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Brief Original Article

Impact of colistin-initiation delay on mortality of ventilator-associated pneumonia caused by *A. baumannii*

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Abstract

Introduction: There has been increased incidence and high mortality in cases with ventilator-associated pneumonia (VAP) caused by colistin-only-susceptible *Acinetobacter baumannii* (COS-AB). Colistin has emerged as a therapeutic option for VAP caused by multidrug-resistant Gram-negative organisms including COS-AB. A retrospective study was conducted to examine the impact of early versus late initiation of colistin on 30-day mortality of critically ill patients with VAP caused by COS-AB.

Methodology: Critically ill patients with VAP caused by COS-AB who received colistin were enrolled. The receiver operating characteristic (ROC) curve was used to identify the temporal breakpoint that maximized the difference in 30-day mortality.

Results: A total of 56 patients (34 men and 22 women) were included in the study. About 86% of all cases were late-onset VAP. The 30-day mortality was 46.4%. The rate was higher among patients with admission Acute Physiology and Chronic Health Evaluation II (APACHE II) score > 18 and patients with a delay of more than four days in initiating colistin treatment. The mortality rate was 26.9% among patients with treatment delay of four or fewer days and 63.3% for patients with a treatment delay of more than four days.

Conclusions: A delay of four days or more in initiating colistin in patients with VAP caused by COS-AB significantly increases mortality. Colistin should be considered in the empirical protocols in late-onset VAP cases when COS-AB is highly suspected.

Key words: *Acinetobacter*; colistin; ventilator-associated pneumonia; multidrug resistant.

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Introduction

Ventilator-associated pneumonia (VAP) is the most common infectious complication in intensive care units (ICUs), with an incidence of 10%–30% and mortality rates ranging from 24%–76% [1-3]. There is increasing incidence of VAP caused by multidrug-resistant (MDR) *Acinetobacter baumannii*, a Gram-negative bacillus [4]. Approximately 98% of *Acinetobacter* strains are susceptible to colistin [5]. Colistin is an antibiotic of the polymyxin family produced by *Bacillus colistinus* that has been available since 1959 to treat infections caused by Gram-negative bacteria [6]. It was discontinued in 1970s due to significant nephrotoxicity and neurotoxicity [7,8]. Although experience using colistin to treat VAP is limited, it has been recently recommended in the guidelines as a treatment option for VAP caused by MDR Gram-negative organisms [9]. Guidelines also stress the importance of using empiric treatment regimens based on local pathogen prevalence and susceptibilities to provide adequate initial therapy [10]. The mortality rate increases when the initial antimicrobial therapy is inappropriate [11] and when appropriate therapy is delayed [12].

The aim of this study was to evaluate patients who received colistin for VAP caused by colistin-only-susceptible *Acinetobacter baumannii* (COS-AB), and to measure the impact of a delay in colistin initiation as an appropriate therapy on 30-day mortality.

Methodology

Study design and location

A retrospective, observational study was performed at the critical care unit of King Abdullah University Hospital (KAUH), the main affiliated hospital of Jordan University of Science and Technology (JUST). KAUH is a 640-bed tertiary referral hospital in north Jordan with 24 beds in the critical care unit. The study evaluated clinical and microbiological data of all cases

diagnosed with VAP caused by COS-AB who received intravenous colistin as a definitive monotherapy between January 2009 and November 2014.

Case selection and definitions

All critically ill adult patients (≥ 16 years of age) who developed VAP caused by culture-proven COS-AB and received intravenous colistin during the study period were eligible. Only cases that received colistin as monotherapy were included. When colistin was used as empirical therapy in combination with other antibiotics, only cases who continued with colistin as monotherapy after microbiologic confirmation were included. Patients who received colistin for less than 24 hours, and patients who died within 48 hours of receiving colistin, or who had polymicrobial infection, were excluded. Demographic variables, length of ICU and hospital stay, presence of chronic organ-function insufficiencies (as defined by the acute physiology and chronic health evaluation II [APACHE II] score) upon admission to the ICU, time of intubation, duration of mechanical ventilation, duration of colistin therapy, and nephrotoxicity were recorded. The endpoint of the study was all-cause mortality.

VAP diagnosis is performed by relying on the new surveillance definition of probable pneumonia initiated by Centers for Disease Control and Prevention (CDC) [13,14]. Primary VAP events were categorized as early-onset VAP (within the first four days of endotracheal intubation) or late-onset VAP (after four days of endotracheal intubation). COS-AB strains were defined as *Acinetobacter baumannii* resistant to all routinely tested antibiotic agents, including penicillins, ampicillin/sulbactam, cephalosporins, aztreonam, carbapenems, aminoglycosides, fluoroquinolones, tetracyclines, tigecycline, and rifampin (excluding polymyxin E [colistin]). Identification of isolates was performed according to standard microbiological procedures. Antimicrobial susceptibility testing was performed by either the Kirby-Bauer disk-diffusion method (Oxoid Ltd., Basingstoke, UK) or automated method using the VITEK 2 compact microscan system (BioMérieux, Marcy-l'Étoile, France). The Clinical and Laboratory Standards Institute (CLSI) criteria were used in the interpretation of the susceptibility results [15].

Administration of colistin

All patients treated with intravenous colistimethate-sodium (Profile Pharma, Chechister, UK) as monotherapy were treated for 14 days after microbiologic confirmation. Empiric colistin without microbiological confirmation was only administered by an infectious disease specialist when COS-AB was highly suspected according to local microbiologic epidemiological observation at the time of VAP diagnosis. The dose for colistin was 2,000,000 units every eight hours, adjusted based on renal function. The time delay in starting colistin from the time of VAP diagnosis was recorded. Receiver operating characteristic (ROC) curve analysis was used to examine the temporal breakpoint that maximized the difference in 30-day mortality between clinical diagnosis of VAP and the administration of colistin treatment. In this curve analysis, the study population was divided into two groups: those with a low likelihood of 30-day mortality (early-treatment group) and those with a high likelihood of 30-day mortality (delayed-treatment group). Nephrotoxicity was evaluated using the Risk, Injury, Failure, Loss and End-stage renal disease (RIFLE) criteria [16]. Patients who had end-stage renal disease or required renal replacement therapy (RRT) prior to initiation of colistin were excluded from the analysis of colistin effects on renal function.

Statistical analysis

SPSS version 20 (IBM, Armonk, USA) was used to analyze data. Data was explained with the help of percentages, standard deviations, and mean values. Independent t-test was used to compare the means of demographic and clinical characteristics between patients who died and those who survived. The Chi-square test was used to compare the rates of 30-day mortality based on demographic characteristics and treatment delay of more than four days. Binary logistic regression was used to determine factors associated with 30-day mortality. A p value of < 0.05 was considered statistically significant.

Results

A total of 56 patients (34 men and 22 women) fulfilling the clinical and microbiological criteria for VAP caused by COS-AB were included. Patients' ages ranged between 17 and 85 years with a mean (standard deviation [SD]) of 53.4 (21.5) years. The mean (SD) APACHE II score for all patients was 17.9 (6.6) (range: 5–31). The mean (SD) number of days on colistin was 14.6 (9.7) days. Of all patients, 46.7% had hypertension, 32.1% had diabetes mellitus, 14.3% had chronic kidney disease, 10.7% had heart failure, 7.1% had coronary artery disease, and 5.4% had chronic obstructive pulmonary disease. The ROC curve analysis showed that the number of days of delay has

good discriminative power to predict 30-day mortality. The area under the curve was 0.70 (p = 0.011). The cutoff value of the four-day delay was the best value to categorize the days of delay. The sensitivity was 0.65 and specificity was 0.73. The 30-day mortality was 46.4%. The demographic and clinical characteristics of patients who died and those who survived are shown in Table 1. Patients who died were significantly older than patients who survived (p = 0.015). Other studied characteristics were similar between patients who died and those who survived.

Table 2 shows the 30-day mortality rate based on the studied characteristics. The 30-day mortality rate increased significantly with increasing age. The rate was also higher among patients with ICU admission APACHE II score > 18, and patients with a delay in colistin treatment of more than four days. The 30-day mortality rate was 63.3% for patients with a treatment delay of more than four days, and 26.9% among patients with a treatment delay of four or fewer days. In the multivariate analysis using logistic regression, the only factors associated with 30-day mortality were APACHE II score > 18 and delay in initiating colistin of more than four days (Table 3). The odds of 30-day mortality were significantly higher among patients with a treatment delay of more than four days (OR = 5.2; 95% CI = 1.3–20.3) and among patients with ICU admission APACHE II score > 18 (OR = 5.2; 95% CI = 1.6–25.2).

Table 3. Multivariate analysis of factors associated with 30-day mortality.

Variable	OR	95% CI	P value
APACHE II score at ICU admission			
> 18	6.4	1.6–25.2	0.008
≤18			
Treatment delay of four days or more			
Delay	5.2	1.3–20.3	0.019
No delay			

OR: odds ratio; CI: confidence interval; APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: intensive care unit.

Table 1. Demographic and clinical characteristics of patients.

	Surviving (n = 30)		Deceased (n = 26)		P value
	Mean	SD	Mean	SD	
Age at hospital admission	46.93	21.14	60.77	19.70	0.015
Length of stay in hospital before VAP	8.03	5.66	9.19	7.92	0.527
Length of stay in ICU before VAP	7.03	4.82	8.54	7.82	0.383
Duration of MV before VAP	6.70	4.86	6.38	5.93	0.828
APACHE II score at VAP	17.91	6.87	20.76	5.47	0.118
APACHE II score at ICU admission	5.43	6.49	17.84	6.30	0.199
Length of MV after VAP	14.70	16.05	15.44	7.46	0.839

VAP: ventilator-associated pneumonia; ICU: intensive care unit; MV: mechanical ventilation; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 2. The rate of 30-day mortality based on demographic characteristics and treatment delay of four days or more.

	Surviving		Deceased		
	N	%	N	%	P value
Age (years)					0.040
< 40	14	77.8%	4	22.2%	
40–65	7	46.7%	8	53.3%	
> 65	9	39.1%	14	60.9%	
Gender					0.327
Male	20	58.8%	14	41.2%	
Female	10	45.5%	12	54.5%	
Co-morbidities					0.266
No	16	61.5%	10	38.5%	
Yes	14	46.7%	16	53.3%	
APACHE II score at ICU admission					0.004
> 18	6	26.1	17	73.9	
≤ 18	17	68.0	8	32.0	
Treatment delay of more than four days					0.006
No delay	19	73.1%	7	26.9%	
Delay	11	36.7%	19	63.3%	

APACHE II: Acute Physiology and Chronic Health Evaluation II.; ICU: intensive care unit.

Renal function evaluation

Renal function was analyzed in 51 eligible cases. According to RIFLE criteria, 17 cases (33.3%) developed acute kidney injury: 6 cases in the risk (11.8%), 7 cases in the injury (13.7%), and 4 cases in the failure (7.8%) categories. None of these cases developed persistent acute renal failure with complete loss of renal function, or required RRT. Renal injuries in all cases were reversible after finishing the course of colistin therapy.

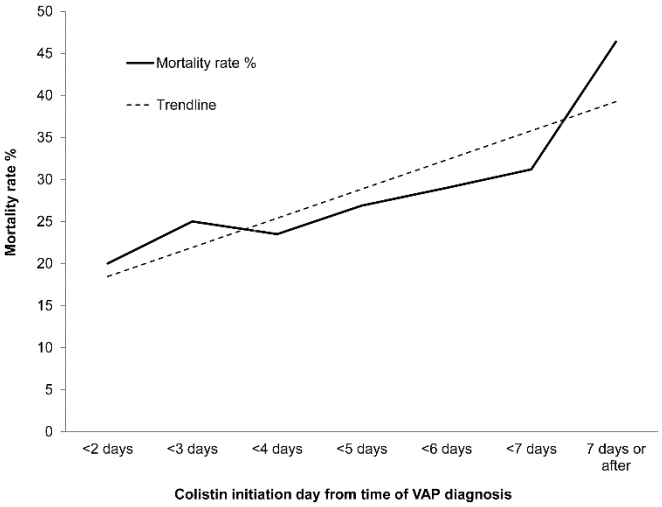
Discussion

Few studies have evaluated the impact of intravenous colistin on overall mortality when it is given as monotherapy to treat VAP caused by COS-AB [5,17-19]. This study confirms that delaying colistin therapy increases mortality in these cases (Figure 1), and that a time delay of more than four days after the clinical diagnosis of VAP can result in a significant increase in mortality rate (63.3%) compared to cases with treatment delay of four or fewer days (26.9%) ($p = 0.006$). Although this is by no means a definitive outcome study, it certainly adds to the body of the literature.

Microbiological confirmation of *A. baumannii* is not immediately available; the average waiting delay is 96 hours [20]. Delaying appropriate therapy, such as colistin, while waiting for susceptibility data or microbiological confirmation might increase mortality, particularly when empirical initial therapy for VAP is inadequate [11]. While waiting for microbiologic confirmation might increase mortality, the effect of early colistin on future resistance to colistin should not be underestimated. Inappropriate empiric or frequent monotherapy use of colistin has raised a concern about development of resistance to colistin, with reported cases of infections with polymyxin-resistant *A. baumannii* strains [21,22]. Therefore, facts that would raise clinical suspicion or assist in early recognition can be valuable in choosing appropriate empiric therapy, particularly in institutions with higher rates of VAP caused by COS-AB. This study shows that most VAP cases caused by COS-AB (48; 86%) were of late-onset VAP with an onset of five days or more post-endotracheal intubation. Applying this finding as part of systemic analysis of local microbiologic data during the development of institutional specific treatment guidelines would help guide appropriate initial therapy, probably improve outcome, and decrease inappropriate use of colistin and future development of resistance.

The ideal dose and duration of colistin has not yet been established [23]. An earlier study demonstrated

Figure 1. Cumulative mortality rate in reference to time of colistin initiation.



that a therapeutic colistin dose of 2 million IU every eight hours resulted in low plasma concentration and undetectable level in the broncho-alveolar lavage. Dose effectiveness was explained by the fact that colistin binds extensively to tissues, including the lungs [24,25]. Recent studies indicated that in most cases, colistin-related nephrotoxicity is characteristically reversible [26-28], with the most consistent risk factor associated with nephrotoxicity being the colistin dose administered [29]. The current study indicates that treatment with intravenous colistin when used in a regimen of 2 million every eight hours decreases mortality, with results comparable to the mortality outcome of a higher dose of colistin (4.5 million units every eight hours) [18]. All renal injuries reported in the study were reversible, with no long-term renal dysfunction after the course of colistin therapy was completed.

In addition to the small sample size coming from a single institution, and to the retrospective methodology, the study lacks post-colistin therapy microbiologic data to evaluate microbiologic response rate in correlation with the clinical response. However, findings are consistent with those of other studies [5,17,18], suggesting that they may be applicable to other populations.

Conclusions

VAP caused by COS-AB is associated with high mortality. Most cases in our study were of late onset. Colistin significantly decreased mortality when used four days or earlier after the clinical diagnosis of VAP. Our data shows that intravenous colistin can be safe and effective. Though we do not suggest that colistin should

be used as first-line therapy for VAP caused by MDR Gram-negative organisms, it might be considered as empirical therapy in cases with late-onset VAP when local microbiologic data highly suggests infection with COS-AB. Subsequent clinical trials to evaluate the impact of empirical therapy of colistin on outcome and to determine the safety and efficacy of different doses of colistin would be beneficial.

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