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Research Article

Colistin Monotherapy versus Colistin Based Combination Therapy in the Treatment of Extensive Drug Resistant *Acinetobacterbaumannii* (XDRAB) Infections: A Retrospective Cohort Study

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Abstract

Introduction: *Acinetobacterbaumannii* (*A. baumannii*) is a Gram-negative coccobacillus and is a frequent cause of hospital-acquired infections. Because some strains of *A. baumannii* are resistant to many antibiotics (i.e., extensively drug resistant *A. baumannii*, or XDRAB), selecting antibiotics to treat infected patients is challenging. Clinical outcomes in critically ill patients with XDRAB infections are poor. In this study, we evaluated the clinical effectiveness of colistin as monotherapy and in combination with other antibiotics.

Methods: 94 critically ill patients clinical effectiveness of treating XDRAB pulmonary infections with colistin, either in monotherapy or in combination with tigecycline, meropenem, or both. Clinical and microbiological data were obtained from patient records. We included patients suffering from XDRAB ventilation-associated pneumonia (VAP) or VAP with bacteremia.

Results: The mean age of the patients was 53.3 years (standard deviation =23.7 years) and the mean APACHE II score was 22.7 (SD =7.1). Respiratory tract infections and bacteremia were found in 84% and 16% of patients, respectively. Half (51%) of patients achieved microbiological clearance. The median ICU stay was 29 days and the mean mechanical ventilation (MV) duration was 21 days. MV duration and ICU length of stay were lower in the group of patients treated with colistin and meropenem than in those treated with colistin alone. Mortality was significantly lower in patients who received (colistin and tigecycline 30%) than in those who were treated with monotherapy (75%).

Conclusions: Colistin-based combination treatment regimens mainly with tigecycline or with tigecycline and meropenem are potentially more effective for the treatment of XDRAB induced VAP than colistinmonotherapy.

ABBREVIATIONS

VAP: Ventilator-Associated Pneumonia; VAT: Ventilator-Associated Tracheobronchitis; *A.baumannii*: *Acinetobacterbaumannii*; XDR: Extensive Drug Resistant; MDR: Multi-Drug-Resistant; ICU: Intensive Care Unit; SFH: Security Forces Hospital; SD: Standard Deviation; CI: Confidence Interval; APACHE II: Acute Physiology and Chronic Health Evaluation II; MV: Mechanical Ventilation; LOS: Length of Stay; BSI: Blood Stream Infection; CFU: Colony-Forming Unit; FDA: Food and Drug Administration; RIFLE: Risk, Injury, Failure, Loss, and End-stage renal disease; ESRD: End-Stage Renal Disease; CLSI: Clinical and Laboratory Standards Institute; USA: United States of America; CPIS: Clinical Pulmonary Infection Score

INTRODUCTION

*A. baumannii*is a Gram-negative, round, rod-shape coccobacillus that acts as an opportunistic human pathogen. Numerous reports of infection in soldiers serving in Iraq and Afghanistan led to an increased interest in *A. baumannii* [1]. *A. baumannii* primarily affects critically ill Intensive Care Unit (ICU) and immune compromised patients [2]. Several mechanisms of drug resistance have been acquired by *A. baumannii*, and these have led to an increased prevalence of multi-drug-resistant (MDR) strains [3]. Drug resistance mechanisms include the production of antimicrobial inactivation enzymes, efflux pumps, target modifiers, and altered porins [3]. *A.baumannii*is a major cause of various nosocomial infections, such as VAP, bacteremia, surgical site infection and urinary tract infection. Infections are particularly problematic in ICU patients [2], in whom mortality rates approach 34–43% [4].Treatments for *A. baumannii* include sulbactam, carbapenems, amikacin, and some tetracyclines (doxycycline and minocycline) [5,6]. Polymyxin-class agents such as colistin and polymyxin B gained popularity after the emergence of carbapenem-resistant strains, and although these agents were clinically effective [7], nephrotoxicity induced by colistin was observed in 27-58% of patients [8].Clinical outcomes in critically ill patients with MDRAB and XDRAB infections are poor, and existing studies regarding treatment options are limited. In addition, research using newer anti-infective agents, such as tigecycline for the treatment of ICU patients with VAP, is lacking [9].Treatment of patients with XDRAB infection is hampered by the lack of evidence supporting effective treatments, and clinical controversies and challenges remain. In this study, we evaluated the clinical effectiveness of colistin as monotherapy and in combination with tigecycline or meropenem in the treatment of critically ill patients with XDRAB infection.

PATIENTS AND METHODS

Study design

A retrospective cohort study of 94 adult patients with XDRAB pneumonia and bacteremia was conducted between January 1st and December 31st 2012, at Security Forces Hospital (SFH) ICU in Saudi Arabia. SFH is a tertiary care center that receives approximately 18000-19000 admissions annually and has 29 ICU beds. For this study we identified adult patients (age ≥18 years) who received any of the following regimens: colistin alone, colistin and meropenem, colistin and tigecycline, or colistin, meropenem, and tigecycline. Pregnant patients and patients who received colistin therapy for <72 hours were excluded from the study. For polymicrobial infections, patients were included only if antibiotic treatment was determined based on the presence of XDRAB. This study was approved by the research ethics board at our institution. We did not take consent for participation in the study because it is a retrospective study and was accepted by the ethics committee in our hospital.

Data extraction

XDRAB infections were diagnosed via positive cultures in 94 ICU patients with VAP or VAP with bacteremia. Data were collected for each patient as follows: patient demographics, microbiological variables (site of infection, with bacterial culture identification and sensitivity), current antibiotics, antibiotic treatment duration, renal replacement therapy, and outcomes of interest (ICU length of stay, duration of mechanical ventilation, and mortality). Disease severity was assessed using Acute Physiology and Chronic Health Evaluation II (APACHE II) scores at ICU admission and on Day 1 of antibiotic therapy. All-cause mortality was recorded 30 days from the onset of antibiotic treatment. Death caused by primary infection (attributable to *A.baumannii* infection) was defined as death occurring without resolution of signs and symptoms of infection and with no other cause of death identified.

Bacterial identification and antimicrobial susceptibility testing

Bacterial identification and antibiotic susceptibility were determined using a microdilution method with a commercial dehydrate panel (Siemens Healthcare Diagnostic Ltd. MicroScan, Sacramento, CA, USA), according to the manufacturer's instructions, and by using the Kirby-Bauer disk diffusion test on Mueller-Hinton agar (Bio-Rad, Marnes-la-Coquette, France) according to the Clinical and Laboratory Standards Institute (CLSI) (formerly NCCLS). MDRAB strains were detected by using CHROMagar Acinetobacter (CHROMagar, Paris, France), which is a recently developed selective agar that contains agents for inhibiting the growth of the most Gram-positive organisms as well as carbapenem-susceptible Gram-negative Bacilli. Screening of carbapenemase activity in order to analyze the production of class B and D carbapenemase-resistant isolates was first performed by a modified Hodge test (MHT). (34)

Study outcomes

Retrospective data were collected on the length of stay in the ICU or death in the ICU. Clinical and microbiological responses were evaluated on the fifth day of treatment and at the end of the treatment. Evaluations were based on pre-specified definitions as described in the Definitions section below.

Definitions

1-According to the criteria of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the United States Food and Drug Administration (FDA):

Multi-drug-resistant *Acinetobacterbaumannii* (MDRAB): *A. baumannii* isolates were considered to be multi-drug-resistant if resistance was shown against at least three different classes of antimicrobial agents, including aminoglycosides, anti-pseudomonal penicillins, carbapenems, cephalosporins, quinolones, colistin, ampicillin/sulbactam, and tetracycline [10].

Extensively drug-resistant *Acinetobacterbaumannii* (XDRAB): *A. baumannii* isolates were considered to be Extensively-drug-resistant if resistance was shownto one or more agent in all but less than or equal to 2 categories (including aminoglycosides, anti-pseudomonal penicillins, carbapenems, cephalosporins, quinolones, colistin, ampicillin/sulbactam, and tetracycline) [10].

Clinical cure: Clinical cure was defined as the resolution of clinical signs and symptoms of pneumonia or bacteremia compared with baseline clinical status, improvement or lack of

progression in chest imaging, and no requirement for additional antibacterial treatment [11].

Clinical failure: Clinical failure was defined as the persistence or worsening of baseline signs and symptoms of pneumonia or bacteremia after 2 or more days of treatment, progression of baseline imaging abnormalities, or development of new pulmonary or extra-pulmonary clinical findings (like fever, chills and hypotension) consistent with active infection [11].

Microbiological eradication: Microbiological eradication was defined as the absence of *A. baumannii* from cultures obtained from the primary infection site [11].

Microbiological persistence: Microbiological persistence was defined as the continued presence of *A. baumannii* in cultures obtained from the primary infection site despite antibiotics therapy [11].

Length of stay (LOS): ICU length of stay was defined as the number of days spent in the ICU [12].

Ventilator-Associated Pneumonia (VAP): VAP was defined as pneumonia (CPIS score >6) in patients requiring mechanical ventilation (MV) for more than 48 hours [13].

Ventilator-Associated Tracheobronchitis: VAT was diagnosed if all of the following criteria were present: (a) fever (>38°C) with no other recognizable cause, (b) purulent sputum production, (c) positive ($\geq 10^6$ colony-forming units [cfu] per milliliter) endotracheal aspirate culture containing novel *A.baumannii* (not present at intubation), and (d) no radiographic signs of new pneumonia [14].

Nosocomial Bloodstream infections (BSI): Patients were considered to have nosocomial blood stream infection if they showed clinical signs of infection (like fever, chills and hypotension) and also provided at least one *A. baumannii* positive blood culture drawn at least 72 hours after hospital admission [15].

Ventilator-Free Days: Ventilator-free days were defined as days alive and off mechanical ventilation [16].

Nephrotoxicity: Colistin-related nephrotoxicity was assessed using risk, injury, failure, loss, and end-stage kidney disease (RIFLE) criteria [17]. Nephrotoxicity was evaluated in patients who received colistin therapy for 5 or more days.

STATISTICAL ANALYSIS

Data from 94 patients were assessed in this retrospective study. This sample size was sufficient to allow the assessment of more than five variables when using a linear regression model with continuous outcomes (e.g., the duration of MV and ICU length of stay) with statistical power of 80% at a significance level of 0.05, assuming a medium effect size corresponding to $R^2 = 0.13$ [18]. Baseline clinical characteristics and outcomes were summarized using descriptive statistics such as mean and standard deviation [19], for normally distributed continuous variables, median and interquartile range (IQR) for non-normally distributed continuous variables, and count and percentage for categorical variables. Multiple linear regression models, with adjustment for age and sex, were used to assess the effect of synergistic therapies on MV duration and ICU length of stay. Model assumptions and goodness-of-fit were evaluated using the residuals plot and the R^2. Where appropriate, outcome variables were logarithmically transformed to achieve a better goodness-of-fit. For logarithmically transformed outcomes, estimated coefficients were exponentiated and reported as changes in the ratio of expected mean of the outcome variables. Logistic regression was used to investigate the association between synergistic therapies and mortality. Results from logistic regression analysis were reported as odds ratios (OR) and corresponding 95% confidence intervals (CI). The above analyses were also conducted separately for subgroups of patients with VAP and VAT to assess the effect of synergistic therapies in different subgroups. All analyses were performed using SAS version 9.2 (Cary, NC).

RESULTS

Clinical and statistical analysis

Ninety-four patients were included in the study (mean age ± SD = 53.3 ± 23.7 years). The mean APACHE II score was 22.7 (SD = 7.1). Respiratory infection (VAP and VAT) was more prevalent (84.0% of patients) than bloodstream infection (16.0% of patients). The number of patients that received colistin alone, colistin + meropenem, colistin + tigecycline, or colistin + meropenem + tigecycline were 12, 36, 13 and 33 respectively. Approximately 28.6% of patients had end-stage renal disease (ESRD) and received hemodialysis and, overall, 35.1% of patients developed acute kidney injury that required hemodialysis. Microbiological clearance was achieved in 48/94 patients or 51% of patients receiving colistin, combination of colistin with other antibiotics showed similar eradication rate. Patient characteristics are summarized in Table1**.** Median MV duration was 21.0 days (IQR: 12.0, 42.0) and median ICU stay length was 29.0days (IQR: 17.0, 55.0). The mortality rate was 47.9% (45/94 patients). Summary of these outcomes for patients receiving different antibiotic therapies are presented in Table 2. Results from linear regression analysis showed that MV duration for patients receiving colistin alone was 2.33-fold longer compared to patients treated with colistin + meropenem therapy (ratio of colistin + meropenem therapy to colistin alone, 0.43; 95% CI: 0.22, 0.85; *p*-value = 0.02). However, MV duration was not significantly lower for patients treated with any of the combined regimens compared to patients receiving colistin alone (Table 3). Similarly, the ICU length of stay increased 96% for patients treated with colistin alone compared to patients receiving colistin + meropenem therapy (ratio of colistin + meropenem therapy to colistin alone, 0.51; 95% CI: 0.28, 0.93; *p*-value = 0.03), but ICU stay was not significantly lower for patients with combined treatments compared to patients receiving colistin alone (Table 3). Risk of death was significantly lower in patients treated with colistin and meropenem (OR = 0.12; 95% CI: 0.02, 0.79; *p*-value = 0.03), colistin and tigecycline (OR = 0.03; 95% CI: 0.00, 0.32; *p*-value <0.01), and colistin, meropenem and tigecycline (OR = 0.07; 95% CI: 0.01, 0.50; *p*-value <0.01) compared to patients receiving colistin alone. Patients with VAP and VAT were analyzed separately (Tables 1–3). Forty-four patients were diagnosed with VAP (mean age ± SD = 62.0 ± 21.6 years). In this subgroup, the duration of MV was 4 times longer (ratio of colistin + meropenem

Table 1: Summary of patient characteristics.

Characteristics	Entire	Mono	Double Therapy		Triple Therapy
		Colistin	Colistin + Meropenem	Colistin + Tigecycline	Colistin + Meropenem +Tigecycline
Overall	Mean (SD*)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
	(n = 94)	(n = 12)	(n = 36)	(n = 13)	(n = 33)
	n (%)	n (%)	n (%)	n (%)	n (%)
Age	53.3 (23.7)	54.5 (23.7)	54.2 (22.3)	49.5 (28.3)	53.5 (24.2)
APACHE II	22.7 (7.1)	19.1 (8.7)	23.1 (6.3)	25.0 (8.0)	22.6 (6.9)
Infection site					
Respiratory	79 (84.0%)	11 (91.7%)	29 (80.6%)	11 (84.6%)	28 (84.8%)
Bloodstream	15 (16.0%)	1	-8.30%	7 (19.4%)	2 (15.4%)
Microbiological clearance					
Cleared	48 (51.0%)	7	-58.30%	19 (52.8%)	7 (53.8%)
Not cleared	23 (24.5%)	4	-33.30%	8 (22.2%)	3 (23.1%)
Missing data	23 (24.5%)	1	-8.30%	9 (25.0%)	3 (23.1%)
ESRD+ with haemodialysis	26 (28.6%)	4	-36.40%	11 (32.3%)	3 (23.1%)
Acute kidney	33 (35.1%)	4	-33.30%	13 (36.1%)	5 (38.5%)
injury requiring haemodialysis					

Table 2: Summary of patient outcomes.

Outcome	Overall (n = 94)	Mono Therapy (n = 12)	Double Therapy (n = 49)		Triple Therapy (n = 33)
		Colistin Alone	Colistin +Meropenem (n = 36)	Colistin + Tigecycline (n = 13)	Colistin + Meropenem + Tigecycline
Overall	Median (IQR#)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
	n (%)	n (%)	n (%)	n (%)	n (%)
Duration of MV* (days)	21.0 (12.0, 42.0)	23.5 (16.0, 50.0)	18.0 (8.5, 30.5)	27 (15.0, 58.0)	20 (14.0, 47.0)
ICU+ length of stay	29.0 (17.0, 55.0)	35.0 (20.5, 80.0)	28.0 (16.0, 44.0)	34.0(27, 58.0)	25.0 (16.0, 61.0)
Died	45 (47.9%)	9 (75.0%)	19 (52.8%)	4 (30.8%)	13 (39.4%)
VAP$ subgroup	Median (IQR#)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
	n (%)	n (%)	n (%)	n (%)	n (%)
Duration of MV* (days)	20.0 (12.0, 52.0)	23.0 (16.0, 247.0)	12.0 (7.0, 25.0)	50.5 (17.0, 84.5)	20.0 (16.0, 52.0)
ICU+ length of stay (days)	30.5 (16.5, 68.5)	108.0 (39.0,247.0)	24.0 (7.0, 46.0)	59.5 (36.0, 84.5)	30.5 (17.0, 74.0)
Died	27 (61.4%)	5 (100.0%)	10 (66.7%)	2 (50.0%)	10 (50.0%)
VAT& subgroup	Median (IQR#)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
	n (%)	n (%)	n (%)	n (%)	n (%)
Duration of MV* (days)	17.0 (11.0, 25.0)	22.0 (15.5, 27.5)	21.0 (4.0, 29.0)	16.0 (9.0, 28.0)	14.0 (9.0, 21.5)
ICU+ length of stay (days)	24.0 (16.5, 34.0)	20.5 (15.0, 34.0)	27.0 (17.0, 43.0)	28.0 (19.0, 34.0)	20.5 (14.0, 24.5)
Died	12 (33.3%)	3 (50.0%)	6 (40.0%)	1 (14.3%)	2 (25.0%)

* MV: Mechanical Ventilation; + ICU: Intensive Care Unit; # IQR: Interquartile Range; VAP: Ventilator-Associated Pneumonia; VAT: Ventilator-Associated Tracheobronchitis

therapy to colistin alone, 0.25; 95% CI: 0.09, 0.68; *p*-value = 0.01) and the ICU length of stay was 5 times longer (ratio of colistin + meropenem therapy to colistin alone, 0.20; 95% CI: 0.08, 0.54; *p*-value < 0.01) for patients receiving colistin alone compared to patients treated with colistin + meropenem. In addition, the ICU length of stay was 2.94 times longer for patients receiving colistin therapy alone compared to patients treated with the triple therapy (ratio of colistin + tigecycline + meropenem therapy to colistin alone, 0.34; 95% CI: 0.13, 0.89; *p*-value = 0.03). By contrast, MV duration and ICU length of stay for the 36 patients diagnosed with VAT (mean age ± SD = 41.1 ± 19.7 years) did not differ significantly for patients receiving different treatments.

Microbiological analysis

In 2012, more than 90% of *A. baumannii* isolates from our hospital were XDRAB and causative agents of nosocomial

infections. Twelve unique *A. baumannii* strains were isolated and were susceptible to colistin, four of them were susceptible to gentamycin, one was susceptible to tigecycline and two were susceptible to ampicillin/sulbactam. Culture on CHROMagar Acinetobacter medium (CHROMagar, Paris, France) and modified CHROMagar supplemented with an antimicrobial (France) confirmed that all 12 strains studied were MDRAB. The inhibition of *Pseudomonas aeruginosa* growth confirmed the medium was specific medium for *Acinetobacter*. According to the criteria of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the United States Food and Drug Administration (FDA), all of these 12 isolates were XDRAB (53). A MHT was used for detection of carbapenemases other than metallo-beta-lactamases. Overall, carbapenemase activity was detected in all clinical isolates (12/12) of XDRAB. Molecular studies confirmed that the main carbapenem resistance mechanism was mediated by class-OXA-type enzymes (oxa-23 and oxa-24/40) (34).

DISCUSSION

In ICUs, MDRAB Pneumonia is the most common type of infection with a mortality rate of up to 43 % (2). Colistin is usually combined with sulbactam, cephalosporins, carbapenems, piperacillin-tazobactam, monobactams, aminoglycosides, fluroquinolones, rifampin, tetracyclines and tigecycline (34) In this study, we investigated several treatment regimens for effectiveness against XDRAB infections. *A.baumannii* is resistant to a wide range of antibiotics and several studies found that antibiotics belonging to older classes are used preferentially for the treatment of the different infections caused by these strains, including colistin, polymyxin E, and polymyxin B. Despite the nephrotoxicity and neurotoxicity that often occurs when using these agents [20], colistin remains the antibiotic of choice for treating XDRAB infections, and has a cure rate of 55–80% as observed by some studies [21]. In recent years, *A. baumannii* isolates have become increasingly carbapenem-resistant as a result of the activity of OXA-type carbapenemases; however, *Al-obeid et al* detected the carbapenemase activity in all clinical isolates of XDRAB described in his study from Saudi Arabia, and found that OXA-23 was detected in11 out of 12 isolates and OXA-24/40 was detected in only one isolate (39). The use of carbapenem therefore may increase the carbapenemase-producing *A. baumannii* and increases the risk of the emergence of multidrug-resistant strains [22]. Correspondingly, a significant decrease in the prevalence of MDRAB infections was achieved through restriction of carbapenem use in the ICU [23]. Despite the lack of strong clinical evidence supporting the use of combination therapy over colistinmonotherapy, combination therapy is frequently used as a therapeutic approach. Combination therapy is used due to its enhanced efficacy, and also to combat colistin-induced heteroresistance development [24], rapid resistance selection, and drug toxicity. *In vitro, Al obeid et al* detected good synergy between colistin and tigecycline against 25 % of the isolates studied; this synergy was moderate for other antibiotics tested (carbapenem or piperacillin-tazobactam) (34). However, in this retrospective study, our results showed that the combination antibiotic therapies (especially colistin with tigecycline or with meropenem) were associated with better clinical outcomes (reduced mortality, ICU length of stay, and MV duration), than treatment with colistin alone, for patients with VAP and VAT, (Table 2).

Similar to VAP, VAT was associated with a high mortality rate [25]; however, little is known regarding disease management and optimal treatments. In this study, we used retrospective data to compare the effects of colistinmonotherapy and various combination therapies in patients with VAT and VAP. However, numerous confounding factors are present in ICU patients, such as co-morbid conditions, severity of underlying diseases, and

Table 3: Regression analysis with combination as a predictor.

Outcome	Therapy	Overall		VAP[$] subgroup		VAT[&] subgroup	
		Ratio (95% CI*)	p-value	Ratio (95% CI*)	p-value	Ratio (95% CI*)	p-value
%Duration of MV+	Colistin Alone	Reference		Reference		Reference	
	Colistin + Meropenem	0.43 (0.22, 0.85)	0.02	0.25 (0.09, 0.68)	0.01	0.78 (0.27, 2.25)	0.64
	Colistin + Tigecycline	0.78 (0.35, 1.75)	0.54	0.60 (0.17, 2.18)	0.44	0.88 (0.28, 2.72)	0.82
	Colistin + Meropenem+ Tigecycline	0.69 (0.35, 1.36)	0.28	0.50 (0.19, 1.34)	0.17	0.84 (0.27, 2.61)	0.76
%ICU# length of stay	Colistin Alone	Reference		Reference		Reference	
	Colistin + Meropenem	0.51 (0.28, 0.93)	0.03	0.20 (0.08, 0.54)	<0.01	1.28 (0.57, 2.94)	0.55
	Colistin + Tigecycline	0.91 (0.44, 1.92)	0.81	0.54 (0.16, 1.90)	0.34	1.32 (0.54, 3.25)	0.54
	Colistin + Meropenem+ Tigecycline	0.70 (0.38, 1.30)	0.26	0.34 (0.13, 0.89)	0.03	1.11 (0.45, 2.66)	0.83
		Odds Ratio (95% CI*)					
Died	Colistin Alone	Reference					
	Colistin + Meropenem	0.12 (0.02, 0.79)	0.03				
	Colistin + Tigecycline	0.03 (0.00, 0.32)	<0.01				
	Colistin + Meropenem+ Tigecycline	0.07 (0.01, 0.50)	<0.01				

* CI: Confidence Interval; + MV: Mechanical Ventilation; ICU: Intensive Care Unit,
% Outcome was logarithmically transformed in the analysis; VAP: Ventilator-Associated Pneumonia; VAT: Ventilator-Associated Tracheobronchitis

variations in antibiotic treatment onset; therefore our results must be interpreted accordingly. A randomized controlled trial is necessary to confirm or dispute the initial findings of this study. The mean APACHE II score in our study population was 22.7. Prior studies suggested that high APACHE II scores in patients with MDRAB infection are associated with higher 14–30 day mortalities. The mortality rate in our study population was 47.9%, which was similar to that reported in other studies [26]. A recent Turkish study examined 214 patients from more than 27 locations and found that the cure rate and 14-day survival rate were higher in the colistin-based combination treatment group than in the colistinmonotherapy group [27]. This was accompanied by a higher microbiological eradication rate in the combination group than in the single therapy group [27]. Our results also showed that the microbiological eradication rate was higher under combination therapy than in therapy with colistin alone. Lee and colleagues noted that combination carbapenem-sulbactam therapy was associated with better clinical outcomes in critically ill patients with MDRAB bacteremia [28]. Moreover, multiple *in vitro* studies found that antibiotic combination therapy was more effective than monotherapy in treating *A. baumannii* infection [29,30]. Several studies, including the present, showed that tigecycline, which is active against most carbapenemase-producing strains, may be used as an alternative to, or in combination with, polymyxin for the treatment of *A. baumannii* infection. Tigecycline has nevertheless been approved for the treatment of complicated intra-abdominal infections and complicated skin and soft tissue infections [32]. To the best of our knowledge [9,31], this is the first study with sufficient numbers of ICU patients to compare monotherapy with combination therapy in critically ill patients with XDRAB infections. However, a number of study limitations should be considered. First, the number of patients receiving colistinmonotherapy was small (11 patients). Moreover, the results were limited by imprecision, despite having an overall significant effect. Second, retrospective studies are associated with higher risks of bias and greater difficulty in adjusting for confounding factors than randomized controlled trials. Third, the varied colistin dosages used in different patients may have produced variable clinical responses: recent studies suggested that standard doses of colistin might be insufficient for the treatment of Gram-negative MDR infection [33]. Finally, we observed in a number of ICU patients that all-cause mortality was lower with adjuvant inhaled colistin, falling from 45% to 18.75%, with colistin-IV and to 7% with colistin-IV+ Tigecycline intravenous (unpublished observation) [34].

CONCLUSION

In conclusion, we believe that there is an urgent need to enforce infection control measures and antimicrobial stewardship programs to prevent the further spread of these resistant *Acinetobacter* species, especially XDRAB, and to delay the emergence of increased resistance in the bacteria. We propose that colistin-based combination treatment regimens (mainly with tigecycline or with tigecycline and meropenem) are potentially more effective for the treatment of XDRAB induced VAP and VAT than colistinmonotherapy, However, the limitations of the study indicate that our conclusions must be viewed with caution, and that a large randomized controlled trial is needed to confirm these initial findings.

KEY MESSAGE

In treating XDRAB VAP and VAT colistin based combination therapy is more effective than monotherapy.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution at which the studies were conducted.

AVAILABILITY OF DATA AND MATERIALS

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request

AUTHOR CONTRIBUTIONS

AO, WA, MS, HA, HS, SA, SO were involved in data collection and study design. JM carried out the statistical analysis. SS and ZM carried out literature review and final review of the study. All authors read and approved the final manuscript.

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REFERENCES

1. Davis KA, Moran KA, McAllister CK, Gray PJ. Multidrug-resistant *Acinetobacter* extremity infections in soldiers. Emerging infectious diseases. 2005; 11: 1218-1224.
2. Peleg AY, Seifert H, Paterson DL. *Acinetobacterbaumannii*: emergence of a successful pathogen. Clin Microbiol Rev. 2008; 21: 538-582.
3. Fournier PE, Richet H. The epidemiology and control of *Acinetobacterbaumannii* in health care facilities. Clin Infect Dis. 2006; 42: 692-699.
4. Falagas ME, Kasiakou SK, Rafailidis PI, Zouglakis G, Morfou P. Comparison of mortality of patients with *Acinetobacterbaumannii* bacteraemia receiving appropriate and inappropriate empirical therapy. J Antimicrob Chemother. 2006; 57: 1251-1254.
5. Aronson NE, Sanders JW, Moran KA. In harm's way: infections in deployed American military forces. Clin Infect Dis. 2006; 43: 1045-1051.
6. Ferrara AM. Potentially multidrug-resistant non-fermentative Gram-negative pathogens causing nosocomial pneumonia. Int J Antimicrob Agents. 2006; 27: 183-195.
7. Michalopoulos A, Kasiakou SK, Rosmarakis ES, Falagas ME. Cure of multidrug-resistant *Acinetobacterbaumannii* bacteraemia with continuous intravenous infusion of colistin. Scandinavian journal of infectious diseases. 2005; 37: 142-145.
8. Levin AS. Treatment of Acinetobacter spp infections. Exp Opin Pharmacother. 2003; 4: 1289-1296.
9. Shin JA, Chang YS, Kim HJ, Kim SK, Chang J, Ahn CM, et al. Clinical outcomes of tigecycline in the treatment of multidrug-resistant *Acinetobacterbaumanni* infection. Yonsei Med J. 2012; 53: 974-984.
10. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug- resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for

interim standard definitions for acquired resistance. Clin Microbiol Infec. 2012; 18: 268-281.

11. Wunderink RG, Niederman MS, Kollef MH, Shorr AF, Kunkel MJ, Baruch A, et al. Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis. 2012; 54: 621-629.

12. Williams TA, Ho KM, Dobb GJ, Finn JC, Knuiman M, Webb SA, et al. Effect of length of stay i intensive care unit on hospital and long-term mortality of critically ill adult patients. Bri J Anaesthesia. 2010; 104: 459-464.

13. Fabregas N, Ewig S, Torres A, El-Ebiary M, Ramirez J, de La Bellacasa JP, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post- mortem lung biopsies. Thorax. 1999; 54: 867-873.

14. Nseir S, Di Pompeo C, Pronnier P, Beague S, Onimus T, Saulnier F, et al. Nosocomial tracheobronchitis in mechanically ventilated patients: incidence, aetiology and outcome. Eur Respir J. 2002; 20: 1483-1489.

15. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections. 1988. Am J Infection Control. 1988; 16: 128-140.

16. Schoenfeld DA, Bernard GR. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med. 2002; 30: 1772-1777.

17. Ratanarat R, Skulratanasak P, Tangkawattanakul N, Hantaweepant C. Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for predicting hospital mortality in critically ill patients with multi-organ dysfunction syndrome. J Med Assoc Thai. 2013; 96: S224-231.

18. Greenspan EM, Bruckner HW. Comparison of regression induction with triethylenethiophosphoramide or methotrexate in bulky stage IIIb ovarian carcinoma National Cancer Institute monograph. 1975; 42: 173-175.

19. Cook D, Meade M Guyatt G. The Protect Investigators for the Canadian Critical Care Trails Group and the Australian and New Zealand Intensive Care Society Clinical Trials G. Dalteparin versus unfractionated heparin in critically ill patients. N Engl J Med. 2011; 364: 1305-1314.

20. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug- resistant gram-negative bacterial infections. Clin Infect Dis. 2005; 40: 1333-1341.

21. Kallel H, Bahloul M, Hergafi L, Akrout M, Ketata W, Chelly H, et al. Colistin as a salvage therapy for nosocomial infections caused by multidrug-resistant bacteria in the ICU. Int J Antimicrob Agents. 2006; 28: 366-369.

22. Kuo SC, Lee YT, Yang SP, Chiang MC, Lin YT, Tseng FC, et al. Evaluation of the effect of appropriate antimicrobial therapy on mortality associated with *Acinetobacternosocomialis* bacteraemia. Clin Microbiol Inf. 2013; 19: 634-639.

23. Ogutlu A, Guclu E, Karabay O, Utku AC, Tuna N, Yahyaoglu M. Effects of Carbapenem consumption on the prevalence of Acinetobacter infection in intensive care unit patients. Ann Clin Microbiol Antimicrob. 2014; 13: 7.

24. Li J, Rayner CR, Nation RL, Owen RJ, Spelman D, Tan KE, et al. Heteroresistance to colistin in multidrug-resistant *Acinetobacterbaumannii.* Antimicrob Agents Chemother. 2006; 50: 2946-2950.

25. Craven DE, Lei Y, Ruthazer R, Sarwar A, Hudcova J. Incidence and outcomes of ventilator- associated tracheobronchitis and pneumonia. Am J Med. 2013; 126: 542-549.

26. Falagas ME, Rafailidis PI. Attributable mortality of *Acinetobacterbaumannii*: no longer a controversial issue. Crit Care. 2007; 11: 134.

27. Batirel A, Balkan, II, Karabay O, Agalar C, Akalin S, Alici O, et al. Comparison of colistin- carbapenem, colistin-sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant *Acinetobacterbaumannii* blood stream infections. Eur J Clin Microbiol Infect Dis. 2014; 33: 1311-1322

28. Lee NY, Wang CL, Chuang YC, Yu WL, Lee HC, Chang CM, et al. Combination carbapenem- sulbactam therapy for critically ill patients with multidrug-resistant *Acinetobacterbaumannii* bacteremia: four case reports and an in vitro combinationsynergy study. Pharmacotherapy. 2007; 27: 1506-1511.

29. Kiffer CR, Sampaio JL, Sinto S, Oplustil CP, Koga PC, Arruda AC, et al. *In vitro* synergy test of meropenem and sulbactam against clinical isolates of *Acinetobacterbaumannii*. Diagnostic microbiology and infectious disease. 2005; 52: 317-322.

30. Yoon J, Urban C, Terzian C, Mariano N, Rahal JJ. *In vitro* double and triple synergistic activities of Polymyxin B, imipenem, and rifampin against multidrug-resistant *Acinetobacterbaumannii*. Antimicrobial agents and chemotherapy. 2004; 48: 753-757.

31. MutluYilmaz E, Sunbul M, Aksoy A, Yilmaz H, Guney AK, Guvenc T. Efficacy of tigecycline/colistin combination in a pneumonia model caused by extensively drug-resistant *Acinetobacterbaumannii*. Int J Antimicrob Agents. 2012; 40: 332-336.

32. Pankey GA. Tigecycline. J Antimicrob Chemother. 2005; 56: 470-480.

33. Dalfino L, Puntillo F, Mosca A, Monno R, Spada ML, Coppolecchia S, et al. High-dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study. Clin Infect Dis. 2012; 54: 1720-1726.

34. Al-obeid S, Jabri L, Al-Agamy M, Al-Omari A, Shibl A. Epidemiology of extensive drug Resistant *Acinetobacterbaumannii* (XDRAB) at Security Forces Hospital (SFH) in Kingdom of Saudi Arabia (KSA). J Chemother. 2015; 27: 156-162.

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