ORIGINAL ARTICLE
UDC: 616.24-002-008.87-08
https://doi.org/10.2298/VSP180910161M

Inhalatory and intravenous colistin in treating ventilator-associated pneumonia due to *Acinetobacter* species: should we combine them?

Inhalatorni i intravenozni kolistin u lečenju ventilatorom udružene pneumonije izazvane *Acinetobacter* species: da li ih treba kombinovati?

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Abstract

Background/Aim. *Acinetobacter* is one of the most common causes of nosocomial infections, especially ventilator-associated pneumonia (VAP). Considering the increased presence of multidrug-resistant microorganisms and the lack of novel antibiotics, colistin merged as the last-resort antibiotic for life threatening nosocomial infections. Intravenous use of antibiotics is accepted as a gold standard for the treatment of pneumonia, but additional administration of inhaled antibiotics in the treatment of VAP has shown to be advantageous in some clinical trials. The aim of this study was to investigate the effect of inhalatory colistin as an adjunct to intravenous colistin on the survival of patients with VAP caused by *Acinetobacter* species. **Methods.** We conducted a retrospective study to evaluate the efficacy of combination of inhalatory and intravenous colistin vs. intravenous colistin alone in 69 patients in the Intensive Care Units (ICU) with VAP caused by *Acinetobacter baumannii*. The patients were treated in the ICU at the Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica (Serbia) in the period from January, 2013 to March, 2018. Baseline demographic data, severity of the disease, comorbidities, colistin regimen and length of the treatment were collected. The primary outcome was 28-day mortality. **Results.** Twenty seven of total 69 (39.1%) patients received combined intravenous and inhalatory colistin. Forty two (60.9%) patients received only intravenous colistin. Compared to the combined use of the drug (intravenous and inhalatory colistin), patients receiving intravenous colistin alone had a significantly increased risk of death during 28 days [25.9% vs. 61.9%, respectively; odds ratio (OR) 4.464, 95% confidence interval (CI) 1.539–2.925; $p = 0.006$]. Length of colistin use (> 7 days) was also associated with reduced survival (OR 0.22; 95% CI 0.080–0.606; $p = 0.003$). After adjusting for baseline severity of the illness (APACHE score) and length of colistin treatment, patients receiving only intravenous colistin had greater 28-day mortality rate compared to patients receiving both intravenous and inhalatory colistin (OR 6.305; 95% CI 1.795–22.153; $p = 0.004$). **Conclusion.** Our results suggest that adding inhalatory to intravenous colistin might be beneficial in the treatment of VAP caused by *Acinetobacter* species.

Key words:
pneumonia, ventilator-associated; acinetobacter; colistin; administration, inhalation; infusions, intravenous; treatment outcome.

Apstrakt

Uvod/Cilj. *Acinetobacter* je jedan od najčećih uzročnika nozokomijalnih infekcija, posebno pneumonije udružene sa upotrebom ventilatora (VAP). Uzimajući u obzir da je sve veći broj multirezistentnih mikroorganizama, uz nedostatak novih antibiotika, kolistin je našao svoje mesto u lečenju životno ugrožavajućih nozokomijalnih infekcija. Intravenska primena antibiotika je zlatni standard u lečenju pneumonija, ali dodatak inhalatorne, njihovoj sistemskoj primeni u lečenju VAP, pokazala je svoje prednosti u nekim istraživanjima. Cilj naše studije bio je da se ispita efekat inhalatorne primene kolistina, kao dodatka intravenskom načinu primene, na preživljavanje bolesnika sa VAP čiji je uzročnik *Acinetobacter*. **Metode.** Sprovedena je retrospektivna studija kako bi se procenila efikasnost kombinovane inhalatorne i intravenske primene kolistina u odnosu na samo intravensku primenu leka, kod 69 bolesnika sa VAP izazvanim *Acinetobacter* spp. Bolesnici su lečeni u periodu od januara 2013. do marta 2018. godine u Jedinici intenzivnog lečenja Instituta za plućne bolesti Vojvodine u Sremskoj Kamenici (Srbija). Prikupljeni su osnovni demografski podaci, podaci o težini bolesti, komorbiditetima, režimu kolistina i dužini lečenja. Primarni cilj studije bio je 28-dnevni

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mortalitet. **Rezultati.** Dvadeset sedam od ukupno 69 (39,1%) bolesnika primalo je kominaciju intravenskog i inhalatoronog kolistina. Kod 42 bolesnika dat je samo intravenski kolistin (60,9%). U poređenju sa bolesnicima kod kojih je primenjena kombinacija intravenskog i inhalatornog kolistina, bolesnici kod kojih je primenjen samo intravenozni kolistin imali su statistički značajno veći rizik od 28-dnevnog mortaliteta [25,9% vs. 61,9%, *odds ratio* (OR) 4,464; 95% *confidence interval* (CI) 1,539–2,925; p = 0,006]. Dužina lečenja kolistinom (preko 7 dana) takođe je bila povezana sa smanjenim preživljavanjem (OR 0,22; 95% CI 0,080–0,606; p = 0,003). Nakon prilagođavanja uzorka prema težini bolesti (APACHE skor) i dužini lečenja kolistinom, bolesnici koji su primali samo intravenozni kolistin imali su veći 28-dnevni mortalitet u poređenju sa bolesnicima lečenih kombinovanom primenom kolistina: intravenozno i inhalatorno (OR 6,305; 95% CI 1,795–22,153; p = 0,004). **Zaključak.** Rezultati naše studije su pokazali da bi inhalatorna primena kolistina, kao dodatak intravenoznoj primeni leka, mogla da poboljša ishod lečenja VAP uzrokovane *Acinetobacter* spp.

Ključne reči:
pneumonija, respiratorom uzrokovana; acinetobacter; kolistin; inhalaciona primena; infuzije, intravenske; lečenje ishod.

Introduction

According to the Cochrane database review, ventilator associated pneumonia (VAP) occurs in 10% of mechanically ventilated patients [1]. Earlier studies reported that depending on the underlying conditions and the pathogenicity of the infecting organisms, the mortality rates varied from 10% to 70% [2–4]. As stated in guidelines of the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS), the empirical treatment of VAP is based on the risk assessment of multidrug resistant infection. Inadequate initial therapy is associated with higher mortality and prolonged length of stay in an intensive care unit (ICU LOS) [5]. Early application of adequate antibiotic therapy is of crucial importance in the treatment of VAP. Postponement of antibiotic application as well as inadequate antibiotic therapy, even when later changed according to microbiological cultures, lead to higher mortality [6]. The choice of therapy should be based on the initial microbiological map, minding the side effects, as well as the previous antibiotic therapy in the last two weeks [5, 7].

Due to its high virulence and increased antimicrobial resistance, *Acinetobacter* is one of the most common causes of nosocomial infections, especially VAP. Imipenem was recommended as the first line treatment of pneumonia caused by *Acinetobacter baumannii*, until its resistance occurred to most antibiotics including aminoglycosides, carbapenems and fluoroquinolones [8–10].

In the 1950s, antibiotics polymyxin B and E (also known as colistin) were introduced for the treatment of infections caused by Gram-negative bacilli, but even though they were highly effective, they fell out of favor in human medicine due to nephrotoxicity [11, 12]. Considering the increased presence of multidrug-resistant microorganisms (*Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa*), and the lack of novel antibiotics, polymyxins emerged as the last-resort antibiotics for life threatening nosocomial infections in the 21st century [13, 14].

Intravenous use of antibiotics is accepted as a gold standard for the treatment of pneumonia, but additional administration of inhaled antibiotics with their systemic use in the treatment of VAP has shown to be advantageous in some clinical studies [15–18].

Even though the idea to enhance the antibiotic concentration in the lungs by inhalation is rational, there is not enough published reports to elucidate the benefits of such a route of administration [19–21]. The studies related to this subject are scarce and have conflicting results. Despite the emerging colistin use, the recommendations for dosing regimens vary and the beneficial effects of inhalatory treatment remains insufficiently investigated [22, 23].

The aim of this study was to investigate the effect of inhalatory colistin as an adjunct to intravenous colistin on the survival of patients with VAP caused by *Acinetobacter* species.

Methods

A retrospective analysis was conducted in the period from January 2013 to March 2018. All ethical procedures were done in accordance with requirements of the Institute for Pulmonary Diseases of Vojvodina (IPDV), Sremska Kamenica, Serbia.The study included a total of 69 patients who were treated in the ICU of the IPDV. Those 69 patients received colistin for the treatment of VAP caused by *Acinetobacter*. Colistin was administered in two ways, only intravenously or in combination, both inhalatory and intravenously. The experimental group consisted of 27 patients who received both intravenous and inhalatory colistin, while the control group consisted of 42 patients who received only intravenous colistin.

The criteria for diagnosing VAP were based on recommendations for hospital-acquired pneumonia (HAP) and VAP from 2016 [5]. The patients were mechanically ventilated for a minimum of 48 hours, with a new infiltration on the chest X-ray or a progression of already existing infiltration with two of the following three criteria: fever over 38.5 °C or hypothermia below 35.5 °C, leukocytosis > 10,000/μL or leukopenia < 4,000/μL and purulent endotracheal aspiration. Non-invasive sampling and semi-quantitative determination were performed to determine the microbiological cause. The significant non-invasive quantitative sampling value was ≥ 10^5 colony forming unit (CFU)/mL. If the sampling was invasive with the quantitative determination of the causative agent, the threshold for the diagnosis of VAP was ≥10^4 CFU/mL for bronchoalveolar lavage [5].

Baseline demographic data and severity of illness [the Acute physiology and chronic health evaluation (APACHE) II [24], and the Sequential organ failure assessment (SOFA) scores] [25], presence of acute respiratory distress syndrome (ARDS) [26], septic shock [27] and acute renal failure (defined by the Kidney Disease: Improving Global Outcomes – KDIGO) [28], comorbidities, colistin regimen (intravenous vs. intravenous and inhalatory) and length of treatment were recorded. The primary outcome was 28-day mortality.

For statistical analysis, continuous variables were presented as mean and standard deviations (SD), while categorical variables were expressed as whole numbers and percentages. The influence of different colistin protocols on 28-day mortality was investigated using binary logistic regression analysis. All predictors that were statistically significant in the univariate analysis were entered into the multivariate model. The final model included APACHE score, length of treatment and colistin regimen. Statistical significance for all variables was set on p value 0.05. All statistical tests were performed using SPSS version 21.

Results

A total of 69 patients, 48 (69.6%) men, median age 56.64 ± 14.22 years, were included in the study. Mean APACHE score was 20.8 (± 5.8) and mean SOFA score was 6.8 (± 2.8). At admission, 55.1% of the patients were diagnosed with ARDS, 33.3% with septic shock and 36.2% with acute kidney injury. Almost 25% of patients, who developed VAP, had chronic respiratory diseases, primarily chronic obstructive pulmonary disease (COPD). Among other comorbidities, cardiovascular diseases, immune deficiency and diabetes were most common. The ICU mortality was 53.6% (37/69), 28-days mortality was 47.8% (33/69) and median ICU LOS was 19.59 (± 12.5) days. The differences in baseline characteristics between the patients who received intravenous and those who received combined intravenous and inhalatory colistin are presented in Table 1. There was no difference in length of hospital stay (35 ± 17 days in combined regimen group vs. 27 ± 19 days in intravenous regimen group; $p = 0.07$).

In Table 2 the univariate analysis of the factors associated with 28-days mortality is presented. In our study, 27 (39.1%) of total 69 patients received combined intravenous and inhalatory colistin. Forty two (60.9%) patients received only intravenous colistin. Compared to the combined use of the drug, patients receiving intravenous colistin alone had a significantly increased risk of death during 28 days (OR 4.464; 95% CI 1.539–2.925; $p = 0.006$). Length of colistin use was also associated with the increased risk of death (OR 0.22; 95% CI 0.080–0.606; $p = 0.003$ for patients receiving colistin for more than 7 days). In the multivariate analysis when adjusted for baseline severity of illness and length of colistin treatment, patients receiving only intravenous colistin had greater 28-day mortality rate compared to the patients receiving both intravenous and inhalatory colistin (OR 6.305; 95% CI 1.795–22.153; $p = 0.004$) (Table 3).

Table 1

Baseline characteristics of patients

Characteristcs	Values
Total number, n (%)	48 (69.6)
Gender, n (%)	
male	48 (69.6)
female	21(30.4)
Severity of illness, mean (± SD)	
APACHE	20.8 (± 5.8)
SOFA	6.8 (± 2.8)
ARDS, n (%)	
no	31 (44.9)
yes	38 (55.1)
Sepsis, n (%)	
no	23 (33.3)
yes	46 (66.7)
Septic shock, n (%)	
no	46 (66.7)
yes	23 (33.3)
Acute kidney failure, n (%)	
no	44 (63.8)
yes	25 (36.2)
Chronic comorbidities, n (%)	
COPD	
no	52 (75.4)
yes	17(24.6)
diabetes	
no	57 (82.6)
yes	12 (17.4)
malignancy	
no	63 (91.3)
yes	6 (8.7)
chronic kidney insufficiency	
no	67 (97.1)
yes	2 (2.9)
hepatic insufficiency	
no	66 (95.7)
yes	3 (4.3)
cardiovascular comorbidities	
no	55 (79.7)
yes	14 (20.3)
neurological comorbidities	
no	62 (89.9)
yes	7 (10.1)
immune compromise	
no	52 (75.4)
yes	17 (24.6)
gastric ulcer	
no	65 (94.2)
yes	4 (5.8)
Need for CRRT, n (%)	
before colistin use	
no	52 (75.4)
yes	17 (24.6)
after colistin use	
no	41 (59.4)
yes	28 (53.6)

APACHE – Acute physiology and chronic health evaluation;
ARDS – Acute respiratory distress syndrome;
SOFA – Sequential organ failure assessment;
COPD – Chronic obstructive pulmonary disease;
CRRT – Continuous renal replacement therapy;
SD – standard deviation.

Table 2
Impact of predictive factors on 28-day mortality by univariate analysis

Predictive factors	*p*	OR	95% CI	
			lower limit	upper limit
Gender				
male	0.308			
female		1.00[a]		
		1.174	0.609	4.828
Age	0.211	1.022	0.988	1058
*APACHE	0.023	1.114	1.015	1.233
SOFA	0.287	1.098	0.925	1.303
WBC ($\times 10^{-9}$)	0.639	0.988	0.942	1.037
ARDS				
no	0.570	1.00[a]		
yes		0.759	0.293	1.965
Sepsis				
no	0.308	1.00[a]		
yes		1.697	0.613	4.696
Septic shock				
no	0.051	1.00[a]		
yes		2.917	1.028	8.273
Acute kidney insufficiency				
no	0.601	1.00[a]		
yes		1.300	0.486	3.477
COPD				
no	0.299	1.00[a]		
yes		1.801	0.594	5.466
Diabetes mellitus				
no	0.159	1.00[a]		
yes		2.560	0.691	9.481
Malignancy				
no	0.103	1.00[a]		
yes		6.250	0.690	56.621
Hepatic insufficiency				
no	0.514	1,00[a]		
yes		2.258	0.195	26.132
Cardiovascular comorbidities				
no	0.437	1.00[a]		
yes		1.600	0.490	5.288
Neurological comorbidities				
no	0.605	1.00[a]		
yes		1.517	0.313	7.351
Immune compromise				
no	0.528	1.00[a]		
yes		0.528	0.231	1.965
Gastric ulcer				
no	0.929	1.00[a]		
yes		1.097	0.146	8.264
CRRT before colistin				
no	0.627	1.00[a]		
yes		1.312	0.438	3.933
CRRT after colistin				
no	0.079	1.00[a]		
yes		2.415	0.902	6.462
Febrile				
no	0.204	1.00[a]		
yes		0.528	0.197	1.415
Creatinine clearance	0.75	1.004	0.981	1.027
*Intravenous and inhalatory colistin				
no	0.006	4.464	1.539	2.925
yes		1.00[a]		
Bolus dose of colistin	0.527	0.942	0.782	1.134
Dose of colistin	0.686	2.362	0.037	151.692
Dosing interval of colistin	0.257	1.080	0.946	1.233

Table 2 (*continued*)

Predictive factors	*p*	OR	95% CI	
			lower limit	upper limit
*Length of colistin treatment				
≤ 7days	0.003	1.00[a]	0.080	0.606
> 7 days		0.220		
Ventilator days	0.402	1.018	0.976	1.063
ICU days	0.461	0.985	0.946	1.025

APACHE – Acute physiology and chronic health evaluation; SOFA – Sequential organ failure assessment; ARDS – Acute respiratory distress syndrome; COPD – Chronic obstructive pulmonary disease; CRRT – Continuous renal replacement therapy; WBC – white blood cells; ICU – intensive care unit; OR – odds ratio; CI – confidence interval. [a] – reference category; *statistically significant.

Table 3
Impact of predictive factors on 28-daily mortality by multivariate analysis

Predictive factors	*p*	OR	95% CI	
			lower limit	upper limit
APACHE	0.008	1.171	1.042	1.317
Intravenous and inhalatory colistin				
no	0.004	6.305	1.795	22.153
yes		1.00[a]		
Length of colistin treatment				
≤ 7days	0.019	1.00[a]	0.069	0.733
> 7days		0.225		

APACHE – Acute physiology and chronic health evaluation; [a] – reference category; OR – odds ratio; CI – confidence interval.

Considering the adverse effects of colistin use, need for continuous renal replacement therapy (CRRT) before and after colistin use was recorded. There was no difference in frequency of renal failure requiring continuous renal replacement therapy between the two groups of patients (17/42, 40.5% vs. 11/27, 40.7%; $p = 0.98$).

Discussion

The results of this study indicated that intravenous treatment with colistin was associated with 6-fold increase in 28-days mortality compared to combined intravenous and inhalation colistin regimen (61.9% vs. 25.9%, respectively; OR 6.305; 95% CI 1.795–22.153). The combined treatment resulted in prolonged length of hospital stay in relation to the intravenous only regimen, that was not statistically significant difference (35 vs. 27 days, respectively; $p = 0.07$).

Literature search revealed a small quantity of published studies that investigated the relation of the inhalatory colistin addition to the intravenously administered drug and their correlation with the 28-day mortality rate. Nevertheless, results from previous studies examining effects of the inhalatory colistin addition to the intravenous monotherapy treatment are conflicting [21, 29, 30]. These discrepancies among published studies were explained in the conclusion of the study by Tumbarello et al. [30] where it was stated that their investigation was conducted on a substantially larger population (being the largest study so far with 208 patients) and significant improvement of clinical cure rates were observed [31, 32]. These findings are in direct correlation with our investigation elucidating the substantial decrease in risk of ICU mortality and 28-day mortality when a combined treatment was carried out. Moreover, Tumbarello et al. [30] emphasized that an important role in further investigation should be to optimize the colistin use in order to enhance the efficacy without increasing the adverse renal effects. Additionally, it was stressed out that randomized controlled trials are needed for further clarification of benefits and risks of the combined treatment. Earlier review studies indicated that major adverse effect of colistin use could be nephrotoxicity, but results were inconclusive and could not allow for a more significant conclusion concerning the correlation of nephrotoxicity and colistin use [33]. These concerns have also been raised in recent publications for both intravenous and inhalatory route of the drug administration, where no increase in nephrotoxicity was reported with inhaled colistin as adjunctive therapy to the intravenous one, which is also in accordance with our findings [21, 34–36]. The overall conclusion of these studies was that the inhaled colistin seems to be beneficial in the VAP therapy and can be considered as safe, even though limitations and drawbacks were observed, mainly as inconsistent and limited data. A more detailed investigation of colistin nephrotoxicity and neurotoxicity was recently reported in the study of Abdellatif et al. [37], where renal safety was underlined as one of several benefits of aerosolized colistin regimen vs. intravenous.

It should be noted that the significant benefits of the colistin inhalotory enrollment in the combined therapy was

recognized in the latest hospital-associated pneumonia (HAP) and VAP guidelines of IDSA and ATS suggesting both inhaled and systemic antibiotics for patients with VAP, but with very low quality evidence [5]. Therefore, the results of our study could contribute to stronger evidence, essential for future guidelines as well as to the ongoing investigation of this therapeutic approach. Two studies out of nine, that were cited in the mentioned guidelines, directly concentrated their research on the beneficial effects of the inhaled colistin combined with intravenous colistin monotherapy [36, 38]. Korbila et al. [36] concluded that the application of the inhaled colistin was an independent predictor of cure of VAP, but no difference in all-cause in-hospital mortality and all-cause ICU mortality was detected. Three years later, Doshi et al. [38] published their results, obtained from three tertiary-care academic medical centers, stating that the addition of aerosolized colistin to intravenous colistin may improve clinical cure and mortality for patients with multidrug resistant gram-negative (MDR-GN) pneumonia. These findings are in accordance with our results elucidating the hypothesis of our research.

As previously mentioned, results obtained in our study showed that patients receiving only intravenous colistin had greater ICU mortality compared to the group of patients who received combined intravenous and inhalatory colistin (24/42, 57.1% vs. 13/27, 48.1%, respectively; $p = 0.465$). These results are in correlation with other studies comparing these two regimens of colistin administration, where collected data showed ICU mortality of 35.9–52.9% vs. 24–43.3%, respectively [21, 30, 36, 38].

The present study has some limitations that are very similar to the limitations stated in almost all previous investigations published on this subject. The limitations of our study are retrospective single-center nature, slight variations in the administration of the inhalatory colistin as well as dosing variations.

Conclusion

Our study demonstrated that adjunct of inhalatory colistin to intravenous colistin may significantly decrease 28-day and ICU mortality in the treatment of VAP caused by *Acinetobacter*. Therefore, we suggest the use of the mentioned treatment approach. High quality randomized controlled multicenter trials are urgently needed to validate the additional benefits of inhaled colistin in this setting.

Acknowledgement

The authors would like to thank Zoran Topalov for statistical analysis and Milica Hadnadjev Kostić for significant scientific contribution in writing this manuscript.

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Received on September 10, 2018.
Revised on September 28, 2018.
Accepted on October 2, 2018.
Online First October, 2018.