Original Article

Effectiveness and Safety of Nebulized Colistin in Ventilator Associated Pneumonia

Mithun Kumar Mondal[1], Sanghita Dutta[2]

DOI: https://doi.org/10.3329/bccj.v13i1.81304

Abstract:

Background: *Colistin is one of the few remaining effective antimicrobial agents against multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria, and is currently regarded as one of the last therapeutic options. After giving aerosol delivery, colistin concentrations were significantly higher in the pulmonary epithelial lining fluid compared to plasma. This study investigates the effectiveness and safety of nebulized colistin as monotherapy (without concomitant IV administration of colistin) in the treatment of ventilator-associated pneumonia.*

Objective: *Evaluation of the effectiveness and safety of nebulized colistin in ventilator-associated pneumonia.*

Methods: *This prospective randomized clinical trial was conducted in the ICU of the Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine, Dhaka Medical College Hospital. The study included patients on mechanical ventilation with ventilator-associated pneumonia sensitive to colistin organisms (Acinetobacter, Pseudomonas, Klebsiella) without prior renal impairment. Then, the patients were divided into two equal groups by computer-generated randomization by a research randomizer. Group A received intravenous colistin, and group B received nebulized colistin as a monotherapy. The analysis was carried out using descriptive and inferential statistics with the help of SPSS.*

Result: *This prospective randomized clinical trial was conducted to see the effectiveness and safety of nebulized colistin compared to intravenous colistin. The clinical cure rate was higher in group B than in group A (65.7% in nebulized group B, 51.5% in intravenous group A), although it was not statistically significant (p=0.743). The microbiological eradication rate was also higher in nebulization group B (94.3%) compared to intravenous group A (85.7%), although it was not statistically significant (p=0.075). Nephrotoxicity is the major adverse event at 25.7% among intravenous group A compared to 5.7% in nebulized group B (p=0.001). Colistin nebulization therapy is usually well tolerated, with only a few side effects being reported. These include coughing, bronchospasm, and throat irritation, which are frequently brought on by the osmolality and preservatives in solutions. We found bronchospasm in nebulized colistin in 1 patient (1.96%). An almost equal proportion of mortality was present in both groups: 28.5% in intravenous group A and 25.7% in nebulization group B (p=0.453). Mean duration of mechanical ventilation in intravenous group A and nebulized group B were 8.19 ± 5.59 and 7.96±3.63 days, respectively (p=0.802). The mean ICU duration of the patients in intravenous group A and nebulized group B were 10.08±6.44 and 9.45±3.76 days, respectively (p=0.55). The mean CPIS (Clinical Pulmonary Infection Score) score reduction of the patients exposed to nebulized and intravenous colistin were 3.8±1.04 and 4 ± 1.17, respectively, which is not statistically significant (p= 0.372). The mean TLC (Total Leukocyte Count) normalization duration of patients in intravenous group A and nebulized group B were 7.43±2.836 and 6.51±2.87 days, respectively (p=0.14).*

Conclusion: *Both nebulized and intravenous colistin are equally effective for treating colistin-sensitive ventilator-associated pneumonia, though intravenous colistin is more nephrotoxic.*

Key Words: *Nebulized Colistin, Nephrotoxicity, Multidrug-resistant, Ventilator-Associated Pneumonia.*

Introduction

Ventilator-associated pneumonia (VAP) ranks as the second most common hospital-acquired infection in the intensive care unit (ICU) and is the leading infection among mechanically ventilated patients.[1] Pseudomonas aeruginosa and Acinetobacter baumannii are the primary organisms involved in VAP, and along with methicillin-resistant Staphylococcus aureus, they contribute to the highest attributable mortality.[2] Timely initiation of appropriate antibiotic therapy is associated with improved clinical outcomes in VAP cases.[3]

Colistin, once considered an 'abandoned' antibiotic, is now one of the few effective agents against MDR and XDR Gram-negative bacteria, serving as a last-resort therapeutic option.[4] Administered in its inactive prodrug form, colistimethate sodium, colistin is often used intravenously, particularly in critical care settings, to treat Ventilator Associated Pneumonia (VAP).[5] However, the effectiveness of intravenous (IV) colistin in treating pneumonia has been questioned due to its limited penetration into pulmonary parenchyma.[6] Colistin levels remain undetectable in lung tissue of piglets and in the bronchoalveolar lavage (BAL) fluid of critically ill adults following IV administration. The safety of IV colistin in critically ill patients is also debated, as it has been linked to variable nephrotoxicity and neurotoxicity.[3,6,7]

Inhaled colistin is gaining popularity as it may address the challenges associated with IV administration.[8] This method allows colistin to reach high concentrations in the respiratory

Received : December 18, 2024; Accepted : March 02, 2025

tract while minimizing systemic effects.[9,10] A recent pharmacokinetic study showed that colistin levels in the pulmonary epithelial lining fluid were approximately 100- to 1000-fold higher than plasma concentrations following aerosol delivery.[11]

Accordingly, the latest guidelines from the Infectious Diseases Society of America and the American Thoracic Society recommend adding inhaled colistin to IV polymyxin (colistin or polymyxin B) for patients with hospital-acquired pneumonia (HAP)/VAP caused by pathogens susceptible only to colistin. However, combining IV and inhaled administration may carry drawbacks, including an increased risk of nephrotoxicity, the potential for resistance development in the respiratory tract, and higher costs.[12]

There have been several prospective and retrospective studies since 2006 on nebulized colistin. All studies showed colistin is well tolerated without significant complications.[13] In a randomized, single-blind study, nebulized colistin alone demonstrated therapeutic effectiveness comparable to parenteral colistin, with a higher bacterial eradication rate, improved clinical cure rate, earlier ventilator weaning among ICU survivors, and reduced nephrotoxicity.[14]

Thus, this study investigates the effectiveness and safety of nebulized colistin as monotherapy (without concomitant IV administration of colistin) in treating ventilator-associated pneumonia.

Methods

This prospective randomized clinical trial was conducted in the ICU of the Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine, Dhaka Medical College Hospital (DMCH).

Patients on mechanical ventilation with tracheal aspirate cultures having growth of organisms sensitive to colistin without any prior renal impairment were included in the study. Then, the patients were divided into two groups by computer-generated randomization by research randomizer. Group A received intravenous colistin and group B received nebulized colistin as a monotherapy.

Group A received IV colistin as a loading dose of 9 MU (300 mg) followed by 4.5 MU (150 mg) twice daily. The duration of the therapy is maintained for up to 10 days or clinical resolution of VAP, whichever comes earlier. In case of acute kidney injury which may develop later, the doses of IV clearance from Sanford guideline as follows: ≥90 to 50 colistin modified according to the calculated creatinine mL/min 4.5 MU 12 hourly, <50 to 30 mL/min 3.7 MU 12 hourly, <30 to 10 mL/min 5.4 MU per day, if <10 mL/min 3.5 MU per day. The loading dose of 9 MU was maintained for all patients.

The optimal dose of inhaled colistin ranges from 75 to 150 mg colistin base activity (2.25 to 4.5 million international units Colistimethate Sodium (CMS) twice daily. In this study group B received 4.5 million units (MU) of colistin by nebulization up to 30 minutes two times per day via ventilator. There is no commercially available nebulized preparation for colistin. Both colistin sulfate and colistimethate sodium intravenous formulations are used for nebulization. Both dissolved in 4–6 ml of normal saline or sterile water for nebulization via ventilator nebulizer. Colistin is mixed immediately prior to nebulization to prevent adverse effects.

Intravenous and nebulized colistin continued until a clinical cure was achieved; otherwise, it continued for up to 10 days. Both IV and Nebulised Colistin were continued even when the subsequent tracheal aspirate culture was negative, but the patient was not clinically cured, as cultures may be falsely negative in some patients. A physical examination (includes temperature measurement and assessment of tracheal secretions) and a biological exploration (includes complete blood cell count, arterial blood gas analysis, renal function) and radiological test, Chest X-ray, are conducted daily. CPIS (Clinical Pulmonary Infection Score) is done daily to see the clinical outcomes of patients. Tracheal aspirate for culture sensitivity is performed every three days according to the patient's clinical condition and microbiological outcome. The patient followed up until ICU discharge to check the duration of mechanical ventilation and mortality.

Clinical outcome was classified as clinical cure, clinical improvement, and clinical failure according to CPIS. The microbiological outcome was defined as eradication of the pathogen, the persistence of the pathogen, and recurrence of the pathogen according to the culture sensitivity report.

All adverse effects related to colistin use, such as nephrotoxicity and respiratory distress (bronchospasm) during nebulization, were recorded. The total leukocyte count was checked daily to see each patient's Total leukocyte count (TLC) normalization time.

Operational definitions

Ventilator-associated pneumonia: A VAP episode is clinically defined by a Clinical Pulmonary Infection Score (CPIS) greater than six, occurring 48 hours after intubation.

Positive tracheal culture: Growth of microorganisms in appropriate culture media and observation of pus cell during microscopy from tracheal aspirate.

Clinical cure: Resolution of initial infection symptoms and signs by the end of colistin therapy, indicated by a CPIS below 3.

Clinical improvement: Partial improvement of initial infection symptoms and signs by the end of colistin treatment, indicated by a CPIS of 3 to 6.

1. Specialist in Charge, Emergency & Casualty Centre, Combined Military Hospital (CMH), Dhaka.

2. Industrial & Production Engineer, Ahsanullah University of Science and Technology, Dhaka

Corresponding Author:
Dr Mithun Kumar Mondal
Intensivist, Specialist in Charge, Emergency & Casualty Centre
Combined Military Hospital (CMH), Dhaka
E-mail: m1989n.k64@gmail.com

Clinical failure: Persistence or worsening of initial symptoms and/or signs of infection by the end of colistin treatment, indicated by a CPIS consistently above 6.

Eradication of the pathogen: No pathogen growth was observed in the final culture of specimens following colistin treatment.

Persistence of the pathogen: Continued growth of the identified pathogen in culture after colistin treatment.

Recurrence (regrowth) of the pathogen: Isolation of the same pathogen identified in the initial culture following subsequent negative cultures during colistin treatment.

Nephrotoxicity: An increase in serum creatinine of ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours; or an increase in serum creatinine to ≥ 1.5 times the baseline, which is known or presumed to have occurred within the previous seven days; or a urine volume of <0.5 ml/kg/h for 6 hours. (KDIGO AKI definition)[22]

Total leukocyte count (TLC) normalization time: TLC normalization is defined as how many days are required for intravenous/nebulized colistin to normalize leukocyte count (normal range 4 x 10^9/L to 11 x 10^9/L)

Statistical analysis:

Data analysis was conducted using descriptive and inferential statistics with SPSS (Statistical Package for Social Science) version 23 for Windows. The analysis was aligned with the study objectives. Descriptive statistics included frequency, percentage, mean, median, and standard deviation (SD) for socio-demographic factors such as age. Inferential statistics were employed to assess associations between independent and dependent variables. The Chi-square test, t-test, and Fisher's exact test were utilized to evaluate the significance of associations among various factors. The results were presented in tabular form, and all two-sided statistical tests were performed at a significance level of $p \leq 0.05$.

RESULTS

Table I: Distribution of patients by age (N= 70)

Age group	Treatment groups		Total	Test of significance
	Group A (Intravenous) (n=35)	Group B (Nebulization) (n=35)		
≤30	10 (55.5)	8 (44.5)	18 (25.7)	p = 0.078
31-40	5 (35.7)	9 (64.3)	14 (20)	NS
41-50	7 (77.7)	2 (22.3)	9 (12.9)	
51-60	5 (38.5)	8 (61.5)	13 (18.6)	
61-70	4 (57.1)	3 (42.9)	7 (10)	
≥70	4 (44.4)	5 (55.5)	9 (13)	
Total	35 (50)	35 (50)	70 (100)	

Minimum age 18 year

Maximum age 80 year

Mean age 33.34 ± 9.38 year

*Percentage in parentheses *NS=non-significant

Table no. I shows the distribution of patients by age. Chi-squared Test (χ^2) was performed to compare between two groups (χ 2=12.337, df=5). Statistically significant relationship was not found between group A and B in distribution of age (p=0.078).

Table II: Distribution of patients by Co-morbidities (N= 70)

Co morbidities	Treatment groups		Total	Test of significance
	Group A (Intravenous) (n= 35)	Group B (Nebulization) (n=35)		
Chronic Pulmonary Disease	0(0)	2(100)	2(2.9)	p=0.707
Chronic Lung Disease	1(100)	0(0)	1(1.4)	NS
Diabetes Mellitus	9(60)	6(40)	15(21.4)	
Ischemic Heart Disease	4(44.5)	5(55.5)	9(12.9)	
Hypertension	10 (52.6)	9 (47.4)	19 (27.1)	
No comorbidities	11 (45.8)	13 (54.2)	24 (34.3)	
Total	35(50)	35(50)	70(100)	

* Percentage in parentheses *NS=non-significant

Table no. II shows distribution of patients by co-morbidities. Fisher's exact test was done. (Fisher's Exact value = 3.445) Statistically significant relationship was not found between group A and B for comorbidities (p=0.707)

Table III: Distribution of patients by initial culture report (N= 70)

Growth of organism	Treatment groups		Total	Test of significance
	Group A (Intravenous) (n= 35)	Group B (Nebulization) (n= 35)		
Acinetobacter	15(42.8)	18(51.4)	33(47.1)	p=0.712
Pseudomonas	14(40)	12(34.3)	26(37.1)	NS
Klebsiella	6(17.2)	5(14.3)	11(15.8)	
Total	35(50)	35(50)	70(100)	

*Percentage in parentheses *NS=non-significant

Table no. III shows the distribution of patients by initial culture report. Acinetobacter is the most frequently found bacteria in both groups, followed by Pseudomonas. Chi-squared Test (χ^2) was performed to compare between two groups ($\chi2$=0.813, df=2). Statistically significant relationship was not present between group A and B for initial culture report (p=0.712).

Table IV: Distribution of patients by clinical outcome (N= 70)

Clinical Outcome	Treatment groups		Total	Test of significance
	Group A (Intravenous) (n= 35)	Group B (Nebulization) (n= 35)		
Cure	18(51.5)	23(65.7)	41	p=0.743
Improvement	10(28.5)	7(20)	17	NS
Failure	7(20)	5(14.3)	12	
Total	35(50)	35(50)	70	

*Percentage in parentheses *NS=non-significant

Table no. IV shows distribution of patients by clinical outcome. Fisher's exact test was done (Fisher's Exact value= 1.788). Statistically significant relationship for clinical outcome was not found between group A and B for clinical outcome (p=0.743).

Table V: Distribution of patients by bacteriological outcome (N= 70)

Bacteriological Outcome	Treatment groups		Total	Test of significance
	Group A (Intravenous) (n= 35)	Group B (Nebulization) (n= 35)		
Eradication	30(85.7)	33(94.3)	63	p=0.075
Persistent	3(8.6)	2(5.7)	05	NS
Recurrence	2(5.7)	0(0)	2	
Total	35(50)	35(50)	70	

*Percentage in parentheses *NS=non-significant

Table no V shows distribution of patients by bacteriological outcome. Fisher's exact test was done (Fisher's Exact value= 4.720). Statistically significant relationship was not found for bacteriological outcome between group A and B for bacteriological outcome (p=0.075).

Table VI: Distribution of patients by adverse events (N= 70)

Adverse Event	Treatment groups		Total	Test of significance
	Group A (Intravenous) (n= 35)	Group B (Nebulization) (n= 35)		
Nephrotoxicity	9(25.7)	2(5.7)	11	p=0.001
None	26(74.3)	33(94.3)	59	S
Total	35(50)	35(50)	70	

*Percentage in parentheses *S=Significant

Table no. VI shows distribution of patients by adverse events. Nephrotoxicity and bronchospasm measured in both groups. Chi-squared Test (χ^2) was performed to compare nephrotoxicity between two groups ($\chi2$=19.26, df=5). Statistically significant relationship was found for nephrotoxicity between group A and B for nephrotoxicity (p=0.001). Only 1 patient in group B developed bronchospasm.

Table VII: Distribution of patients by mortality (N= 70)

Adverse Event	Treatment groups		Total	Test of significance
	Group A (Intravenous) (n= 35)	Group B (Nebulization) (n= 35)		
Death	10(28.5)	9(25.7)	19	p=0.453
Alive	25(71.4)	26(74.3)	51	NS
Total	35(50)	35(50)	70	

*Percentage in parentheses *NS=non-significant

Table no VII shows distribution of patients by mortality. Almost equal proportion of mortality was present in both groups. Chi-squared Test (χ^2) was performed to compare between two groups ($\chi 2$=0.746, df=1). Statistically significant relationship for mortality was not present between group A and B for mortality (p=0.453)

Table VIII: Distribution of patients by CPIS score reduction (N= 70)

Variable	Treatment groups		P-value
	Group A (Intravenous) (n= 35)	Group B (Nebulization) (n= 35)	
Mean of CPIS score reduction	4 (±1.17)	3.8 (±1.04)	0.372

Table no VIII shows distribution of patients by CPIS score reduction. The independent sample t test was not significant for CPIS score reduction between group A and B. (p=0.372).

Table IX: Distribution of patients by duration of mechanical ventilation (N= 70)

Variable	Treatment groups		P-value
	GroupA (Intravenous) (n= 35)	Group B (Nebulization) (n= 35)	
The mean duration of mechanical ventilation(days)	8.19 (±5.59)	7.96 (±3.63)	0.802

Table no. IX shows distribution of patients by duration of mechanical ventilation. The independent sample t test was not significant for duration of mechanical ventilation between group A and B. (p=0.802)

Table X: Distribution of patients by length of stay in ICU (N= 70)

Variable	Treatment groups		P-value
	Group A (Intravenous) (n= 35)	Group B (Nebulization) (n= 35)	
Mean Length of stay in ICU(days)	10.08 (±6.44)	9.45 (±3.76)	0.55

Table X shows the distribution of patients by length of stay in the ICU. The independent sample t test was not significant for length of stay in the ICU between group A and B (p=0.55).

Table XI: Distribution of patients by duration required for total leukocyte count (TLC) normalization (N= 70)

Variable	Treatment groups		P-value
	Group A (Intravenous) (n= 35)	Group B (Nebulization) (n= 35)	
Duration required for TLC normalization(days)	7.43 (±2.83)	6.51 (±2.87)	0.14

Table XI shows the distribution of patients by the duration required for TLC normalization. The independent sample t test was not significant for the duration required for TLC normalization between group A and B (p=0.14).

Discussion

This study compared the effectiveness and safety of nebulized colistin to intravenous colistin. No statistically significant difference between groups A and B was observed for socio-demographic features (p=0.078) and comorbidities (p=0.707).

Acinetobacter baumannii was the most common organism (47.1%), followed by *Pseudomonas aeruginosa* (37.1%) and *Klebsiella pneumoniae* (15.8%). A statistically significant relationship was not found between groups A and B for the initial culture report (p=0.712).Maximum studies dealt with either Acinetobacter or Pseudomonas or both. Very few studies included all three organisms. Among them, Athanassa et al. found A. baumannii in 55% of patients, P. aeruginosa in 40%, and K. pneumoniae in 10% of patients, which correlates with our study.[10]In another study, Abdellatif et al. found 45% A. baumannii, 14% P. aeruginosa, and 19%

Enterobacteriaceae. [14]Maskin et al. found a very high percentage of P. aeruginosa (85%) and 15% of K. pneumoniae in their ICU.[15]

The clinical cure rate was higher in group B than in group A (65.7% in nebulized group B, 51.5% in intravenous group A), although it was not statistically significant (p=0.743). Kwa et al. found a similar result, with a clinical success rate of 57.1% in the nebulized colistin group.[16] In a more recent retrospective study, Hsieh et al. found that the clinical cure rate in the nebulized group was 50.9%.[17] Although the clinical cure rate is better in a nebulized group than the intravenous group, it is not clinically significant. A similar outcome was found by Abdellatif et al. with a clinical cure rate of 67.1 % in the nebulized group and 72 % in the intravenous group (p = 0.59)[14]

The microbiological eradication rate was also higher in nebulization group B (94.3%) compared to intravenous group A (85.7%), although it was not statistically significant (p=0.075). These findings correlate with Abdellatif et al., eradicating 93.2% of cases in the nebulized group and 89.1% in the intravenous group. However, less favorable microbiological outcomes were found by Rattanaumpawan et al. (60.9%) because they used 2.25 MU nebulized colistin in the treatment arm, which is half of our study population.[14,18]

Nephrotoxicity is the major adverse event, 25.7% among intravenous group A compared to 5.7% nebulized group B (p=0.001). These findings are consistent with other studies. Rattanaumpawan et al. conducted a randomized controlled study that showed renal impairment in 25% of patients in the intravenous colistin group and 12.5% in the nebulized group.[18] In another randomized, single-blind study, the nebulized group had a significantly lower incidence of nephrotoxicity, 17.8% vs 39.4 % in the intravenous group. (p = 0.004) They noted a significantly higher incidence of acute renal failure (ARF), a greater need for renal replacement therapy (RRT), and an earlier onset of acute kidney injury (AKI) with parenteral administration.[14]

Colistin nebulization therapy is typically well tolerated, with few reported side effects, such as throat irritation, cough, and bronchospasm, which may be attributed to the osmolality and preservatives in certain solutions. We found bronchospasm in nebulized colistin in 1 patient (1.96%). This patient has a previous history of Bronchial asthma. The bronchospasm resolved after taking nebulized bronchodilators and continued throughout the treatment of this patient. Rattanaumpawanet al. found bronchospasm in 2 patients, Abdellatifet al. found bronchospasm in 2 (2.7%) patients, Kwa et al. found in 1 (4.8%), Maskin et al. found bronchospasm in 2 (10%) patients. Only one patient has to discontinue the treatment for severe bronchospasm.[14,15,16]

Almost equal proportions of mortality were present in both groups: 28.5% in intravenous group A and 25.7% in nebulization group B (p=0.453). Abdellatif et al. found almost the same mortality in the nebulized (27%) and intravenous (24%) colistin groups. Although they measured mortality for 28 days, this study measured mortality until ICU discharge.[14]However, Lu et al. found that the aerosolized group experienced a longer length of stay in the ICU and an extended duration of ventilation1.[19]

The mean duration of mechanical ventilation in intravenous group A and nebulized group B were 8.19 ± 5.59 and 7.96±3.63 days, respectively (p=0.802). The mean ICU duration of the patients in intravenous group A and nebulized group B were 10.08±6.44 and 9.45±3.76 days, respectively (p=0.55). Similarly, S.C.Kuo et al. found that the Duration of mechanical ventilation in the nebulized group was 5.7 ± 6.7 days, and in the control group, it was 7.9 ± 6.6 days.[20] However, Kofteridis et al. found that the ICU stay was 20 days in the intravenous group and 18 days in the nebulized group, and the duration of the MV was 16.5 days in the intravenous group and 15 days in the nebulized group.[21] This happened because they dealt with older patients with immunosuppressive therapies.

The mean CPIS score reduction of the patients exposed to nebulized and intravenous colistin were 3.8 ± 1.04 and 4 ± 1.17, respectively, which is not statistically significant (p= 0.372). Abdellatif et al. reported no significant difference in CPIS between the two groups (3.8 vs 4.5, p = 0.12). However, in cured patients, the CPIS improved more in the nebulized group (3.02 vs 3.68, p = 0.027).[14]

The mean TLC normalization duration of patients in intravenous group A and nebulized group B were 7.43±2.836 and 6.51±2.87 days, respectively (p=0.14). Similar findings were found by Kwa et al. that it took less time to normalize TLC in patients who took nebulized colistin therapy.[16]

Limitations

- The patients were monitored only briefly until their discharge from the ICU.
- The study included only a small number of patients due to the limited study period.

Conclusion

Both nebulized and intravenous colistin are equally effective for treating colistin-sensitive ventilator-associated pneumonia, though intravenous colistin is more nephrotoxic. There is no difference in clinical cure rate, microbiological eradication rate, duration of mechanical ventilation, ICU stay and overall mortality with the use of nebulized colistin over intravenous colistin.

References

1. Hunter JD. Ventilator-associated pneumonia. BMJ. 2012;344:e3325.
2. Rello J, Sa-Borges M, Correa H, Leal SR, Baraibar J. Variations in etiology of ventilator-associated pneumonia across four treatment sites. Am J Respir Crit Care Med. 1999; 160(2):608-13.
3. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005; 171(4):388-416.

4. Falagas ME, Kasiakou SK, Saravolatz LD. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis. 2005; 40(9):1333-41.
5. Linden PK, Paterson DL. Parenteral and inhaled colistin for treatment of ventilator-associated pneumonia. Clin Infect Dis. 2006; 43 Suppl 2:S89-94.
6. Imberti R, Cusato M, Villani P, Carnevale L, Iotti GA, Langer M, et al. Steady-state pharmacokinetics and BAL concentration of colistin in critically ill patients after IV colistin methanesulfonate administration. Chest. 2010; 138(6):1333-9.
7. Lu Q, Girardi C, Zhang M, Bouhemad B, Louchahi K, Petitjean O. Nebulized and intravenous colistin in experimental pneumonia caused by Pseudomonas aeruginosa. Intensive Care Med. 2010; 36(7):1147-55.
8. Palmer LB. Aerosolized antibiotics in critically ill ventilated patients. Curr Opin Crit Care. 2009; 15(5):413-8.
9. Ratjen F, Rietschel E, Kasel D, Schwiertz R, Starke K, Beier H. Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. J Antimicrob Chemother. 2006; 57(2):306-11.
10. Athanassa ZE, Markantonis SL, Fousteri MZ, Myrianthefs PM, Boutzouka EG, Tsakris A, et al. Pharmacokinetics of inhaled colistimethate sodium (CMS) in mechanically ventilated critically ill patients. Intensive Care Med. 2012; 38(11):1779-86.
11. Boisson M, Jacobs M, Grégoire N, Gobin P, Marchand S, Couet W, Mimoz O. Comparison of intrapulmonary and systemic pharmacokinetics of colistin methanesulfonate (CMS) and colistin after aerosol delivery and intravenous administration of CMS in critically ill patients. Antimicrob Agents Chemother. 2014; 58(12):7331-9.
12. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016; 63(5):e61-e111.
13. Gurjar M. Colistin for lung infection: An update. J Intensive Care. 2015; 3(1).
14. Abdellatif A, Trifi AH, Daly F, Mahjoub K, Nasri R, Ben Lakhal S. Efficacy and toxicity of aerosolized colistin in ventilator-associated pneumonia: a prospective, randomized trial. Ann Intensive Care. 2016; 6(1):26.
15. Maskin LP, Setten M, Rodríguez PO, Bonelli I, Attie S, Stryjewski ME, et al. Inhaled colistimethate sodium in ventilator-associated tracheobronchitis due to multidrug-resistant gram-negative bacteria. Int J Antimicrob Agents. 2015; 45(2):199-200.
16. Kwa AL, Loh C, Low JG, Kurup A, Tam VH. Nebulized colistin in the treatment of pneumonia due to multidrug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa. Clin Infect Dis. 2005; 41(5):754-7.
17. Hsieh TC, Chen FL, Ou TY, Jean SS, Lee WS. Role of aerosolized colistin methanesulfonate therapy for extensively-drug-resistant Acinetobacter baumannii complex pneumonia and airway colonization. J Microbiol Immunol Infect. 2016; 49(4):523-30.
18. Rattanaumpawan P, Lorsutthitham J, Ungprasert P, Angkasekwinai N, Thamlikitkul V. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by gram-negative bacteria. J Antimicrob Chemother. 2010; 65(12):2645-9.
19. Lu Q, Luo R, Bodin L, Yang J, Zahr N, Aubry A. Efficacy of high-dose nebulized colistin in ventilator-associated pneumonia caused by multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. Anesthesiology. 2012; 117(6):1335-47.
20. Kuo SC, Lee YT, Yang SP, Chen CP, Chen TL, Hsieh SL. Eradication of multidrug-resistant Acinetobacter baumannii from the respiratory tract with inhaled colistin methanesulfonate: a matched case-control study. Clin Microbiol Infect. 2012; 18(9):870-6.
21. Kofteridis DP, Alexopoulou C, Valachis A, Maraki S, Dimopoulou D, Georgopoulos D, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: A matched case-control study. Clin Infect Dis. 2010; 51(11):1238-44.
22. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1-138.