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Inhaled Colistin for Treatment of Pneumonia due to Colistin-Only-Susceptible *Acinetobacter baumannii*

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Purpose: Colistin is used for the treatment of pneumonia associated with multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. However, the best route of administration and dosage is not known. We report our experience with aerosolized colistin in twelve patients with pneumonia caused by colistin-only-susceptible (COS) *A. baumannii*. **Materials and Methods:** We retrospectively reviewed patients' medical records who were treated with aerosolized colistin for the treatment of pneumonia. **Results:** Ten patients were treated only with aerosolized colistin inhalation and two patients received a 3-day course intravenous colistin, and then switched to colistin inhalation therapy. The median duration of aerosolized colistin therapy was 17 days (5-31 days). Four patients were treated only with aerosolized colistin, whereas 4 patients received concomitant glycopeptides, and 4 received concomitant levofloxacin or cefoperazone/sulbactam. At the end of the therapy, the clinical response rate and bacteriological clearance rate was 83% and 50%, respectively. Colistin-resistant strains were isolated from 3 patients after aerosolized colistin therapy; however, all of them showed favorable clinical response. The median interval between inhalation therapy and resistance was 7 days (range 5-19 days). Acute kidney injury developed in 3 patients. Two patients experienced *Clostridium difficile* associated diarrhea. One patient developed fever and skin rash after aerosolized colistin therapy. No patient developed neurotoxicity or bronchospasm. **Conclusion:** Colistin inhalation therapy is deemed tolerable and safe, and could be beneficial as an adjuctive therapy for the management of pneumonia due to COS *A. baumannii*. However, the potential development of colistin resistance cannot be overlooked.

Key Words: *Acinetobacter baumannii*, colistin, pneumonia

INTRODUCTION

The growing epidemic of multidrug-resistant (MDR) gram-negative bacteria has led clinicians to prescribe colistin. However, due to inadequate penetration in the lung parenchyma, the effectiveness of intravenous (IV) colistin therapy for pneumonia has been questioned.[1]

Although inhaled colistin has been used successfully to prevent and cure pulmonary infections in patients with cystic fibrosis colonized with *Pseudomonas aeru-*

ginosa,[2] there is limited data supporting effectiveness and tolerability of inhaled colistin therapy in non-cystic fibrosis patients with pneumonia due to MDR *A. baumannii*.[3] We report here our experience with critically ill patients who received colistin inhalation therapy for the treatment of colistin-only-susceptible (COS) *A. baumannii* pneumonia.

MATERIALS AND METHODS

Study design

A retrospective review of medical records of patients who received inhaled colistin therapy for >72 h was performed at a tertiary care university hospital in Wonju, Korea. A pharmacy-generated list identified patients aged ≥18 years who received inhaled colistin therapy from March 2012 through September 2012. Colistin methanesulfonate was used in all patients. The daily dosage of nebulized colistin was 150 mg divided into 2 doses, and 75 mg of colistin was diluted in 4 mL of sterile normal saline. The solution was nebulized through a conventional nebulizer. Patients demographic characteristics, underlying diseases, Acute Physiologic and Chronic Health Evaluation (APACHE) II scores on the first day of colistin inhalation therapy, concomitant use of antibiotics, and nephrotoxicity were reviewed. The study was approved by the Institutional Review Board (YWMR-12-5-042) of Yonsei University Severance Hospital.

Microbiological testing

All causative micro-organisms were identified using conventional microbiological methods. Identification and susceptibility tests were done using the Vitek 2 system (BioMérieux, Marcy l'Étoile, France) and MicroScan WalkAway System (Siemens Healthcare Diagnostics, Sacramento, CA, USA). Antimicrobial susceptibilities of all isolates were interpreted by the Clinical and Laboratory Standards Institute recommended interpretive guidelines. Susceptibility to colistin was tested using broth microdilution method. An isolate was defined as COS if it was resistant to all anti-pseudomonal agents except colistin.

Definitions

Pneumonia was diagnosed on the basis of a radiographic findings of a new and progressive pulmonary infiltrate and at least 2 of the following clinical criteria: body temperature, >38°C or <35.5°C; leukocytosis (leukocyte count, >12000 cells/mm^3); and clinical evidence of suggestive of pneumonia such as purulent bronchial secretions and a decrease in oxygenation.[4] The etiology of the pneumonia was established by isolation of the organism from endotracheal aspirates or bronchoalveolar lavage with a concentration of ≥10^4 CFU/mL.

Clinical outcome was classified as clinical cure (i.e. resolution of presenting symptoms and signs of infection by the end of colistin treatment), improvement (i.e. partial resolution of presenting symptoms and signs of infection), failure (i.e. persistence or worsening of presenting symptoms and/or signs of infection during colistin administration), and recurrence of infection (i.e. occurrence of a new episode of infection at least 72 h after clinical resolution of a preceding episode). Favorable clinical response was defined as clinical cure or clinical improvement.[5] Microbiological outcome was rated as eradication of the pathogen (i.e. no growth of the pathogen in the final culture of specimens during the entire hospitalization), persistence of the pathogen (i.e. persistent growth of the responsible pathogen regardless of the clinical outcome of the infection), recurrence (re-growth) of the pathogen (i.e. re-isolation of the same pathogen regardless of the clinical outcome of the infection), or colonization (i.e. persistence or reemergence of the pathogen without symptoms and signs of infection).[5]

Pneumonia-related mortality was defined as death that occurred during the treatment period when the signs of pneumonia remained.

Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria were used to evaluate the nephrotoxicity of colistin.[6] Glomerular filtration rate was calculated by the Modification of Diet in the Renal Disease Study equation: $175\times(\text{serum creatinine})^{-1.154}\times(\text{age})^{-0.203}\times(0.742 \text{ if female})$. We reviewed information on patients' creatinine level until their hospital discharge.

All adverse effects related to colistin use, such as bronchospasm, neurotoxicity, hypersensitivity reactions (including rash, pruritus, urticaria and fever) were also recorded.

RESULTS

During the study period, 12 (7 males) patients were treated with inhaled colistin for COS *A. baumannii* pneumonia. Table 1 describes the demographic and clinical features of these patients. The median age of the patients was 75 years, and median APACHE II score on the day of inhaled colistin treatment was 19.5 (range 12-29). Polymicrobial infections were observed in 5 patients. In 2 of these 5 patients (Case 9 and

Table 1. Demographics and Clinical Characteristics of Patients Treated with Inhaled Colistin Therapy

Case	Sex	Age, yrs	Prior use of IV colistin, days	Duration of aerosolized colistin, days	Underlying diseases	Isolated pathogen	Location	Concomitant bacteremia	Tracheostomy	Prior use of antibiotics within 72 h	Concomitant antibiotics	APACHE II score	BUN	Cr	GFR	Alb
1	F	73	4	17	Neurovascular disease	*A. baumannii*	ICU	No	Yes	Cefoperazone/sulbactam, oral vancomycin	-	23	19	0.62	100.6	2.4
2	M	78	0	31	ESRD, neurovascular disease	*A. baumannii*	Ward	No	No	Meropenem, rifampicin	-	27	126	6.27	9.2	2.4
3	F	77	3	24	CKD, neurovascular disease	*A. baumannii*	ICU	Yes	Yes	Meropenem, teicoplanin	Teicoplanin, vancomycin, cefoperazone/sulbactam	25	33	2.86	16.9	3.1
4	F	75	0	9	Neurovascular disease	*A. baumannii*, MRSA	ICU	No	Yes	Ceftazidime, vancomycin	Vancomycin	17	22	0.21	347.6	2.8
5	M	75	0	14	CHF, neurovascular disease	*A. baumannii*	ICU	No	No	Meropenem, vancomycin	-	29	45	1.54	47	2.4
6	M	81	0	26	COPD	*A. baumannii*	ICU	No	Yes	Imipenem/cilastatin, vancomycin	Levofloxacin	20	34	1.83	37.9	2.9
7	F	73	0	5	DM, CHF, neurovascular disease	*A. baumannii*	Ward	No	Yes	Ceftazidime, vancomycin	-	12	60	1.45	37.6	3.2
8	M	62	0	17	Malignancy, COPD, neurovascular disease	*A. baumannii*, MRSA	ICU	No	Yes	Imipenem/cilastatin, teicoplanin, metronidazole	Teicoplanin, metronidazole	19	30	0.77	109.1	2.8
9	M	78	0	23	DM, CHF, CKD, neurovascular disease	*A. baumannii*, *P. aeruginosa*	ICU	No	Yes	Imipenem/cilastatin	TMP/SMX, rifampicin	27	45	1.63	43.7	3
10	M	75	0	15	CHF, CKD	*A. baumannii*	ICU	No	No	Imipenem/cilastatin, teicoplanin	Cefoperazone/sulbactam	13	45	1.97	35.3	2.8
11	M	47	0	21	DM, neurovascular disease, alcoholic LC	*A. baumannii*, *P. aeruginosa*	ICU	No	Yes	Meropenem, vancomycin	Cefoperazone/sulbactam	15	20	0.93	92.3	3.9
12	F	75	0	15	DM, neurovascular disease	*A. baumannii*, MRSA	ICU	No	No	Imipenem/cilastatin	Vancomycin	15	12	0.33	206.3	2.8

F, female; ICU, intensive care unit; M, male; ESRD, end-stage renal disease; CKD, chronic renal disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; LC, liver cirrhosis; MRSA, methicillin-resistant *Staphylococcus aureus*; APACHE, acute physiologic and chronic health evaluation; BUN, serum blood urea nitrogen; Cr, serum creatinine; GFR, glomerular filtration rate; Alb, serum albumin; TMP/SMX, trimethoprim-sulfamethoxazole.

11), *P. aeruginosa* was isolated from the same culture specimen. Methicillin resistant *Staphylococcus aureus* was isolated in the other 3 patients (Case 4, 8, 12). All patients were spontaneously breathing without mechanical ventilation. However, most patients were severely ill (10 were in intensive care unit), and had many underlying diseases. One patient (Case 3) had concomitant COS *A. baumannii* bacteremia. She received IV colistin for 3 days, and then switched to colistin inhalation with IV cefoperazone/sulbactam therapy. Because inhaled colistin was administered as definitive therapy in all patients, inhalation treatment started 3-5 days after symptom onset. Therefore, all patients had received other broad spectrum antibiotics before colistin inhalation therapy. Inhaled colistin monotherapy was administered to 4 patients (Case 1, 2, 5, and 7). In 5 patients, an additional antimicrobial agent with activity against gram-negative bacteria was given during the course of inhaled colistin treatment.

Favorable clinical response (cure or improvement) was observed in 10 of the 12 patients (Table 2). Follow-up cultures were available for all patients and *A. baumannii* was eradicated in 6 patients. The all-cause in-hospital mortality was 33.3% (4/12 patients). Pneumonia-associated mortality was 8.3% (1/12 patients). One patient died from subsequent clinical sepsis related to severe *Clostridium difficile* infection, by 47 days after resolving from pneumonia episode (Case 9). In addition, other 2 patients died from acute bleeding and myocardial infarction. Since *A. baumannii* isolates in our case series were resistant to other antimicrobials, we expected that the clinical outcomes could be attributed to

Table 2. Treatment Outcomes of Inhaled Colistin Therapy

Case	Clinical outcomes	Microbiologic outcomes	In hospital mortality	Associated mortality	Length of hospital stay, days
1	Cure	Recurrence			375
2	Improvement	Eradication			372
3	Improvement	Eradication			290
4	Improvement	Persistent			99
5	Failure	Eradication	Yes	Yes	484
6	Cure	Eradication			117
7	Failure	Persistent	Yes	Gastrointestinal bleeding	415
8	Improvement	Persistent			107
9	Cure	Persistent	Yes	Sepsis, severe CDAD	507
10	Improvement	Eradication	Yes	Acute myocardial infarction	112
11	Cure	Eradication			301
12	Cure	Colonization			102

CDAD, *Clostridium difficile* associated diarrhea.

Table 3. Adverse Events during Colistin Inhalation Therapy

Case	Nephrotoxicity, RIFLE	Hypersensitivity	Others	Superinfection	Colistin resistant *A. baumannii*	Time between colistin inhalation and development of resistance, days
1	None			MRSA		
2	-		CDAD	-	Yes	5
3	None			MRSA		
4	R			-	Yes	0
5	R			MRSA		
6	None			-		
7	None	Yes, fever & skin rash		MRSA		
8	None			Burkholderia cepacia		
9	None		CDAD	-	Yes	19
10	None			MRSA		
11	None			-		
12	I			-	Yes	7

RIFLE, risk, injury, failure, loss, and end-stage kidney disease; CDAD, *Clostridium difficile* associated diarrhea; MRSA, methicillin-resistant *Staphylococcus aureus*.

nebulized colistin rather than systemic antimicrobial agents. However, the outcomes were different from our expectations. Among the 4 patients treated with colistin inhalation therapy alone, favorable clinical response was observed in 2 (50%) patients. Two of the 4 patients died during the hospitalization and one patient died from pneumonia. By contrast, all the 8 patients who received concurrent systemic antimicrobial agents showed favorable outcome, and only one died from acute myocardial infarction.

Colistin inhalation therapy was well tolerated (Table 3). During treatment, no patient experienced bronchospasm or neurotoxicity. Only one patient experienced fever and skin rash after colistin inhalation therapy (Case 7). The physician suspected colistin hypersensitivity and changed her antibiotic regimen. Two patients experienced *Clostridium difficile* associated diarrhea. Three patients suffered from acute kidney injury: 2 RIFLE-R, and one RIFLE-I. Among them, 2 patient's peak serum creatinine levels were within normal reference range (Case 4 and 12) and renal functions returned to baseline at the time of hospital discharge. One patient (Case 5) died and follow up of the creatinine level was not possible for this patient. None of the patients discontinued colistin treatment or required renal replacement therapy because of colistin induced nephrotoxicity. Colistin resistance in subsequent sputum culture isolates developed in 3 patients. Median interval between colistin inhalation therapy and resistance was 7 days (range 5-19 days). One patient (Case 4) received colistin inhalation therapy based on the result of culture study performed 5 days prior to the treatment. Subsequent sputum culture obtained on the treatment initiation day was reported as a colistin resistant *A. baumannii* thereafter. Despite colistin resistance, colistin inhalation therapy was continued and clinical outcomes were favorable in all of 4 patients. *Burkholderia cepacia* superinfection was observed in one patient (Case 8).

DISCUSSION

Colistin has a narrow spectrum of use and is primarily used for infections with *P. aeruginosa* and *A. baumannii*. Gram-positive bacteria, *Burkholderia cepacia*, *Serratia marcescens*, *Moraxella catarrhalis*, *Proteus* spp., *Providencia* spp., and *Morganella morganii* are inherently resistant to colistin.[7] Nephrotoxicity and neurotoxicity are the main adverse effects of colistin treatment. Despite these shortcomings, IV colistin has been used as salvage therapy in the treatment of pneumonia caused by MDR or COS gram negative pathogens due to the absence of effective alternative options.[8]

There are several studies evaluating the use of nebulized colistin either as monotherapy or as combination with systemic antibiotics for the treatment of pneumonia associated with MDR pathogens (Table 4). In some case-series studies, colistin inhalation adjunctive to IV colistin therapy has shown high favorable clinical and microbiological responses.[9-12] However, the results from studies including control groups are not consistent. Korbila, et al.[13] demonstrated that the outcome of ventilator-associated pneumonia was better in patients who received colistin inhalation with IV colistin than those who received IV colistin alone. By contrast, other studies showed that addition of aerosolized colistin to IV colistin resulted in no additional benefit.[5,14] Aerosolized colistin inhalation with systemic antibiotics other than colistin also showed favorable clinical (61-100%) and microbiologic responses (60.9-83.3%).[3,15-22] These studies include different combinations of concurrent antimicrobial regimen; therefore, the optimal combination and dosage should be determined by further studies. Colistin inhalation monotherapy without concurrent IV antimicrobial is rarely reported. In a case series by Falagas, et al.[23] two children received inhaled colistin monotherapy for tracheobronchitis and both cases showed a favorable response.

In our study, 8 patients who were treated with concurrent systemic antibiotics other than colistin, showed 100% clinical response, which was similar to the results from previous studies.[3,15-22] However, colistin inhalation as monotherapy in our study showed only a 50% clinical response.

Four patients were treated with an inhaled colistin only, and the other 3 patients received concomitant IV antimicrobial, which has no gram negative activity. Understanding why physicians treated their patients with a colistin inhalation monotherapy is of interest. First, all of these patients were older and had neurovascular diseases. Accordingly, the physicians might be worried about neurotoxicity associated with systemic administration of colistin. The second reason is possible concern for nephrotoxicity. All the patients had hypoalbuminemia (2.4-2.8 g/dL) and two patients (Case 4 and 12) received IV vancomycin concurrently. The other 2 patients (Case 5 and 7) showed impaired renal function at that time. The third reason is likely financial. Except for co-infection by COS *A. baumannii* and colistin-resistant bacteria, The Korean National Health Insurance system often refuses reimbursement for colistin combination therapy with other antimicrobial agent having gram negative activity.

Two major risks are arising from the wide use of colistin: the emergence of colistin resistance and an increase of infections due to gram-positive and gram-negative bacteria that are inherently resistant to colistin. With respect to resistance, colistin heteroresistance and colistin resistance in *A. baumannii* have been reported in several studies.[24-33] In Korea, colistin resistance in *A. baumannii* was reported as 9.1% and 30.6%, respectively, in two different reports.[32,33] In our hospital, colistin resistance rate in *A. baumannii* has been less than 1%. Although some studies suggested that nebulized antibiotic decreases bacterial resistance,[34,35] colistin inhalation monotherapy may be problematic for treatment of

Table 4. Summary of Previous Studies on Colistin Inhalation Therapy for Pneumonia

Authors/yr	Number of patients	Susceptibility and pathogen	Route of administration and other antibiotics	Colistin inhalation dose	APACHE II score	Duration of therapy	Therapeutic response (%)	Nephrotoxicity (%)
Hamer,[15] 2000	3	MDR *P. aeruginosa*	INH+other antibiotics	150/100/140 mg q12 h	NA	11-14	100	0
Michalopoulos, et al.[9] 2005	8	COS/MDR *A. baumannii*	INH+IV	0.5-2 million IU q8 h	14.6	10.5	87.5	0
Motaouakkil, et al.[16] 2006	16	MDR *A.baumannii*	INH+IV rifampicin	1 million IU q8 h	4-15	15	100	0
Falagas, et al.[10] 2006	9	COS GNB	INH+IV	1 million IU q12 h	NA	13	85	7
Pereira, et al.[17] 2007	14	MDR GNB	INH+IV or other antibiotics	0.5 million IU q12 h	NA	14 (4-25)	93	NA
Michalopoulos, et al.[18] 2008	60	MDR GNB	INH+other antibiotics	1 million IU q8 h	16.7	16.4	Microbiologic 83.3, clinical 83.3	NA
Mastoraki, et al.[11] 2008	8	COS *P. aeruginosa*	INH+IV	0.5 million IU q8 h	NA	15.9	70	NA
Falagas, et al.[19] 2009	5	COS/MDR *P. aeruginosa*, *A. baumannii*	INH+other antibiotics	0.5-1 million IU q8 h	11-27	6-11	80	0
Korbila, et al.[13] 2010	78	MDR GNB	INH+IV	1 million IU q24 h	17.4		79.5	NA
Rattanaumpawan, et al.[3] 2010	51	GNB	INH+other antibiotics	75 mg q12 h	19.1	12	Microbiologic 60.9, clinical 51	25.5
Kofteridis, et al.[5] 2010	43	MDR GNB	INH+IV	1 million IU q12 h	16.95	13 (5-56)	Microbiologic 45, clinical 75	19
Lin, et al.[12] 2010	45	MDR *A. baumannii*	INH+IV or carbapenem	2 million IU q8-24 h	22.5	34	Microbiologic 37.8, clinical 57.8	0
Falagas, et al.[23] 2010	3	*A. baumannii*, *P. aeruginosa*	INH/INH+ other antibiotics	75 mg q12 h	NA	25/32/15	100	0
Naesens, et al.[20] 2011	6/9	MDR *P. aeruginosa*	INH+other antibiotics/ INH+IV+other antibiotics	2 million IU q8 h	NA	27.2/19.3	100/78	0/20
Nakwan, et al.[21] 2011	8 neonates	COS *A. baumannii*	INH+other antibiotics	4 mg/kg q12 h	NA	4-14	100	NA
Kalin, et al.[14] 2012	29	MDR *A. baumannii*	INH+IV	75 mg q12 h	22	14	Microbiologic 76, clinical 14	41
Celik, et al.[22] 2012	3, neonates	MDR *A. baumannii*, *P. aeruginosa*	INH+other antibiotics	5 mg/kg q12 h	NA	14/14/16	100	0

MDR, multidrug-resistant; GNB, gram negative bacilli; COS, colistin-only sensitive; NA, not available; INH, colistin inhalation therapy; IV, intravenous colistin therapy; APACHE, acute physiologic and chronic health evaluation.

pneumonia caused by colistin heteroresistant *A. baumannii*. To prevent the appearance of colistin resistance and to improve treatment efficacy, the optimization of the colistin dose is essential. Although previous studies with inhaled colistin therapy did not report any colistin-resistant isolates in patients with persistent isolation of *A. baumannii* or *P. aeruginosa*, our study results support this concern in that 3 patients showed resistance to colistin in subsequent sputum culture isolates within 20 days of colistin inhalation.

The side effects of nebulized colistin include bronchoconstriction, cough, chest tightness, and apnea due to neuromuscular blockade.[36] In this report, no patients were seen developing such adverse events. Our experience suggests that aerosolized colistin for pneumonia due to COS *A. baumannii* may offer advantages over systemic administration in respect to the occurrence of side effects. Theoretically, the use of the aerosolized colistin can minimize potential renal and neurologic toxicities because of negligible systemic absorption. A pharmacokinetic study of aerosolized colistin in cystic fibrosis patients revealed that the maximum observed serum colistin concentration was 0.178 mg/L, <10% of the level in sputum, and much less than the maximal level of 2.8-13.9 mg/L achieved by the IV route and this was undetectable 12 hours after the inhalation.[2] We did not measure the plasma level of colistin in our patients, but it is reasonable to assume low-serum levels and therefore a lower risk of systemic side effects in our patients. In our cases, nephrotoxicity was higher than previous studies. This seems to be due to the severity of patients' diseases and concurrently administered glycopeptides. In addition, our definition of nephrotoxicity was more sensitive than in previous studies. Although the serum concentration is low, the possibility of systemic accumulation by repeated nebulization cannot be excluded. This could result in an increased risk for the selection of colistin resistant strains of *A. baumannii*.

Our study has some limitations. First, it was adapted from a single center, and a small case series were enrolled using a retrospective design. In addition, there we had no control group to compare our results. Second, neurotoxicity may not have been detected in our patients because most of them had underlying neurovascular diseases. Third, we identified *Acinetobacter* species by phenotypic method only; therefore, it is possible that non-*baumannii* species were included. Fourth, there is the possibility of isolated *A. baumannii* was not the etiology of pneumonia but colonization.

In summary, it is difficult to decide whether to use inhaled colistin monotherapy in pneumonia caused by COS *A. baumannii*. Moreover, superinfection with inherently colistin-resistant pathogens and the development of colistin resistant *P. aeruginosa* or *A. baumannii* should be prospectively monitored. The appropriate dose of aerosolized colistin, effective combination with other antimicrobial agents, and adequate indications remains to be determined in order to minimize these risks. A larger prospective and controlled study is needed.

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