Original Article

Comparison of Microbiological Eradication and Mortality in Patients Receiving Single Therapy of Aerosolized Colistin and Combination Therapy of Aerosolized Colistin and Intravenous Antibiotics

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Objective: Aerosolized colistin has been used for multidrug-resistant gram-negative bacilli pneumonia. The aim of this study was to compare the clinical response and microbiological eradication of single therapy with aerosolized colistin and combination therapy of aerosolized colistin and intravenous antibiotics.

Methods: Patients older than 18 years with pneumonia caused by gram-negative bacilli and receiving colistin therapy during January 1, 2013 to June 30, 2014 were retrospectively included in this study. Demographic data, clinical information, outcome, and microbiological eradication were compared between the single therapy and combination therapy groups.

Results: During the study period, 84 patients were included. Among these, 53 (63.1%) were male and the mean age was 69.3 years. The most prevalent comorbidity was hypertension (56%), followed by chronic kidney disease (35.7%). Nineteen (22.6%) patients received aerosolized colistin alone and 65 (77.4%) used combination therapy of aerosolized colistin and intravenous antibiotics. The overall eradication rate of microorganism was 66.7%. *Pseudomonas aeruginosa* was more difficult to be eradicated than *Acinetobacter baumannii* (adjusted odds ratio [OR], 5.43; 95% confidence interval [CI], 1.44 – 20.44; $p = 0.012$). Single therapy of aerosolized colistin was significantly associated with eradication failure (adjusted OR, 4.42; 95% CI, 1.07 – 18.23; $p = 0.040$). Chronic obstructive pulmonary disease (adjusted OR, 11.49; 95% CI, 2.61 – 50.49; $p = 0.001$) and failure of microbiological eradication (adjusted OR, 7.11; 95% CI, 1.55 – 32.63; $p = 0.012$) were independent risk factors of mortality in patients who received aerosolized colistin treatment.

Conclusions: Combination therapy of intravenous antibiotics and aerosolized colistin is suggested in patients with multidrug-resistant gram-negative bacilli pneumonia.

Keywords: Colistin, aerosolized therapy, multidrug resistance, gram-negative bacilli, pneumonia

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Introduction

Aerosolized antibiotics have been used for a long time in the treatment of lower airway infection in patients with cystic fibrosis.[1,2] Increasing data support the use of aerosolized antibiotics in non-cystic fibrosis pulmonary infection, such as ventilator-associated pneumonia. For recently emerging multidrug-resistant *Acinetobacter* and *Pseudomonas* pulmonary infections, colistin has been regarded as the last-line antimicrobial therapy.[3] However, the use of intravenous colistin is limited due to its nephrotoxicity and poor lung pharmacokinetics.[4,5] By contrast, aerosolized colistin has been increasingly used in Europe and the USA for the treatment of chronic *P aeruginosa* infection.[2]

Several studies have demonstrated that aerosolized colistin is an effective adjuvant treatment for multidrug-resistant gram-negative bacilli pneumonia.[6-11] Some studies revealed that aerosolized antibiotics alone may be also effective for the treatment of pneumonia.[12-16] However, little information is available on the risk factors of microbiological failure and case-fatality in patients with aerosolized colistin treatment. The aim of this study was to compare the microbiological eradication rates of single therapy with aerosolized colistin and combination therapy of aerosolized and intravenous antibiotics. We also investigated the risk factors of mortality in patients receiving aerosolized colistin therapy for multidrug-resistant gram-negative bacilli pneumonia.

Materials and Methods

Study setting and study design

This retrospective study was conducted at a 1,000-bed university-affiliated medical center that serves more than 2 million people in Taiwan. This study was approved by the hospital's Institutional Review Board (EMRP-104-039). Patients older than 18 years with pneumonia caused by gram-negative bacilli and receiving aerosolized colistin therapy during January 1, 2013 to June 30, 2014 were enrolled in this study. A single multidrug-resistance gram-negative bacilli was cultured from each enrolled patient's sputum. Patients with cystic fibrosis were excluded from this study. Patients were categorized into two groups: group 1, single therapy with aerosolized colistin alone; and group 2, combination therapy of aerosolized colistin and intravenous antibiotics. The dose and frequency of aerosolized colistin therapy were prescribed according to the suggestion of literature.[17] Demographic characteristics, clinical information, acute physiology and chronic health evaluation (APACHE) II score, laboratory data, and 30-day mortality were collected from medical records.

Definitions

Pneumonia were diagnosed by respiratory medicine specialists according to the clinical symptoms, signs, microbiological data, and radiologic findings.[18] Sputum culture were performed before and one week after the treatment of colistin. "Multidrug-resistant" gram-negative bacilli was defined as the gram-negative bacilli isolate is non-susceptible to at least one agent in three or more antibiotic classes. The susceptibilities of microorganisms were evaluated according to the interpretive standards of the Clinical and Laboratory Standards Institute guidelines. The success of microbiological eradication was defined as negative sputum culture 7 days after aerosolized colistin treatment. Microbiological failure was defined as persistently positive sputum culture 7 days after the treatment. The dosage of aerosolized colistin is expressed as milligrams of colistin base activity (CBA).

Data analysis

The data were analyzed using Statistical Product and Service Solutions (SPSS)

Table1. Demographic data, comorbidity, pathogen, systemic antibiotics use and clinical outcome of included patients

Variable	Total patients (n = 84) (%)	Aerosolized colistin only (n = 19) (%)	Combination therapy of aerosolized and intravenous antibiotics (n = 65) (%)	*p* value
Age (mean ± SD) (year)	69.3 ± 14.0	68.6 ± 12.2	69.5 ± 14.6	0.819
Sex, male	53 (63.1)	11 (57.9)	42 (64.6)	0.593
APACHE II score (mean ± SD)	18.0 ± 6.9	16.4 ± 6.3	18.5 ± 7.0	0.259
Comorbidity				
Hypertension	47 (56.0)	10 (52.6)	37 (56.9)	0.740
Chronic kidney disease	30 (35.7)	4 (21.1)	26 (40.0)	0.176
Diabetes mellitus	29 (34.5)	5 (26.3)	24 (36.9)	0.392
Cardiovascular disease	29 (34.5)	7 (36.8)	22 (33.8)	0.809
Cerebrovascular disease	25 (29.8)	6 (31.6)	19 (29.2)	0.844
Chronic obstructive pulmonary disease	18 (21.4)	5 (26.3)	13 (20.0)	0.555
Cancer	17 (20.2)	3 (15.8)	14 (21.5)	0.751
End-stage renal disease	12 (14.3)	1 (5.3)	11 (16.9)	0.282
Liver cirrhosis	5 (6.0)	0	5 (7.7)	0.583
Pathogen				
Acinetobacter baumannii	45 (53.6)	10 (52.6)	35 (58.3)	0.926
Pseudomonas aeruginosa	25 (29.8)	8 (42.1)	17 (26.2)	0.181
Others	5 (6.0)	0	5 (7.7)	0.583
No identification	9 (10.7)	1 (5.3)	8 (12.3)	0.677
Duration of aerosolized colistin (mean ± SD) (day)	10.3 ± 7.7	8.5 ± 3.5	10.8 ± 8.5	0.262
Dose and frequency of aerosolized colistin				0.278
66.8 mg Q8H–Q12H	57 (67.9)	15 (78.9)	42 (64.6)	
133.6-167 mg Q8H–Q12H	27 (32.1)	4 (21.1)	23 (35.4)	
Systemic antibiotics				
Carbapenem	24 (28.6)		24 (36.9)	
Anti-Pseudomonas beta-lactams	19 (22.6)		19 (29.2)	
Tigecycline	14 (16.7)		14 (21.5)	
Ciprofloxacin or levofloxacin	5 (6.0)		5 (7.7)	
Colistin	2 (2.4)		2 (3.1)	
Ampicillin/sulbactam	1 (1.2)		1 (1.5)	
Length of hospital stay (mean ± SD) (day)	41.8±30.6	48.5±44.5	40.0±25.3	0.284
Length of ICU stay (mean ± SD) (day)	19.2±12.4	23.0±15.0	18.5±12.1	0.464
Mortality	21 (25.0)	3 (15.8)	18 (27.7)	0.376

APACHE : acute physiology and chronic health evaluation; SD: standard deviation

version 24.0 (IBM, Armonk, NY, USA). For the univariate analysis, categorical variables were compared with the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using Student's t-test or Mann-Whitney U-test. Two-tailed p values < 0.05 were considered to be statistically significant. To identify the risk factors of mortality and microbiological eradication, factors with a level of significance < 0.20 in univariate analyses were included in the multivariate logistic regression analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results

Characteristics and clinical manifestations of included patients

During the study period, 84 patients were included in this study (Table 1). This study include ventilator-associated pneumonia (33, 39.3%), heathcare-associated pneumonia (non-ventilator-associated pneumonia) (21, 25.0%), ventilator-associated tracheobronchitis (17, 20.2%) and non-ventilator-associated tracheobronchitis (13, 15.5%).There were no significant differences of age, sex, APACHE II scores, and comorbidities between these two groups. *A baumannii* and *P aeruginosa* were identified in 45 (53.6%) and 25 (29.8%) patients, respectively. The mean duration of aerosolized colistin was 10.3days (standard deviation, 7.7 days). There were no differences in the duration, dosage, and frequency of aerosolized colistin between these two groups. The overall mortality rate of included patients was 25%. The mortality, length of ICU stays, length of hospital stays non-significantly differed between the single therapy of aerosolized colistin and combination therapy of aerosolized colistin and intravenous antibiotics.

Risk factor of microbiologic eradication failure

Of the 84 patients, 57 were evaluated for microbiological eradication (Table 2). There are 27 patients who didn't have repeat sputum culture after aerosolized colistin treatment. Therefore, we cannot evaluate the result for microbiological eradication among these patients. The overall eradication rate of microorganism was 66.7% (38/57). The eradication rate of *A baumannii* was 76.3%. In contrast, the successful eradication of *P aeruginosa* was only 37.5%. Multivariate analysis showed *P aeruginosa* was more difficult to be eradicated than *A baumannii* (adjusted OR, 5.43; 95% CI, 1.44 – 20.44; $p = 0.012$). There were no significant influences of corticosteroid use and dose/frequency of aerosolized colistin in the eradication of pathogens. Failure of microbiological eradication was significantly higher in patients

Table2. Risk factors of microbiological failure

Variable	Failure of eradication (n = 19) (%)	Success of eradication (n = 38) (%)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Pathogen						
Acinetobacter baumannii	9 (23.7)	29 (76.3)	0.28 (0.09–0.90)	0.033	1 (referent)	
Pseudomonas aeruginosa	10 (62.5)	6 (37.5)	5.93 (1.69–20.76)	0.005	5.43 (1.44–20.44)	0.012
Other pathogens	0	3 (100)	0	0.999	0	0.999
Corticosteroid use	4 (30.8)	9 (69.2)	0.86 (0.23–3.26)	0.823		
Dose and frequency of aerosolized colistin						
133.6-167 mg Q8H–12H	6 (26.1)	17 (73.9)	0.57 (0.18–1.82)	0.342		
66.8 mg Q8H–Q12H	13 (38.2)	21 (61.2)	1.75 (0.55–5.59)	0.342		
Aerosolized colistin alone	8 (61.5)	5 (38.5)	4.80 (1.30–17.78)	0.019	4.42 (1.07–18.23)	0.040

Table3. Risk factors of 30-day mortality

Variable	Death (n = 21) (%)	Survival (n = 63) (%)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Age ≥ 65 years	16 (76.2)	40 (63.5)	1.84 (0.60–5.68)	0.289		
Sex, male	13 (61.9)	40 (63.5)	0.93 (0.34–2.59)	0.896		
APACHE II score (mean ± SD)	21.0 ± 7.9	17.0 ± 6.3	1.09 (1.01–1.17)	0.030	1.10 (0.99–1.23)	0.066
Comorbidity						
Hypertension	13 (69.1)	34 (54.0)	1.39 (0.51–1.89)	0.527		
Diabetes mellitus	6 (28.6)	23 (36.5)	0.70 (0.24–2.04)	0.509		
Cardiovascular disease	8 (38.1)	21 (33.3)	1.23 (0.44–3.43)	0.691		
Cerebrovascular disease	3 (14.3)	22 (34.9)	0.31 (0.08–1.17)	0.084	0.94 (0.19–4.79)	0.944
Liver cirrhosis	1 (4.8)	4 (6.3)	0.74 (0.08–7.00)	0.791		
Chronic kidney disease	9 (42.9)	21 (33.3)	1.50 (0.55–4.12)	0.432		
End-stage renal disease	4 (19.0)	8 (12.74)	1.62 (0.43–6.04)	0.474		
Chronic obstructive pulmonary disease	11 (52.4)	7 (11.1)	8.80 (2.75–28.13)	<0.001	11.49 (2.61–50.49)	0.001
Cancer	4 (19.0)	13 (20.6)	0.91 (0.26–3.15)	0.875		
Corticosteroid use	9 (42.9)	13 (20.6)	2.89 (1.01–8.31)	0.045	2.79 (0.63–12.30)	0.17
Pathogen						
Acinetobacter baumannii	12 (57.1)	33 (52.4)	1.21 (0.48–3.28)	0.705		
Pseudomonas aeruginosa	5 (23.8)	20 (31.7)	0.67 (0.22–2.10)	0.493		
No identification	3 (14.3)	6 (9.5)	1.58 (0.36–6.98)	0.544		
Others	1 (4.8)	4 (6.3)	0.74 (0.77–6.99)	0.791		
Dose and frequency of aerosolized colistin						
133.6-167 mg Q8H–Q12H	4 (19.0)	23 (36.5)	0.41 (0.12–1.36)	0.146	0.19 (0.04–1.07)	0.060
66.8 mg Q8H–Q12H	17 (81.0)	40 (63.5)	2.44 (0.73–8.15)	0.146	5.13 (0.93–28.51)	0.060
Failure of microbiological eradication	9 (42.9)	10 (15.9)	3.98 (1.33–11.91)	0.014	7.11 (1.55–32.63)	0.012

APACHE : acute physiology and chronic health evaluation; SD: standard deviation

who received single therapy of aerosolized colistin than those received combination therapy of aerosolized colistin and intravenous antibiotics (adjusted OR, 4.42; 95% CI, 1.07 – 18.23; $p = 0.040$).

Risk factor of mortality

We further investigated the risk factor of mortality in patients who received aerosolized colistin treatment (Table 3). Univariate analysis showed that patients with a higher APACHE II score (OR, 1.09; 95% CI, 1.01 – 1.17; $p = 0.030$), chronic obstructive pulmonary disease (OR, 8.80; 95% CI, 2.75 – 28.13; $p < 0.001$), corticosteroid use (OR, 2.89; 95% CI, 1.01 – 8.31; $p = 0.045$), and failure of microbiological eradication (OR, 3.98; 95% CI, 1.33 – 11.91; $p = 0.014$) were at risk for mortality. Multivariate analysis revealed that chronic obstructive pulmonary disease (adjusted OR,11.49; 95% CI, 2.61 – 50.49; $p = 0.001$) and failure of microbiological eradication (OR, 7.11; 95% CI, 1.55 – 32.63; $p = 0.012$) were independent risk factors of mortality in patients who received aerosolized colistin treatment.

Discussion

Few studies investigated the efficacy of aerosolized colistin single therapy on lower respiratory tract infections in non-cystic fibrosis patients. A recent study found that aerosolized colistin decreased tracheal secretion, purulence, and bacterial load in a group of patients with ventilator-associated tracheobronchitis due to

multidrug-resistant gram-negative bacilli.[19] In our study, the microbiological eradication succeeded in 66.7% of patients, which was similar to previous reports.[6-10] Nevertheless, our study revealed combination therapy of aerosolized colistin and intravenous antibiotics had a better microbiological outcome than the single therapy of aerosolized colistin alone.

Regarding to the multidrug-resistant pathogens, the eradication rate of *P aeruginosa* by colistin was significantly lower than that of *A baumannii*. Previous studies also described similar results.[8,20] Tumbarello et al. reported the eradication rates of multidrug-resisant *A baumannii* and *P aeruginosa* by aerosolized colistin were 64% and 25%, respectively.[8] Lu et al. described the eradication rates were 91% in *A baumannii* and 59% in *P aeruginosa*.[20] The reason for this difference may be caused by the variation of colistin minimum inhibitory concentrations (MICs) between *A baumannii* and *P aeruginosa.* One large-scale study examined the colistin MICs in 3,480 isolates of gram-negative bacilli in Canada.[21] Approximately 80% of *A baumannii* exhibited a MIC ≤ 1 μg/ml to colistin, but only 30% of *P aeruginosa* had a MIC ≤ 1 μg/ml. Unfortunately, the MIC data were not available in this study. Further researches are warranted to unveil the reasons for this difference.

Our study has several limitations. This study is a retrospective, single center study. The number of participants was too small. Furthermore, the dose of aerosolized colistin was inconsistent, with some patients using a higher dose and some using the standard dose. Moreover, microbiological data, such as the MIC of colistin, are not available. Therefore, we did not know whether the poor results for aerosolized colistin were due to a high MIC. We also did not know whether treatment failure was related to the emergence of colistin resistance during treatment. However, physicians may avoid intravenous colistin due to intravenous colistin possesses many adverse effects, such as nephrotoxicity.

A meta-analysis showed combination therapy of intravenous and aerosolized colistin significantly improved the clinical outcome of patients with multidrug-resistant gram-negative bacilli infections.[6] Other studies also revealed a better outcome of combination therapy of intravenous and aerosolized colistin in patients with ventilator-associated pneumonia.[9,22] Our study demonstrated the similar results. The mortality between single therapy of aerosolized colistin and combination therapy of aerosolized colistin and intravenous antibiotics had not significant difference, but combination therapy had higher successful rate of microbiological eradication may be related to small sample size in our study. However, this finding of our study is similar to previous study Valachis et al. reported a significant improvement in microbiological eradication was observed with the addition of aerosolized colistin to intraveous treatment, whereas did not affect overall mortality.[16] Our and other studies revealed that aerosolized colistin could be used only as an adjuvant therapy of intravenous antibiotics. Therefore, intravenous antibiotics is still necessary for infections caused by multidrug-resistant gram-negative bacilli.

Conclusion

Our study showed combination therapy of aerosolized colistin and intravenous antibiotics exhibited a higher successful rate of microbiological eradication. Failure of microbiological eradication was significantly associated with a higher mortality rate. Combination therapy of intravenous antibiotics and aerosolized colistin is suggested in patients with multidrug-resistant gram-negative bacilli pneumonia.

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