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Original Article

Aerosolized Colistin for the Treatment of Multidrug-resistant *Acinetobacter baumannii* Pneumonia: Experience in a Tertiary Care Hospital in Northern Taiwan

Cheng-Chih Lin[a], Te-Chu Liu[b,c,d], Chen-Feng Kuo[a], Chang-Pan Liu[a,e], Chun-Ming Lee[a,e,f]*

[a]Division of Infectious Disease, Department of Medicine, Mackay Memorial Hospital, Taipei, Taiwan.

[b]Department of Emergency Medicine, Mackay Memorial Hospital, Taipei, Taiwan.

[c]Department of Nursing, Mackay Memorial Hospital, Taipei, Taiwan.

[d]Graduate Institute of Nursing, Chang Gung University, Taoyuan, Taiwan.

[e]Mackay Medicine, Nursing and Management College, Taipei, Taiwan.

[f]Taipei Medical University, Taipei, Taiwan.

BACKGROUND/PURPOSE: Ventilator-associated pneumonia (VAP) due to multidrug-resistant (MDR) *Acinetobacter baumannii* in critically ill patients presents an emerging challenge to clinicians. Administration of aerosolized colistin as an adjunctive therapy is one therapeutic option mentioned in limited evidence-based studies. This study aimed to evaluate the effectiveness of adjunctive aerosolized colistin treatment for VAP due to MDR pathogens.

METHODS: We retrospectively reviewed the medical records of patients who had received aerosolized colistin for treatment of VAP due to MDR *A. baumannii* in our hospital from August to December 2008.

RESULTS: Forty-five patients were enrolled in our study. The mean age was 71±15 years. The mean Acute Physiological and Chronic Health Evaluation II (APACHE II) scores on the day of intensive care unit admission and on the first day of aerosolized colistin administration were 22.5±6.7 and 18.9±5.7, respectively. The mean duration of intensive care unit stay was 34±16 days. The mean daily dosage of aerosolized colistin was 4.29±0.82 million IU, and the mean duration of administration was 10.29 days. Seventeen patients (37.8%) had a favorable microbiological outcome and 26 (57.8%) showed a clinical response. Mortality due to all causes was 42.2%. No adverse effects related to inhaled colistin were recorded.

*Corresponding author. Division of Infectious Disease, Department of Medicine, Mackay Memorial Hospital, 92 Section 2, Chungshan North Road, Taipei, Taiwan.

E-mail: suhwanjan@gmail.com

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CONCLUSION: Aerosolized colistin may be considered as an adjunct to intravenous treatments in patients with VAP due to colistin-susceptible MDR *A. baumannii* in critically ill patients.

KEYWORDS: *Acinetobacter baumannii*, colistin, drug resistance, inhaled, nosocomial pneumonia, multiple, polymyxin

Introduction

Nosocomial pneumonia due to multidrug-resistant (MDR) Gram-negative bacteria such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa* has become the most serious complication for patients in intensive care units (ICUs). In the past decade, the virulence of these MDR pathogens is especially worrisome owing to limited therapeutic options.

Colistin (colistimethate sodium) is an antibiotic of the polymyxin family first used in 1960. Due to its nephrotoxicity and neurotoxicity, it has not been the drug of choice since 1980. However, intravenous colistin has made a recent comeback for the treatment of MDR Gram-negative bacterial pneumonia.[1,2]

The use of aerosolized colistin had been limited to patients with cystic fibrosis (CF).[3] Currently, there are only a few reports indicating that aerosolized colistin may be a beneficial additional therapeutic intervention in the management of MDR bacterial pneumonia.[4–7] Ventilator-associated pneumonia (VAP) due to colistin susceptible-only *A. baumannii* is one of the most severe complications in critically ill patients in our hospital. Owing to the possible toxicity of intravenous colistin, aerosolized colistin was considered to be an alternative treatment for VAP.

This study is a retrospective analysis of the efficacy of aerosolized colistin in a group of critically ill ICU patients suffering from MDR *A. baumannii* pneumonia. Additional risk factors and mortality were evaluated simultaneously.

Methods

Study design

Patients who received aerosolized colistimethate sodium (Colimycin, TTY Biopharm, Taipei, Taiwan) for more than 72 hours for the treatment of MDR *A. baumannii* infection from August 1 to December 31, 2008 at Mackey Memorial Hospital (a 2,100-bed tertiary care centre in Taiwan, with 72 beds in the medical and surgical ICU) were identified from the pharmacy electronic database and their medical records were carefully reviewed. Only patients under mechanical ventilation in the ICU were enrolled. Two million IU colistin was diluted in 4 mL sterile normal saline and then delivered to the patients via the same route through which they inhaled β_2-agonists.

Data collection and entry

Data for several variables, including demographics, comorbidities and Acute physiological and Chronic Health Evaluation II (APACHE II) scores on ICU admission and on the first day of colistin treatment, the responsible pathogens and the results of laboratory tests were collected from medical records. All available data regarding renal function (serum creatinine and urea levels), liver function tests (serum alanine aminotransferase and aspartate aminotransferase levels) and white blood cell counts, platelet counts, and C-reactive protein levels during the course of aerosolized colistin treatment (before and after) were recorded.

Microbiological testing

Antimicrobial susceptibility testing was performed using both the disk diffusion method and automated broth microdilution method (Vitek II, bioMerieux, Durham, NC, USA). The breakpoints were those defined by the Clinical and Laboratory Standards Institute.[8] Intermediate sensitivity of the isolated pathogens to the antimicrobial agents was considered to be resistance. MDR was defined as resistance to all anti-pseudomonal agents (i.e. anti-pseudomonal penicillins, cephalosporins, carbapenems, monobactams, quinolones, and aminoglycosides).[4] An isolate was defined as colistin-only susceptible when it was resistant to all anti-pseudomonas agents except colistin.

Definitions of pneumonia

Pneumonia was considered to be VAP when it occurred 48 hours after the initiation of mechanical ventilation. Diagnosis of VAP was based on radiological (new or

progressive infiltrate), clinical (body temperature > 38 °C or < 36 °C) and laboratory findings (abnormal white blood cell count, C-reactive protein and gas exchange). The diagnosis of VAP due to MDR *A. baumannii* should be microbiologically confirmed by positive cultures of MDR *A. baumannii* from either bronchial secretions or bronchoalveolar lavage samples of each patient, as in our study.

Definition of outcome

Clinical outcomes were classified as: (1) cured (resolution of presenting symptoms and signs of infection by the end of treatment); (2) improved (partial resolution of presenting symptoms and signs or infection); (3) failed (persistence or worsening of presenting symptoms and/or signs of infection during colistin administration); or indeterminate (clinical assessment was not possible).

Microbiologic outcomes were assessed on the basis of the results of bronchial secretion cultures. The results were classified as: (1) eradication (no growth of the responsible pathogen); (2) persistence (persistent growth of the responsible pathogen); or (3) indeterminate (when microbiological assessment was not possible). Assessment of effectiveness was made at the end of colistin treatment.

Statistical analysis

Continuous variables were compared using the independent *t* test. Categorical variables were compared using the χ^2 test or Fisher exact test. A *p* value of less than 0.05 was considered significant, and two-tailed test was adopted for all probabilities. All significant variables of univariate analysis were put into Logistic Regression analysis to calculate odds ratio so as to interpret the impact of independent variables on dependent variables. All statistical analysis was performed with SPSS version 10.0 (SPSS Inc., Chicago, IL, USA).

Results

From August 1 to December 31, 2008, a total of 102 patients received aerosolized colistin for infections with MDR microorganisms. Of these, 32 had received less than 72 hours of aerosolized colistin and were excluded from all analyses. Medical records were not available for 15 patients. In addition, four patients were still under treatment in the hospital during data collection. There were two patients with VAP due to *Klebsiella pneumonia*-ESBL (extended spectrum β-lactamase) and four patients with VAP due to *A. baumannii* (2 isolates were susceptible to meropenem and colistin, 1 was susceptible to imipenem–cilastatin and colistin, and 1 was susceptible to gentamicin and colistin). As a result, only 45 patients qualified for our study.

Demographic and clinical characteristics

Table 1 shows the demographic and clinical features of the patients, the responsible pathogens and the outcomes of the patients. The age of these 45 patients ranged from 31 to 92 years (mean = 71 ± 15 years) and the majority were male (71.1%). Comorbidities were noted in all patients (most patients had more than one comorbidity). The mean APACHE II scores on the day of ICU admission and on the first day of aerosolized colistin administration were 22.5 ± 6.7 and 18.9 ± 5.7, respectively. The mean length of ICU stay was 34 ± 16 days.

The pathogen responsible for VAP was MDR *A. baumannii*. All patients had received other antimicrobial regimens before aerosolized colistin. In addition, they all received concomitant intravenous treatment (6 patients with colistin and others with mainly carbapenems). All the isolated pathogens were susceptible to colistin only (*in vitro* susceptibility testing for tigecycline was unavailable in our hospital in 2008). The mean daily dosage of aerosolized colistin was $4.29 \pm 0.82 \times 10^6$ IU, ranging from 2 to 6 million IU (divided into 2 or 3 doses), and the mean duration of administration was 10.29 days.

The outcomes of treatment were as follows: 17 patients (37.8%) had a favorable microbiological outcome (eradication); eight (17.8%) had persistent infection; 26 (57.8%) had a favorable clinical outcome (clinically cured or improved); and aerosolized colistin therapy failed in 14 (31.1%). Death due to all causes was noted in 19/45 patients (a crude mortality rate of 42.2%). No adverse effects relating to inhaled colistin were recorded.

Laboratory and bacteriological characteristics

In terms of hematological and biochemical laboratory examinations, the abnormal data for patients before and after receiving aerosolized colistin therapy are shown in Table 2. In addition, we also recorded the bacteriological characteristics after receiving aerosolized colistin therapy. Twenty-seven patients (60.0%) had positive findings in their bronchial secretions or bronchoalveolar lavage. Only a

Table 1. Demographical and clinical characteristic and outcomes in patients receiving aerosolized colistin therapy for ventilator-associated pneumonia due to multidrug-resistant *Acinetobacter baumannii* ($n=45$)[a]

Variable	
Patient characteristics	
Age (yr)	71±15 (31–92)
Sex	
Male	32 (71.1)
Female	13 (28.9)
Comorbidity	
Hypertension	18 (40.0)
Neurology disease	12 (26.7)
Renal disease	16 (35.6)
Cardiovascular disease	14 (31.1)
Pulmonary disease	12 (26.7)
Diabetes mellitus	10 (22.2)
Neoplastic disease	7 (15.6)
Operation	6 (13.3)
Hepatic disease	3 (6.7)
APACHE II on ICU admission	22.5±6.7 (6–35)
APACHE II on 1st day of aerosolized colistin administration	18.9±5.7 (8–30)
Length of hospital stay (d)	65±34 (14–165)
Length of ICU stay (d)	34±16 (9–94)
Microbiology outcome	
Eradication	17 (37.8)
Persistence of colistin susceptible-only *Acinetobacter baumannii*	8 (17.8)
Indeterminate	20 (44.4)
Clinical outcome	
Cure or improvement	26 (57.8)
Failure	14 (31.1)
Indeterminate	5 (11.1)
Discharge from hospital	26 (57.8)
Death	19 (42.2)

[a]Data presented as *n* (%) or mean±standard deviation (range). APACHE II=Acute physiological and Chronic Health Evaluation; ICU=intensive care unit.

few specimens revealed more than one pathogen. The majority of the pathogens were *Chryseobacterium meningosepticum* (9/27 patients) followed by colistin-only susceptible *A. baumannii* (8/27 patients); suggesting persistence of the

Table 2. Laboratory data for patients who received aerosolized colistin therapy for ventilator-associated pneumonia due to multidrug-resistant *Acinetobacter baumannii*[a]

Variable	Before therapy	After therapy
Hematologic exams		
Leucopenia ($<4\times10^9$/L)	2/45 (4.4)	0/45 (0.0)
Leukocytosis ($>10\times10^9$/L)	36/45 (80.0)	28/45 (62.2)
Segment WBC (>75%)	35/45 (77.8)	28/45 (62.2)
Platelet count ($<150\times10^9$/L)	8/25 (32.0)	5/19 (26.3)
Platelet count ($>450\times10^9$/L)	4/25 (16.0)	3/19 (15.8)
Biochemistry exams		
CRP (>0.8 mg/dL)	18/19 (94.7)	13/15 (86.7)
AST (>40 IU/L)	5/16 (31.3)	1/15 (6.7)
ALT (>40 IU/L)	3/12 (25.0)	1/10 (10.0)
BUN (>20 mg/dL)	32/44 (72.7)	30/42 (71.4)
Cr (>1.2 mg/dL)	24/44 (54.5)	18/42 (42.9)

[a]Data presented as number of positive cases/total cases (%). ALT=Alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; Cr=creatinine; CRP=C-reactive protein; WBC=white blood cell count.

responsible pathogen. However, as 18 patients (40.0%) had no subsequent culture data, their microbiological outcomes were inconclusive.

Mortality factors

Significant influential factors related to death were found in the univariate analysis (Table 3).These included comorbid pulmonary disease, APACHE II scores on first day of aerosolized colistin administration, length of hospital stay, platelet counts, blood urea nitrogen and serum creatinine levels and positive cultures from bronchial secretions or bronchoalveolar lavage.

Logistic regression analysis also showed that the mortality odds ratio (OR) for creatinine (after receiving aerosolized colistin therapy) was higher (OR = 7.558); however, it was not significant ($p=0.115$).

Discussion

In recent years, strains of *Acinetobacter* spp. and *P. aeruginosa* have not been susceptible to the majority of antimicrobial

Table 3. Univariate analysis in patients who received aerosolized colistin therapy for ventilator-associated pneumonia due to multidrug-resistant *Acinetobacter baumannii* ($n=45$)[a]

Variable	Surviving ($n=26$)	Casualty ($n=19$)	χ^2/t	p
Patient characteristic				
Age (yr)	68.4±16.6	74.0±12.6	−1.225	0.227[c]
Sex			0.116	0.734[b]
Male	19 (73.1)	13 (68.4)		
Female	7 (26.9)	6 (31.6)		
Comorbidity				
Pulmonary disease				0.046[d,*]
No	16 (61.5)	17 (89.5)		
Yes	10 (38.5)	2 (10.5)		
Hypertension			0.137	0.712[b]
No	15 (57.7)	12 (63.2)		
Yes	11 (42.3)	7 (36.8)		
Cardiovascular disease			0.003	0.954[b]
No	18 (69.2)	13 (68.4)		
Yes	8 (30.8)	6 (31.6)		
Hepatic disease				0.565[c]
No	25 (96.2)	17 (89.5)		
Yes	1 (3.8)	2 (10.5)		
Diabetes mellitus			0.319	0.572[b]
No	21 (80.8)	14 (73.7)		
Yes	5 (19.2)	5 (26.3)		
Renal disease			0.616	0.433[b]
No	18 (69.2)	11 (57.9)		
Yes	8 (30.8)	8 (42.1)		
Neurologic disease				0.517[d]
No	18 (69.2)	15 (78.9)		
Yes	8 (30.8)	4 (21.1)		
Neoplastic disease				0.433[d]
No	23 (88.5)	15 (78.9)		
Yes	3 (11.5)	4 (21.1)		
Operation				0.377[d]
No	24 (92.3)	15 (78.9)		
Yes	2 (7.7)	4 (21.1)		
APACHE II on ICU admission	22.5±7.1	22.6±6.3	−0.058	0.954[c]
APACHE II on 1st day of aerosolized colistin administration	17.0±5.5	21.5±5.2	−2.798	0.008[c*]
Length of stay (d)				
In hospital	73.9±34.6	53.3±30.5	2.064	0.045[c*]
In ICU	30.0±11.8	38.9±20.4	−1.841	0.072[c]
Laboratory reports[e]				
WBC ($\times 10^9$/L)	11.69±3.82	14.39±7.87	−1.385	0.179[c]
Segment WBC (%)	75.6±8.6	79.9±11.0	−1.469	0.149[c]
Platelet ($\times 10^9$/L)	356.5±209.3	159.6±120.3	2.379	0.029[c*]

(*Contd*)

Table 3. *(Continued)*

Variable	Surviving ($n=26$)	Casualty ($n=19$)	χ^2/t	p
Laboratory reports[e] (*Contd*)				
CRP (mg/dL)	7.2±7.4	9.1±2.7	–0.502	0.624[c]
AST (IU/L)	33.8±14.6	31.3±5.6	0.386	0.705[c]
ALT (IU/L)	25.5±17.7	16.2±8.8	1.121	0.295[c]
BUN (mg/dL)	37.5±32.8	66.9±35.7	–2.727	0.009[c]*
Cr (mg/dL)	1.4±1.5	2.9±2.0	–2.712	0.010[c]*
Follow-up cultures[f]				0.035[d]*
Positive	12 (46.2)	15 (78.9)		
No follow-up data	14 (53.8)	4 (21.1)		

[a]Data represented mean±standard deviation or *n* (%); [b]χ^2 test; [c]*t* test of independent samples; [d]Fisher's exact test; [e]after aerosolized colistin administration; [f]follow-up cultures of bronchial secretion or bronchoalveolar lavage; *$p<0.05$. APACHE II=Acute physiological and Chronic Health Evaluation; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; Cr=creatinine; CRP=C-reactive protein; ICU=intensive care unit; WBC=white blood cell count.

agents, including carbapenems were frequently identified as the pathogens responsible for VAP.[9,10] Colistin emerged as a promising therapeutic alternative.

Colistin (polymyxin E) was first produced by the growth of *Bacillus polymyxa subsp. colistinus* in1949,[2] and it exerts bactericidal activity by binding to the bacterial cell membrane and disrupting its permeability, resulting in the leakage of intracellular components. *In vitro* colistin has a broad spectrum of action against Gram-negative aerobic bacilli, including some strains resistant to carbapenems, aminoglycosides, penicillins, cephalosporins and fluoroquinolones. However, *Proteus mirabilis*, *Providencia* spp., *Serratia* spp., *Morganella morgannii*, *Burkholderia cepacia* and *Stenotrophomonas maltophilia* are naturally non-susceptible to colistin.[11,12–14] Severe adverse effects (i.e. nephrotoxicity and neurotoxicity) have been reported and led to the discontinuation of parenteral use of this drug in the 1970s and 1980s.

Most reports regarding the treatment of pneumonia with colistin involved parenteral administration. Levin et al[15] reported their experiences with 60 patients who had nosocomial infections caused by MDR *P. aeruginosa* and MDR *A. baumannii*. Patients with pneumonia had a much less favorable outcome (25% compared with the overall outcome of 58%). The amount of data available regarding demographic and clinical characteristics of VAP due to Gram-negative bacilli susceptible to colistin only is quite limited.[1,14,15] Rios et al[14] studied 61 episodes of VAP caused by *Acinetobacter* spp. or *P. aeruginosa*, of which 31 isolates were colistin-only susceptible micro-organisms. They demonstrated that previous VAP episodes and prior antimicrobial therapy for >10 days are risk factors for contracting colistin-only susceptible VAP. They concluded that colistin-susceptible VAP episodes could be effectively treated by intravenous colistin without significant renal dysfunction.

The main adverse effect of colistin treatment is renal failure, especially in patients with abnormal creatinine levels. Even though several published studies demonstrated that the efficacy and safety of colistin for the treatment of nosocomial infection caused by MDR Gram-negative bacteria,[16–18] renal dysfunction was still frequently reported to be a major adverse effect.[1,15,19] Michalopoulos et al[2] and Markou et al[19] reported the incidence of nephrotoxicity to be 18.6% and 14.3%, respectively in their ICU studies using 9×10^6 units of colistimethate sodium per day. Falagas et al[20] analyzed 19 prolonged intravenous colistin courses (mean dosage=4.4 million IU/day; mean treatment duration=43.4 days) in 17 patients, and found the median serum creatinine value increased by only 0.25 mg/dL during the treatment period compared with the baseline level ($p<0.001$). However, a review article by Falagas and Kasiakou[21] suggests that the incidence of nephrotoxicity in recently published reports regarding the experiences with polymyxins is less common and less severe than suggested by the studies in the 1970s.

Many previous studies have shown that multiple factors (i.e. advanced age, severe sepsis, low cardiac output

syndrome and hypovolemia) are associated with acute renal failure in the critically ill patients in the ICU setting.[22] Therefore, aerosolized colistin could be a reasonable choice for minimizing systemic exposure and to optimize the benefit-risk ratio of therapy.

Administration of polymyxins via inhalation has been adopted and recommended as the adjunctive treatment for MDR pneumonia.[23] Ratjen et al[24] studied the pharmacokinetics of inhaled colistin in patients with CF. The low systemic and high local concentrations of colistin support the use of inhaled colistin in CF patients infected with *P. aeruginosa*. Although the above finding sounds promising, it is not known whether this information can be extrapolated to non-CF patients with MDR nosocomial pneumonia.

There have been many studies assessing the efficacy of aerosolized colistin or polymyxin B in combination with intravenous antibiotic treatment in critically ill patients with VAP caused by MDR Gram-negative pathogens.[4,6,25–29] Although the experience with aerosolized colistin therapy is limited, it is believed that this alternative treatment is associated with more favorable outcomes, which means this approach merits further evaluation.

The major finding of our study is that aerosolized colistin may be an effective and safe adjunctive treatment for VAP due to MDR *A. baumannii* (especially colistin-only susceptible isolates) for critically ill patients. Michalopoulos et al[4] conducted a small retrospective study of eight patients with pneumonia due to *A. baumannii* or *P. aeruginosa* (in which half of the cases were caused by colistin-only susceptible pathogens). Aerosolized colistin was administered in conjunction with systemic colistin or other effective antibiotics. The cure rate for pneumonia was 7/8 (88%). Recently, a prospective study designed to assess the effectiveness of aerosolized colistin as adjunctive treatment for VAP due to MDR Gram-negative bacteria, also demonstrated favorable microbiological and clinical responses in 50/60 patients (83.3%).[6]

Conversely, our study found only 57.8% of patients had clinically favorable outcomes and 37.8% had microbiologic eradication. Both results were not as promising as those in other published reports.[4–6] The difference in outcomes may be related to differences in patient characteristics, potencies of commercial formulations of colistin in different countries, or to other causes. In our study, we prescribed aerosolized colistin with concomitant intravenous antibiotics (colistin or other antimicrobial agents) for treating MDR *A. baumannii* VAP. Both persistent growth of the responsible pathogen (29.6% in positive cultures) and other colistin-resistant species (*S. maltophilia*, *Chryseobacterium* sp., *and M. morganii*) were identified. Because these colistin-resistant isolates remained susceptible to other antibiotics, the subsequent results of microbiologic examinations become very important for evaluating the efficacy of the therapy. The data showed either resistance to colistin or development of concomitant infection with colistin-resistant pathogens. Unfortunately, a high proportion of patients (18/45 patients) had no subsequent culture data after aerosolized colistin administration in our retrospective study.

This study showed several significant influential factors related with death by univariate analysis (Table 3). The clinicians in our hospital prescribed inhaled colistin for patients with MDR *A. baumannii* VAP because of deteriorating renal function in those patients. It is interesting that logistic regression analysis showed that the mortality OR for creatinine (after receiving aerosolized colistin therapy) was higher (OR=7.558) even though there was significant difference ($p=0.115$). Thus impairment of renal function should not be attributed solely to colistin toxicity, as other factors such as the development of septic shock, multiorgan failure, and the use of other nephrotoxic agents in the ICU may also contribute to this condition. As a result, we strongly recommend monitoring renal function during colistin administration (both aerosolized and intravenous).

Treatment with aerosolized colistin may also be complicated by bronchospasm, although this could be eliminated by aerosolized β_2-agonists used before the initiation of inhaled colistin.[9] As in other published reports,[4–6] there were no adverse effects related to aerosolized colistin seen in our study. Colistin heteroresistance had been reported among colistin-susceptible *Acinetobacter* isolates.[30] In one study that aimed to assess potential risk factors for the isolation of colistin-resistant *A. baumannii*, *Klebsiella pneumonia*, and *P. aeruginosa* in hospitalized patients, the use of colistin was identified as the only independent risk factor (adjusted OR=7.78; $p<0.001$).[31] Thus polymyxins should be used both rationally and carefully to decrease the rate of emergence of pan drug-resistant (resistant to all available antibiotics, including colistin) infections.

Though this is the first study of aerosolized colistin treatment in Taiwan, this study has several limitations. It is a retrospective study on a relatively reduced number of patients and we did not have a control group containing patients with MDR *A. baumannii* VAP that received only intravenous antimicrobial agents. Furthermore, some of the patients also received intravenous colistin ($n=6$), which might have influenced the outcome. A randomized controlled study with a larger patient population is necessary to establish the efficacy and safety of aerosolized colistin as an adjunct to intravenous treatment of MDR *A. baumannii* VAP in critically ill patients.

In conclusion, the data in this study suggest that aerosolized colistin may be considered as an adjunct to intravenous treatment in patients with VAP due to colistin-susceptible MDR *A. baumannii*. In spite of some encouraging findings, subsequent randomized controlled studies are still urgently needed. It is crucial to monitor subsequent cultures from bronchial secretions or bronchial lavage in order to accurately evaluate the efficacy of the treatment and to identify possible concomitant infections by colistin-resistant pathogens.

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