7) and microbiological (5/7) response rates were quite high in these patients. Very limited data is available for the optimal therapy regimens of infections with pandrug-resistant *Acinetobacter* strains. Individual treatment combinations may be given to the patients with infection due to colistin-resistant *Acinetobacter* strains.

Research conclusions

High APACHE II scores and prior teicoplanin usage were found to be the risk factors for pneumonia due to colistin resistant *Acinetobacter* strains. Statistically significant difference was not found between the mortality rates of the patients with colistin-susceptible and colistin-resistant strains. Combination antibiotic regimens including sulbactam seemed to be more useful. Further prospective studies are needed to evaluate the optimal therapy regimens. As prior usage of teicoplanin was found to be an independent factor for colistin resistance, patients should be carefully treated with teicoplanin empirically.

Research perspectives

Prospective randomized-controlled studies investigating optimal therapy regimens or new antimicrobials targeting colistin resistant *Acinetobacter* strains are needed. Risk factors for colistin resistance should be well known and strict prevention and control methods should be used in intensive care units.

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