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ORIGINAL ARTICLE

Role of aerosolized colistin methanesulfonate therapy for extensively-drug-resistant *Acinetobacter baumannii* complex pneumonia and airway colonization

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Background: Aerosolized colistin methanesulfonate (CMS) has been used for the treatment of extensively drug-resistant *Acinetobacter baumannii* (XDRAB) pneumonia and eradication of XDRAB colonization in the respiratory tract. The aims of this study were to compare the efficacy, adverse effects, clinical outcomes, and microbiological eradication of the cases of XDRAB pneumonia or colonization.
Methods: We retrospectively reviewed the medical records of patients who received aerosolized CMS for the treatment of pneumonia and airway colonization due to XDRAB.
Results: Clinical data from 118 patients were studied. The mean age of 57 patients in the pneumonia group was 79.4 years, and that of 61 patients in the colonization group was 80.0 years. Patients with XDRAB pneumonia were more likely to be ventilator-dependent than colonized patients (46.5% vs. 21.3%; $p = 0.005$), receive steroid therapy (49.1% vs. 31.1%; $p = 0.046$), and be admitted to an intensive care unit (ICU) at the time of aerosolized CMS treatment (56.1% vs. 32.8%; $p = 0.011$). The in-hospital mortality rate was higher in the pneumonia group than the colonization group (50.9% vs. 33.3%; $p = 0.05$). Microbiological eradication of XDRAB in airway samples was achieved in 75% (89 of 118) patients. In pneumonia

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patients, XDRAB eradication was associated with resolution or improvement of presenting symptoms and signs of infection by the end of treatment relative to the noneradicated group (57.8% vs. 25%; $p = 0.044$), but had no influence on 30-day mortality. In colonized patients, no difference in clinical outcomes was noted between the eradicated and noneradicated groups. *Conclusion:* Aerosolized CMS therapy has acceptable efficacy for XDRAB pneumonia, but no proven efficacy for XDRAB airway colonization.

Introduction

Extensively drug-resistant *Acinetobacter baumannii* (XDRAB) is one of the most notorious and challenging pathogens for health care institutions worldwide. The organism's ability to survive and persist for long periods under various environmental conditions poses great challenges for hospital infection control.[1,2] Patients who are colonized or infected with XDRAB can become a reservoir of infection. Indeed, it has been shown that *A. baumannii* can colonize multiple body sites in hospitalized patients,[3] especially in those who are ventilator dependent.

The commercially available antibiotic most active against XDRAB *in vitro* is polymyxin: polymyxin B or polymyxin E (colistin).[4,5] Colistin methanesulfonate (CMS) is a prodrug that is hydrolyzed after intravenous administration to produce several derivatives, predominately the active drug colistin.[6] However, renal toxicity related to intravenous CMS use remains a major concern in critically ill patients.[7] Another problem is that the colistin concentration in the lung tissue is relatively low when administered intravenously.[8] Therefore, aerosolized CMS has become a reasonable choice for minimizing systemic exposure and optimizing the benefit—risk ratio of therapy. Aerosolized CMS has been used as a monotherapy[9,10] or as an adjuvant to intravenous antibiotics in XDRAB pneumonia.[5,11] Some hospitals in Taiwan have also employed aerosolized CMS for eradication of XDRAB as part of their infection control measures.[12]

Despite the increasing use of aerosolized CMS for XDRAB pneumonia, its clinical benefit has not been well studied. Bacterial colonization of the airway is crucial for development of nosocomial pneumonia.[13] Theoretically, eradication of XDRAB respiratory tract colonization may prevent development of true infection, but the clinical benefits of such eradication in colonized patients remain unproven.

In this study, we evaluated the efficacy and adverse effect of aerosolized CMS and the risk factors of 30-day mortality in cases of XDRAB pneumonia and airway colonization.

Methods

This retrospective study was conducted at Wan Fang Medical Center, a teaching hospital of Taipei Medical University, Taipei, Taiwan. We reviewed the medical charts of the patients who were treated with aerosolized CMS (Colimycin; TTY Biopharm, Taipei, Taiwan) for XDRAB pneumonia or airway colonization from January 1, 2012 to August 31, 2013.

Data collection and definitions

Clinical data or laboratory parameters were collected using a standard form, in which definitions were predefined. The collected data included demographic characteristics, underlying conditions, Acute Physiology and Chronic Health Evaluation (APACHE) II score within 48 hours of the first dose of aerosolized CMS therapy, characteristics of XDRAB isolates, antimicrobial therapy, and clinical and microbiological outcomes of each patient.

Microbiological testing

Acinetobacter calcoaceticus—baumannii complex (Acb complex) identification and antimicrobial susceptibility testing were performed using the Becton Dickinson Phoenix TM Automated Microbiology System (Becton Dickinson, East Rutherford, NJ, USA). The susceptibility to tigecycline (TG) (pfizer, catania, Italy) was assessed by using the disk diffusion method. Antimicrobial susceptibility breakpoints followed those defined by the Clinical and Laboratory Standards Institute.[14] Because Acb complex cannot be separated reliably by phenotypic methods alone, all the species identified as *Acinetobacter baumannii* in this paper were Acb complex. Colistin susceptibility was defined as a colistin minimum inhibitory concentration (MIC) of ≤ 2 mg/L, and colistin resistance as MIC > 2 mg/L, according to the breakpoints published by the European Committee on Antimicrobial Susceptibility Testing for *Acinetobacter* species.[15] The disk diffusion breakpoints for TG were ≥ 19 mm and ≤ 14 mm for susceptible and resistant, respectively, as the criteria recommended by the United States Food and Drug Administration for Enterobacteriaceae.[16] XDRAB was defined as the Acb complex isolates susceptible to only one or two antibiotic categories as described previously.[17]

Inclusion and exclusion criteria

Only adult patients (aged at least 20 years) from whom only XDRAB was obtained from at least one set of airway samples and who received > 72 hours of aerosolized CMS therapy, with available subsequent culture results of airway samples, which were collected every 3—5 days until 14 days after the end of inhaled CMS therapy, were included in this study.

The day that CMS therapy was initiated for the XDRAB isolate in airway samples was defined as the index day, and the XDRAB isolate as the index isolate. The dosage of inhaled CMS used was 2 million international units (IU) twice per day, administered in nebulized form. Patients were categorized as either the pneumonia or colonization group, according to published criteria.[18]

Definitions of outcomes

The 30-day mortality was defined as the crude mortality within 30 days after the index day, and in-hospital mortality as the death during the same hospitalization.

Microbiological eradication was defined as no XDRAB found in subsequent sputum cultures within 14 days after the end of aerosolized CMS therapy. Microbiological failure was the continued isolation of XDRAB from sputum culture under aerosolized CMS or the recovery of XDRAB within 14 days after CMS therapy.

We also recorded the adverse effects related to CMS inhalation. Bronchospasm was defined as new-onset bronchospasm during CMS inhalation, or the need for increasing the dose or frequency of already used bronchodilators. Renal function was assessed by the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria.[19] Nephrotoxicity in this study was referred to the risk group, according to the RIFLE criteria. The patients with renal replacement therapy were excluded from the evaluation of nephrotoxic effects.

In a subgroup analysis of patients with XDRAB pneumonia, we classified clinical outcomes as favorable (resolution or improvement of presenting symptoms and signs of infection by the end of treatment), or unfavorable (no improvement, persistence or worsening of presenting symptoms, and/or signs of XDRAB infection during CMS administration).

Statistical analysis

We compared categorical and continuous variables with χ^2 or Fisher's exact tests and the independent *t* test, respectively. A p value ≤ 0.05 was considered to be statistically significant and two-tailed tests were adopted for all probabilities. The significant variables in the univariate analysis were included in a multivariate logistic regression analysis to calculate odds ratios (ORs). All statistical analysis was performed with SPSS version 21 (IBM, Armonk, NY, USA).

Results

During the study period, a total of 237 patients received aerosolized CMS therapy. However, the Acb complex isolates from 37 patients did not fulfill the criteria of XDR, 17 received aerosolized CMS for other pathogens, and six received aerosolized CMS for $<$ 72 hours. Subsequent sputum cultures were not available in 42 patients, and 17 patients had concurrent bacterial or fungal infections (4 fungemia, 4 complicated intra-abdominal infections, and 9 pneumonia caused by other organisms). The above 119 patients were excluded. Finally, 118 patients were included.

Of 118 patients, 57 (48%) patients had XDRAB pneumonia and 61 (52%) were colonized by XDRAB. The demographic data, underlying medical conditions, microbiological characteristic of XDRAB isolates, antimicrobials therapy, and clinical outcomes of these two groups are summarized in Table 1. Patients with XDRAB pneumonia were more likely to be ventilator dependent than colonized patients (46.5% vs. 21.3%; $p = 0.005$), receive steroid therapy (49.1% vs. 31.1%; $p = 0.046$), and be admitted to an intensive care unit (ICU) at the time of aerosolized CMS treatment (56.1% vs. 32.8%; $p = 0.011$). Only 4 (6.5%) patients with XDRAB had concurrent XDRAB bacteremia. The colonization group was more likely to receive aerosolized CMS alone than the pneumonia group (50.8% vs. 15%; $p = 0.03$). The mean duration of CMS inhalation was longer in the pneumonia group than the colonization group (13.49 $\pm$ 6.5 days vs. 11 $\pm$ 4.8 days; $p = 0.02$). The in-hospital mortality rate was higher in the pneumonia group than in the colonized group (50.9% vs. 33.3%; $p = 0.05$).

Microbiological eradication of XDRAB was achieved in 75% (89 of 118 patients), i.e., 72.1% (44 of 61 patients) with colonization and 78.9% (45 of 57) with pneumonia. The mean duration of CMS use prior to XDRAB eradication was 5.3 $\pm$ 2 days. Follow-up XDRAB isolates from 12 patients with pneumonia and 16 with colonization were analyzed. A two-fold increase of colistin MIC was noted in five (17.8%) of 28 patients, including four with colonization and one with pneumonia. Only one isolate from the colonization group developed colistin resistance (MIC $>$ 2 mg/L).

After excluding three patients with regular hemodialysis, 115 patients were evaluated for renal side effects. Acute kidney injury was noted in 26 (22.6%) of patients and no renal replacement was needed. There were two episodes of bronchospasm related to inhaled CMS in two patients with underlying chronic obstructive pulmonary disease (COPD). Further events were prevented by prophylactic administration of bronchodilator prior to aerosolized CMS therapy. No neurotoxicity related to aerosolized CMS and no treatment interruptions due to drug toxicity were noted in our cases.

In the subgroup analysis of XDRB pneumonia, those with airway eradication of XDRAB had more favorable clinical outcomes than those with eradication (57.8% vs. 25%; $p = 0.044$; Table 2). Patients with XDRAB eradication tended to have a lower 30-day mortality rate than those without eradication (28.9% vs. 58.3%; $p = 0.06$). In the colonization group, there was no difference in 30-day mortality rate between those with and without microbiological eradication (25% vs. 35.3%; $p = 0.42$). However, the development of increased colistin MIC was noted in 23.5% of 17 XDRAB isolates obtained from the colonization group without microbiological eradication.

Clinical factors associated with 30-day mortality are summarized in Table 3. In the pneumonia group, age, sex, and infection sources did not have a significant impact on 30-day mortality. In the multivariate logistic regression model, the two factors significantly associated with 30-day mortality were underlying COPD [adjusted OR (aOR) = 7.0; 95% confidence interval (CI) = 1.8—26.8; $p = 0.004$] and malignancy (aOR = 8.9; 95% CI = 1.7—45.6; $p = 0.01$). In the colonization group, 30-day mortality was significantly related to a previous cerebral vascular accident (CVA) with

Table 1 Clinical and microbiological characteristics of patients with extensively drug-resistant *Acinetobacter baumannii* (XDRAB) pneumonia or airway colonization

Variables	Case number (%) or mean (± standard deviation)		*p*
	Colonization (*n* = 61)	Pneumonia (*n* = 57)	
Male	43 (70.5)	33 (57.9)	0.153
Age (y)	80.0 (± 10.9)	79.4 (± 12.1)	0.563
Body mass index	20.9 (± 4.0)	20.2 (± 3.7)	0.325
APACHE II score	17.0 (± 8.0)	18.1 (± 6.5)	0.413
APACHE II score >21	19 (31.1)	18.0 (31.6)	0.960
Underlying conditions			
COPD	19 (31.1)	18 (31.6)	0.960
Congestive heart failure	37 (60.7)	34 (59.6)	0.911
Cerebral vascular disease	36 (59.0)	33 (59.9)	0.902
Malignancy	7 (11.5)	10 (17.5)	0.348
Diabetes mellitus	29 (47.5)	26 (45.6)	0.834
Chronic renal failure (GFR < 60)	15 (24.0)	14 (24.5)	0.349
End-stage renal disease	3 (4)	0	0.349
Steroid therapy[a]	19 (31.1)	28 (49.1)	0.046
Immunosuppressive therapy	1 (1.6)	2 (3.5)	0.519
Mechanical ventilator use			
Noninvasive	12 (19.7)	16 (28.1)	0.284
Invasive	13 (21.3)	26 (45.6)	0.005
Antibiotic therapy, in addition to aerosolized CMS			0.030
None	31 (50.8)	9 (15)	
Tigecycline	21 (34.4)	29 (50.9)	
Sulbactam	5 (8.2)	6 (10.5)	
Cephalosporin	1 (1.6)	1 (1.8)	
Carbapenem	1 (1.6)	7 (12.3)	
Intravenous CMS	1 (1.6)	4 (7.0)	
Duration of aerosolized CMS therapy (d)	11.0 (± 4.8)	13.5 (± 6.5)	0.02
Acquisition place of XDRAB isolates			
Nursing home	15 (24.6)	10 (17.5)	0.349
ICU	20 (32.8)	32 (56.1)	0.011
Ward	28 (45.9)	15 (26.3)	0.027
XDRAB bacteremia	0 (0)	4 (6.5)	0.031
Tigecycline susceptibility			0.750
Susceptible	38 (62.3)	28 (49.1)	
Intermediate	20 (32.8)	19 (33.3)	
Resistant	3 (4.9)	10 (17.5)	
Clinical and microbiological outcomes			
Length of hospital stay (d)	39.8 (± 22.5)	48.9 (± 30.4)	0.070
Nephrotoxicity	14 (23)	12 (21.1)	0.804
XDRAB airway eradication	44 (72.1)	45 (78.9)	0.390
30-day mortality	17 (27.9)	19 (33.3)	0.519
In-hospital mortality	20 (33.3)	29 (50.9)	0.050

[a] Daily 20 mg prednisolone or its equivalent for at least 1 week in the preceding 2 weeks.
APACHE II = Acute Physiology and Chronic Health Evaluation II; CMS = colistin methanesulfonate; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; ICU = intensive care unit.

bedridden status, chronic renal insufficiency, APACHE II score > 21, and development of nephrotoxicity. However, in the multivariate analysis, only previous CVA with bedridden status was associated with 30-day mortality (aOR = 4.3; 95% CI = 1.1–15.9; $p = 0.03$).

The subgroup analysis of those patients receiving CMS inhalation alone or in combination with intravenous tigecycline (IVTG) is summarized in Table 4. Of note, there were 21 (34.4%) of 61 patients with XDRAB airway colonization receiving IVTG therapy. The colonizations treated with CMS inhalation in combination with IVTG were less likely to achieve microbiological eradication than those with CMS inhalation alone (42.9% vs. 87.9%; $p = 0.001$).

In the pneumonia group, there was no difference in airway XDRAB eradication rate, favorable clinical outcome, or 30-day or in-hospital mortality rate, between those with CMS inhalation alone and those with combination therapy (Table 4). The initial XDRAB isolates in the CMS + IVTG group were more likely to be sensitive to TG (72.4% vs.

Table 2 Comparison of cases of extensively drug-resistant *Acinetobacter baumannii* (XDRAB) pneumonia and colonization with or without microbiological eradication

Variables	Pneumonia ($n = 57$)			Colonization ($n = 61$)		
	Eradicated ($n = 45$)	Noneradicated ($n = 12$)	p	Eradicated ($n = 44$)	Noneradicated ($n = 17$)	p
Male (%)	24 (53.3)	9 (75.0)	0.177	33 (75)	10 (58.8)	0.214
Age (y)	79.5 ± 11.7	78.8 ± 14.4	0.861	80.3 ± 10.5	81.2 ± 11.8	0.774
APACHE II score	17.6 ± 6.0	20.3 ± 8.2	0.310	14.64 ± 6	18.3 ± 8.3	0.082
Underlying conditions						
Congestive heart failure	17 (37.8)	6 (50.0)	0.443	20 (45.5)	4 (23.5)	0.116
COPD	13 (28.9)	5 (41.7)	0.397	14 (31.8)	5 (29.4)	0.856
Cerebral vascular disease	27 (60.0)	6 (50.0)	0.533	25 (56.8)	11 (64.7)	0.574
Malignancy	7 (15.6)	2 (16.4)	0.445	5 (11.4)	2 (11.8)	0.965
Diabetes mellitus	21 (46.7)	5 (41.7)	0.757	21 (47.7)	8 (47.1)	0.963
Chronic renal failure (GFR < 60)	12 (26.4)	14 (24.5)	0.706	7 (15.8)	5 (29.4)	0.224
End-stage renal disease	3 (4)	0	0.473	2 (4.5)	1 (5.9)	0.856
Steroid use[a]	21 (46.7)	7 (58.3)	0.457	14 (31.8)	5 (26.3)	0.531
Mechanical ventilator use						
Noninvasive	11 (24.4)	5 (41.7)	0.238	7 (15.9)	5 (29.4)	0.234
Invasive	21 (46.7)	5 (41.7)	0.757	9 (20.5)	4 (23.5)	0.793
Antibiotic therapy, in addition to aerosolized CMS	0.986			0.028		
None	7 (15.6)	2 (16.7)		27 (61.4)	4 (23.5)	
Tigecycline	23 (51.1)	6 (50.0)		9 (20.5)	12 (70.6)	
Sulbactam	5 (12.1)	1 (8.3)		4 (9.1)	1 (5.9)	
Cephalosporin	1 (2.2)	0 (0)		1 (2.3)	0	
Carbapenem	5 (11.1)	2 (16.7)		1 (2.3)	0	
Intravenous CMS	3 (6.7)	1 (8.3)		1 (2.3)	0	
Acquisition place of XDRAB isolates						
Nursing home	7 (15.6)	3 (25.0)	0.445	8 (18.2)	7 (41.2)	0.061
ICU	24 (53.3)	8 (66.7)	0.408	17 (38.6)	3 (17.6)	0.117
Ward	14 (31.1)	1 (8.3)	0.111	19 (43.2)	9 (52.9)	0.493
Clinical and microbiological outcomes						
Favorable clinical response	26 (57.8)	3 (25.0)	0.044			
30-day mortality	13 (28.9)	7 (58.3)	0.058	11 (25)	6 (35.3)	0.421
In-hospital mortality	21 (46.7)	8 (66.7)	0.218	12 (27.9)	8 (47.1)	0.156
Nephrotoxicity	10 (22.2)	2 (16.7)	0.675	10 (22.7)	4 (23.5)	0.947
Length of hospital stay (d)	46.2 ± 28	58.8 ± 35	0.203	50.4 ± 29	35.8 ± 18	0.068

[a] Daily 20 mg prednisolone or its equivalent for at least 1 week in the preceding 2 weeks.
Results are expressed as the n (%) or mean ± standard deviation.
APACHE II = Acute Physiology and Chronic Health Evaluation II; CMS = colistin methanesulfonate; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; ICU = intensive care unit.

22.2%; $p = 0.02$). Of 28 patients with pneumonia caused by XDRAB isolates susceptible to both colistin and tigecycline, the 30-day mortality rate of those treated by CMS inhalation alone or combination therapy was similar (2/7, 28.6% vs. 6/22, 28.6%, $p > 0.99$).

Discussion

In this retrospective study, we showed that aerosolized CMS therapy could be used for eradication of XDRAB from the respiratory tract with a satisfactory response rate. Airway eradication of XDRAB among the patients with pneumonia was associated with more favorable clinical outcomes than those without XDRAB eradication.

In our study, among the pneumonia group, airway cleaning of XDRAB was associated with more favorable clinical outcomes, but not with a lower in-hospital mortality rate or hospital stay. A poor correlation between microbiological clearance and clinical outcome in patients with XDRAB infection has been reported previously.[18,20] However, in the pneumonia group, a higher 30-day mortality rate was associated with underlying COPD and malignancy. These findings were compatible with previous studies,[11,21] in which underlying comorbidities were associated with unfavorable outcomes in XDRAB infection, irrespective of antimicrobial regimens. Thus, our study indicates that the underlying comorbidity, but not microbiological eradication of XDRAB in the airway, is one of the major determinants of 30-day mortality.

In the colonization group, no improved survival or clinical benefit was noted with eradication of XDRAB from the respiratory tract. In those patients, chronic bedridden status was the only factor associated with 30-day mortality by the multivariate analysis. In a case—control study

Table 3 Univariate and multivariate analyses of clinical variables associated with 30-day mortality in cases of extensively drug-resistant *Acinetobacter baumannii* (XDRAB) pneumonia and colonization

Variables	Univariate analysis	*p*	Multivariate analysis	*p*
	OR (95% CI)		aOR (95% CI)	
XDRAB pneumonia				
COPD	5.2 (1.6–7.5)	0.007	7.0 (1.8–26.8)	0.004
Malignancy	6.1 (1.4–27.2)	0.018	8.9 (1.7–45.6)	0.010
XDRAB colonization				
Old stroke	3.9 (1.2–12.8)	0.023	4.3 (1.2–15.9)	0.030
Chronic renal failure	2.1 (1.2–3.6)	0.011		
APACHE II score > 21	3.8 (1.2–12.5)	0.026		
Nephrotoxicity	5.6 (1.6–20.3)	0.008		

aOR = adjusted odds ratio; APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio.

conducted in Taiwan, when aerosolized CMS was used in a mixed population (both XDRAB-infected and -colonized patients) for eradication of XDRMB from the respiratory tract, recognized benefits were the shortening of contact isolation duration and reduction of cost for isolation measures.[12] As XDRAB can colonize multiple body sites[3] and survive for a long time in the environment,[1,2] eradication of XDRAB from the respiratory tract may not be an effective hospital infection control measure. Further studies are needed to evaluate the impact of such a practice on hospital infection control.

The incidence of renal injury in our study was 21–23%, as assessed by the RIFLE criteria. In a recent study that used the RIFLE criteria to evaluate intravenous CMS-related nephrotoxicity in young patients (average age 27 years) with previously normal renal function, 45% of patients had some degree of renal dysfunction, and 21% of patients stopped therapy secondary to nephrotoxicity.[7] Nephrotoxicity related to intravenous CMS appears to be dose-dependent.[22] The serum level of CMS given by the inhalation route is much lower compared to that of the intravenous route.[23,24] Thus, it was likely but not proven yet that aerosolized CMS therapy may be less nephrotoxic. The incidence of nephrotoxicity in our study was higher than expected. A possible reason is that our study included elderly patients (mean age of 80 years) and those with chronic renal insufficiency at baseline, accounting for 25% of all patients. However, aerosolized CMS can reach the systemic circulation,[23,24] albeit in low doses. Whether low serum CMS levels can result in renal toxicity, especially in

Table 4 Comparison of cases of extensively drug-resistant *Acinetobacter baumannii* (XDRAB) pneumonia and colonization treated by colistin methanesulfonate (CMS) inhalation alone or in combination with intravenous tigecycline (IVTG)

Variables	Pneumonia (n = 38)			Colonization (n = 52)		
	CMS inhalation (n = 9)	CMS inhalation + IVTG (n = 29)	*p*	CMS inhalation (n = 31)	CMS inhalation + IVTG (n = 21)	*p*
Male (%)	3 (33.3)	19 (65.5)	0.088	24 (77.4)	12 (57.1)	0.120
Age (y)	82.2 ± 16.1	79.2 ± 9.9	0.602	81.1 ± 12	81.6 ± 6	0.862
APACHE II score	16.4 ± 4.6	17.8 ± 7.3	0.522	14.8 ± 6.1	18.7 ± 8	0.066
Underlying conditions						
COPD	3 (33.3)	8 (27.6)	0.740	13 (41.9)	4 (19)	0.084
Cerebral vascular disease	6 (66.7)	18 (62.1)	0.803	21 (67.7)	10 (47.6)	0.147
Malignancy	2 (22.2)	6 (20.7)	0.922	3 (9.7)	4 (19)	0.331
Onset at ICU	3 (33.3)	17 (58.6)	0.184	13 (41.9)	4 (19)	0.084
Mechanical ventilator						
Noninvasive	3 (33.3)	9 (31.0)	0.897	6 (19.4)	5 (23.8)	0.700
Invasive	2 (22.2)	14 (48.3)	0.167	6 (19.4)	5 (23.8)	0.700
Tigecycline susceptibility	2 (22.2)	21 (72.4)	0.018	16 (51.6)	16 (76.2)	0.192
Clinical and microbiological outcomes						
XDRAB eradication	7 (77.9)	23 (79.3)	0.922	27 (87.9)	12 (42.9)	0.001
30-day mortality	3 (33.3)	10 (34.5)	0.949	8 (25.8)	7 (33.3)	0.557
In-hospital mortality	5 (55.6)	15 (51.7)	0.841	9 (29)	9 (45)	0.244
Duration of hospitalization (d)	49.0 ± 31	48.9 ± 25	0.922	37 ± 18.9	45.4 ± 26	0.191
Favorable clinical outcome	5 (55.6)	15 (51.7)	0.932			

Results are expressed as *n* (%) or mean ± standard deviation.
APACHE II = Acute Physiology and Chronic Health Evaluation II; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit.

elderly patients with impaired renal function, requires further studies.

In the pneumonia group, age, sex, infection source, underlying conditions, APACHE II score, characteristics of XDRAB isolates, and antimicrobial therapy had no significant impact on eradication of XDRAB. However, in the colonization group, IVTG in combination with aerosolized CMS was negatively associated with XDRAB eradication. Tigecycline-based therapy for the treatment of hospital-acquired XDRAB infections has been reported to be associated with more microbiological failure.[18,20] The mechanism and clinical significance of such findings need to be evaluated further.

Although clinical use of tigecycline for hospital-acquired pneumonia has not been approved by the United States Food and Drug Administration,[25] IVTG has been used in combination with aerosolized CMS in this study and failed to improve clinical outcomes of the patients with XDRAB pneumonia, despite the fact that the majority of XDRAB isolates from the former population were susceptible to tigecycline. Some investigators have suggested that tigecycline at the conventional doses of 100 mg loading followed by 50 mg every 12 hours, is likely to be inadequate for the treatment of pneumonia.[26] However, given the trend in increasing antimicrobial resistance and spread of XDRAB infections,[27,28] salvage tigecycline therapy for the treatment of XDRAB pneumonia will increase and more clinical studies of the tigecycline-based combination therapy will be warranted.

Our study has some limitations. First, it was a single-center, retrospective study involving a limited case number. Second, we identified *A. baumannii* by a phenotypic method; therefore, it is possible that non-baumannii *Acinetobacter* species were included. Third, in our study, subsequent respiratory cultures were collected every 3—5 days after the index day. The duration of CMS use prior to XDRAB eradication depends on the frequency of bacterial cultures of respiratory samples. More frequent collection, such as daily collection of respiratory cultures, may be necessary to determine the exact duration of aerosolized CMS before XDRAB is eradicated. Finally, we used strict criteria to define XDRAB pneumonia, thus some infected patients may be included in the colonization group because they did not fulfill the criteria of pneumonia.

In conclusion, aerosolized CMS therapy for XDRAB pneumonia has acceptable efficacy, but in XDRAB-colonized patients, no survival or clinical benefit was noted in eradication of XDRAB from the respiratory tract. The development of colistin-resistant *A. baumannii* is a concern and warrants cautious monitoring.

Conflicts of interest

All authors declare no conflicts of interest.

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