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NON-INFERIORITY OF NEBULIZED COLISTIN COMPARED WITH CONVENTIONAL SYSTEMIC ANTIBIOTICS FOR THE TREATMENT OF VENTILATOR-ASSOCIATED PNEUMONIA

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ABSTRACT: Background: In the present study, our objective was to determine whether nebulized colistin as an adjunctive therapy to conventional intravenous antibiotics of Ventilator-associated pneumonia (VAP) caused by multi-drug resistant (MDR) was safe and beneficial in critically ill patients. **Methods:** A prospective matched case-control study was performed at the ICUs of the University Hospital of Isfahan, Iran, from January to June 2017. Twenty patients with VAP due to MDR gram-negative bacilli received nebulized colistin and were matched on the basis of age and acute physiology and chronic health evaluation II (APACHE) score with 20 control patients who had received systemic antibiotic therapy according to their responsible physicians. **Results:** The baseline characteristics of the patients and conventional therapy of VAP in both groups were comparable. Most of the cases of VAP were caused by MDR *A. baumannii* (N=25, 75%) and *Klebsiella pneumonia* (N=10, 50%). No significant difference between the groups were observed regarding clinical cure (P: 0.6) and mortality (P: 0.25). The rate of pathogen eradication was significantly better in case patients (75% vs. 5%, P: 0.0001). Renal impairment was observed in 10% of cases and in 15% of control patients (P: 0.6). **Conclusion:** Our finding suggests that inhaled colistin monotherapy even without concurrent administration of intravenous colistin, seems to be an effective and safe treatment option for treatment of VAP due to MDR *A. baumannii*. This mode for colistin administration may deserve further consideration.

INTRODUCTION: Ventilator-associated pneumonia (VAP) is the most common healthcare-associated infection develops in approximately one-third of patients who are mechanically ventilated for more than 48 h [1, 2].

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Commonly gram-negative bacteria with potential multiple-drug resistance (MDR) gram- negative bacteria such as *Acinetobacter baumannii*, *P. aeruginosa* and *Klebsiella pneumoniae* are the predominant species in VAP and account for the highest attributable mortality [3, 4].

The prevalence of VAP in intensive care units intensive care units (ICUs) at Alzahra hospital in Isfahan, Iran is 18-30 episodes per 1000 ventilator days, with a mortality rate of up to 30% [5, 6]. More than 70% of cases of VAP in critically ill patients at Alzahra hospital are caused by the *Acinetobacter*

baumannii and *Klebsiella pneumoniae* [7]. Resistance to β-lactams, including carbapenems, amino-glycosides and flouroquinolones, was observed in 37% of *Acinetobacter baumannii* and 16% of *K. pneumoniae* isolated from patients with VAP at Alzahra hospital [8, 9]. MDR gram-negative pathogens are almost always susceptible to colistin, and parenteral colistin has been used for the therapy of VAP caused by MDR *A. baumannii* and *K. pneumonia* at our institution over the past few years, despite its known nephrotoxicity and neurotoxicity.

Several recent studies have found that a combination regimen using both intravenous (IV) and nebulized colistin provides good therapeutic responses and safety [10 - 18]. A recent meta-analysis by Valachis *et al*., [19] in 2015 included 16 studies on aerosolized colistin in the treatment of VAP. The analysis showed a significant improvement in clinical response (Odds Ratio (OR):1.5, 95% Confidence Interval (CI), 1.14 - 2.15; P: 0.006), microbiological eradication (OR: 1.61, 95% CI, 1.11-2.31; P: 0.01) and infection-related mortality (OR: 0.58, 95% CI, 0.34-0.96; P: 0.04) with the addition of inhaled colistin to IV treatment, whereas the addition of nebulized colistin did not affect overall mortality. This meta-analysis didn't include single-arm studies which in them inhaled colistin has been administered as monotherapy. In these studies, the clinical responses were 57-80 %, the infection-related mortality varied from 0-24% and the nephrotoxicity from 0-17 %.

The latest guideline of IDSA (Infectious Disease Society of America) on VAP, suggest use of both inhaled and systemic antibiotics, rather than systemic anti-biotics alone for treatment of VAP due to gram-negative bacilli. The guideline emphasizes that this is a weak recommendation with very-low quality evidence [20]. Therefore, a definite conclusion on the efficacy of nebulized colistin-especially as mono-therapy for therapy of VAP cannot be accurately established. The objective of this study was to determine whether nebulized colistin as an adjunctive therapy to conventional intravenous antibiotics of VAP was safe and beneficial in critically ill patients.

MATERIAL AND METHODS: This prospective case-control matching study (ratio, 1:1) was performed at the ICUs of Alzahra hospital (Isfahan, Iran) - an 60-bed medical-surgical units. The study was conducted from January to June 2017 and was approved by the ethic committee of Isfahan University of Medical Sciences (IUMS). Informed consent was obtained from all participating patients or their legal representatives. Eligible patients were hospitalized adults, aged ≥ 18 years, with a culture-documented mono or poly microbial VAP due to *Acinetobacter baumannii*, *P. aeruginosaor* and *Klebsiella pneumoniae* that was susceptible only to colistin.

Patient was considered to be ventilator-associated if the onset occurred after the pneumonia was intubated for ≥ 48 hours and the infection was judged not to have been incubating before the initiation of mechanical ventilation. Pneumonia was diagnosed on the basis of a radiographic finding of a new and progressive pulmonary infiltrate at least 2 of the following clinical criteria: body temperature ≥38 ^{o}C or <35.5^{o}C; leukocytosis (leukocyte count, >12000 cells/mm^3) or leukopenia (leukocyte count, <4000 cells/mm^3; and clinical evidence suggestive of pneumonia, such as purulent bacterial secretions and a decrease in oxygenation.

Eligible case patients had received systemic antibiotic (s) plus nebulized colistin. Every 12 hours, 5 ml of colistin equivalent to 80 mg (1000000 IU) of colistin-base reconstituted in 5 ml of normal saline was delivered immediately by means of Hamilton C2 ventilators (Hamilton Medical AG, Bonaduz, Switzerland). The regimen and duration of the systemic antibiotic (s) were chosen by the responsible physician. Nebulized colistin was given for 5 days and each patient was observed for clinical assessment during this period. Microbiological culture of a respiratory specimen aspirated from endotracheal tube was made on day 5 after the end of colistin nebulization. All causative microorganisms were identified using routine microbiological methods. The disk diffusion was used for antibiotic susceptibility testing.

A group of patients with VAP and MDR gram-negative pathogens who were treated with conventional intravenous antibiotic (s) served as controls. The patents demographic and clinical characteristics were evaluated daily for one week and included age, sex, blood urea nitrogen (BUN),

and creatinine level, the time of mechanical ventilation, tracheal intubation and tracheostomy tube, concurrently administered antibiotics, causes of ICU admission, duration of ICU stay and overall mortality. The clinical pulmonary infection score (CPIS) was also calculated for patients.

The primary endpoint of the study was the clinical outcome of VAP. As secondary outcome, we evaluated microbiological outcome, all-cause mortality and the occurrence of adverse events during colistin treatment. Clinical outcome was classified as clinical cure (*i.e*., resolution of presenting symptoms and signs of infection by the end of colistin treatment), clinical improvement (*i.e*., partial resolution of presenting symptoms and signs of infection) and clinical failure (*i.e*., persistence or worsening of symptoms and or signs of infection during colistin nebulization). Clinical success was defined as clinical cure or improvement.

Microbiological outcome was rated as eradication of the pathogen (*i.e*., no growth of the pathogen after the 5 days of colistin nebulization), persistence of the pathogen (*i.e*., persistent re-growth of the responsible pathogen regardless of the clinical outcome of the infection), recurrence (*i.e*., re-isolation of the same pathogen regardless of the clinical outcome of the infection), or colonization (*i.e*., persistence or re-growth of the pathogen without symptoms and signs of infection).

In patients with normal renal function, nephro-toxicity was defined as a serum creatinine value > 2 mg/dl; as a reduction in the calculated creatinine clearance of 50 %, compared with the value of the start of the treatment; or as a decline in renal function that prompted renal replacement therapy. In patients with persisting renal dysfunction, nephro-toxicity was defined as an increase of >50% of the baseline creatinine level or as a reduction in the calculated creatinine clearance of 50% relative to the value at therapy initiation. All adverse effects related to nebulized colistin use, such as broncho-spasm, cough, apnea, or chest tightness and arterial hypoxemia was recorded.

Statistical Analysis: Categorical variables were expressed as percentages and continuous variables as mean ± SD. The data were analyzed by descriptive statistics, unpaired Student t-test, chi-square test or fisher's exact test where appropriate. P-value are 2-tailed, and P values <0.05 was considered as statistically significant. Data were analyzed using SPSS software, version 20.0 (SPSS).

RESULTS: During the study period, 20 patients with MDR-gram negative VAP was assigned as case to receive nebulized colistin in association with systemic antibiotic therapy and 20 corresponding control subjects who received only systemic antibiotics matched for age and acute physiology and chronic health evaluation II (APACHE) score on the day of introduction of nebulized colistin for VAP. The demographics and clinical characteristics of the patients in both groups are summarized in **Table 1**.

The common causative bacteria were MDR *A. baumannii* and *K. pneumoniae* in both groups which was not different statistically. Carbapenems and fluoroquinolones were common antibiotics given to the patients as empirical therapy of VAP. More than 70 % of patients received antibiotic therapy as combination (P: 0.43). the median duration of hospitalization in the ICU was significantly longer in the control group: 59 days (range, 31-169 days) for the case patients and 80 days (range, 39-187 days) for the control group (P:0.03).

The APACHE II score and rate of tracheostomy didn't differ significantly between groups (P>0.05). The microbiological characteristics and systemic antibiotics of patients in both groups were not significantly different. The duration of systemic antibiotic therapy was significantly higher in the control group: 20 days (range, 6-31 days) for the nebulizer group and 30 days (range, 11-62 days) for the control group (P: 0.004).

The clinical and bacteriological outcomes for the both groups are summarized in **Table 2**. We found no statistically significant difference in terms of clinical success in both groups. Eradication of causative microorganism was achieved in 15 (75%) of case patients versus of 1 patient in the control group (P: 0.000). 50% of patients in the control group were colonized with the causative microorganism which was statistically significant (P: 0.000). overall, the mortality rate in the ICU was 45% in case patients and 30% in the control group (P: 0.25).

TABLE 1: DEMOGRAPHICS, CLINICAL, MICROBIOLOGICAL CHARACTERISTICS AND ANTIBIOTIC THERAPY OF THE STUDY PATIENTS

	Colistin group (N=20)	Control group (N=20)	P-value
Gender, male, (%)	6, 30	14, 70	0.03
Mean age ± SD	56.3 ± 22.1	48.9 ± 22.4	0.3
Mean APACHE II score ± SD	15.1 ± 6.2	14.6 ± 5.1	0.7
At diagnosis of VAP			
Admission diagnosis			
Brain hemorrhage	5 (25%)	4 (20%)	0.7
Dyspnea/hypoxia	2 (10%)	2 (10%)	1
CVA	1 (5%)	2 (10%)	0.55
Multiple trauma	1 (5%)	2 (10%)	0.55
LOC	4 (20%)	1 (5%)	0.15
Cancer	1 (5%)	2 (10%)	0.55
other	2 (10%)	4 (20%)	0.37
Type of gram negative bacteria from initial culture (CFU>10^5)			
Acinetobacterbaumannii	13 (65%)	12 (60%)	0.7
Klebsiella pneumonia	5 (25%)	5 (25%)	1
Pseudomonas aeruginosa	1 (5%)	2 (10%)	0.54
Proteus mirabilis	-	1 (5%)	0.3
Combination	15 (75%)	15 (75%)	1
Type of gram negative bacteria from initial culture (CFU<10^5)			
Klebsiella pneumonia	11 (55%)	9 (45%)	0.54
Acinetobacterbaumannii	4 (20%)	4 (20%)	1
Pseudomonas aeruginosa	2 (10%)	1 (5%)	0.54
E. coli	-	2 (10%)	0.3
Initial systemic antibiotic therapy of VAP			
Meropenem	11 (55%)	15 (75%)	0.2
Levofloxacin	6 (30%)	9 (45%)	0.33
Ciprofloxacin	4 (20%)	4 (20%)	1
Ceftazidim	4 (20%)	0	0.03
Ceftriaxone	2 (10%)	0	0.15
Colistin	7 (35%)	6 (30%)	0.7
Vancomycine	14 (70%)	4 (20%)	0.001
Other	5 (25%)	4 (20%)	0.43
Combination	17 (85%)	15 (75%)	0.15
Laboratory data (mean ± SD)			
Serum creatinine (day1)	1.2 ± 0.59	1.1 ± 0.59	0.6
Serum creatinine (day 5)	1.2 ± 0.6	1.1 ± 0.41	0.3
BUN (day1)	25.8 ± 13.3	29.9 ± 24	0.5
BUN (day 5)	25.9 ± 15.5	27.8 ± 16.4	0.7
WBC (day 1)	12740 ± 6409	10757 ± 6360	0.3
WBC (day 5)	11860 ± 3740	9673 ± 4318	0.09

APACHE: acute physiology and chronic health evaluation, BUN: blood urea nitrogen CFU: colony form unit, VAP: ventilator-associated pneumonia; CVA: cerebrovascular accident, LOC: loss of conscious, WBC: white blood cell

TABLE 2: CLINICAL AND MICROBIOLOGICAL OUTCOMES IN BOTH GROUPS

Outcome	Colistin group (N=20)	Control group (N=20)	P-value
Clinical outcome			
Clinical cure	4 (20%)	3 (15%)	0.6
Clinical improvement	9 (45%)	9 (45%)	1
Clinical failure	7 (35%)	9 (45%)	0.5
Bacteriological outcome			
Eradication	15 (75%)	1 (5%)	0.000
Persistent	5 (25%)	9 (45%)	0.2
Recurrence	0	0	1
Colonization	1 (5%)	10 (50%)	0.000
Mortality, all-cause	9 (45%)	6 (30%)	0.25
CPIS (day 1), (mean ± SD)	8.1 ± 0.93	7.4 ± 1.4	0.08
CPIS (day 5), (mean ± SD)	4.7 ± 1.8	5.1 ± 1.8	0.5
Duration of systemic antibiotic therapy	18.4 ± 6.2 (6-31 days)	30 ± 15.8 (11-62 days)	0.004
Length of ICU stay	64 ± 33.4 (31-169 days)	90.3 ± 40 (39-187 days)	0.015
Tracheostomy rate	17 (85%)	14 (20%)	0.26

CPIS: Clinical Pulmonary Infection Score, ICU: Intensive Care Unit

CPIS decreased significantly in both groups (**Table 2**). But the difference on day 0 and 5 was not statistically significant between groups. Serum creatinine remained stable within the treatment period in both groups of patients (**Table 1**). Renal impairment was observed in 10% of case patients and in 15% of control patients (P: 0.6). No adverse events, such as bronchospasm, apnea or chest tightness, were associated with nebulized colistin therapy. In addition, neurotoxic adverse effects were not observed in any patient.

DISCUSSION: The main finding of this prospective case-control study was that the inhaled colistin as adjunctive to conventional systemic antibiotics provided the same therapeutic benefit compared to systemic antibiotic (s) therapy in patients with MDR VAP due to gram-negative bacteria. Eradication of gram-negative bacteria with inhaled colistin was achieved in 75% of patients. All of the patients in our study tolerated inhaled colistin well. Nephrotoxicity or direct toxicity on the airways, was not observed.

As we mentioned before, the prevalence of MDR gram-negative bacteria is high in our center. Most of the organisms are only susceptible to colistin. Despite a very-low quality evidence, the 2016 IDSA guideline considers inhaled colistin as an adjutant to systemic antibiotics for treatment of MDR nosocomial pneumonia and VAP in adults [20]. Recent meta-analyses also showed that the role of nebulized colistin might be adjunctive to IV colistin. Vardakas *et al*., [21] meta- analyzed studies that evaluated inhaled colistin as monotherapy in the treatment of respiratory tract infections caused by MDR (or colistin-only susceptible gram-negative bacteria). Twelve studies (373 patients) were included. Eight of them were single-arm studies (prospective and retrospective cohorts) and the remaining two arm studies. The pooled all-cause mortality was 33.8% (95% CI, 24.6%-34.6%), clinical success was 70.4% (95% CI, 58.5%-81.1%) and the eradication of gram-negative bacteria was shown in 71.3% of cases (95% CI, 57.6%-83.2%).

The main drawbacks of these studies were retrospective design of most studies and the lack of control groups and adjustment for potential confounding factors. Despite the limitations of our study, such as small number of patients and no randomization; it should be noted that eradication of MDR gram-negative microorganisms was significantly higher in the patients who received nebulized colistin. Moreover, it was observed that nebulized colistin decreased the duration of systemic antibiotic therapy significantly (at least 15 days). For the resource-limited setting (such as our hospital), this finding is considerable; as systemic antibiotic therapy are a common mode of treatment and a significant proportion of critically ill patients received systemic antibiotics as long as their hospitalization. Inhaled colistin (as monotherapy) may deserve further consideration as a mode for colistin administration for the treatment of VAP due to MDR gram-negative bacteria (especially *A. baumannii* and *K. pneumoniae*).

A sample size of 20 patients might be too small to derive a conclusion about the therapeutic benefit of inhaled colistin. Based on our results, there was no significant difference regarding the clinical success between both groups. A recent retrospective matched cohort study of therapy of patients with VAP caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB) revealed that inhaled colistin as monotherapy (without concurrent administration of IV colistin) has significantly lower the rate of clinical failure and ICU mortality (P: 0.008 and P: 0.006, respectively).

This study suggested that monotherapy with inhaled colistin might be an effective and safe treatment option for VAP caused by CRAB [13]. Although the duration of nebulized colistin was short in our study (only 5 days) but the rate of clinical failure was even lower in case patients (7/20 vs. 9/20, P: 0.5). Therefore, it might be possible that by extending the duration of treatment, the rate of clinical cure increase in the patients.

Jang *et al*., [22] retrospectively compared 95 critically ill surgical patients who were diagnosed with VAP (due to *A. baumannii*) and received high dose nebulized or IV colistin (4.5 million Iu every 8 hours). This study showed that frequent use of nebulized colistin was effective for preventing nephro-toxicity and also had non-inferior clinical and microbiological outcomes compared to IV group.

Inhaled colistin dosing scheme (daily dose, dose interval and treatment duration) was different between studies. But regarding the adverse effects of colistin, it seems that nebulized colistin (even with high dosage) could be a reasonable choice for therapy, to minimize systemic exposure and to optimize the benefit risk-ratio of colistin therapy.

Another finding of our study is that patients who received systemic antibiotic therapy were colonized with MDR gram-negative bacilli. This condition would affect physician decision regarding continuation of systemic antibiotic therapy. The longer duration of systemic antibiotics in our control group, confirms this. Extensive use of antibiotics increase emergence of resistant bacteria, health-associated costs, and length of hospital stay. Therefore, regarding the efficacy and safety of nebulized colistin, it seems reasonable to encourage our physicians to use this mode of treatment instead of traditional one. Small sample size, no randomization, running of study in a single center are some our study limitations which are associated with well-known risks of bias. Despite these limitations, this study is meaningful because it provides preliminary data regarding the safety and efficacy of nebulized colistin as monotherapy in patients with MDR gram-negative VAP.

However, we should consider the risk of super infection with inherently colistin-resistant pathogens and the development of colistin resistant pathogens in the use of inhaled colistin monotherapy in pneumonia. The appropriate dose of inhaled colistin, effective combination with other antimicrobial agents and adequate indications should be evaluated in larger prospective and controlled studies.

CONCLUSION: All in all, our experience corroborates previous studies and reports that nebulized colistin as monotherapy might be a viable therapeutic option for pneumonia caused by MDR gram-negative bacteria. It also provides support for the recommendations in the guideline on the management of VAP. Well-designed prospective and if possible randomized studies are required to further evaluate the effectiveness and safety of inhaled colistin monotherapy for the management of VAP.

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REFERENCES:

1. Mietto C, Pinciroli R, Patel N and Berra L: Ventilator associated pneumonia: Evolving definitions and preventive strategies. Respir Care 2013; 58(6): 990-1007.
2. Kalanuria AA, Zai W and Mirski M: Ventilator-associated pneumonia in the ICU. Crit Care 2014; 18(2): 208.
3. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C and Bauer TT: Attributable mortality of ventilator-associated pneumonia: A meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis 2013; 13(8): 665-71.
4. Royer S, Faria ALS, Seki LM, Chagas TPG, de Campos PA, da Fonseca Batistão DW, *et al*., Spread of multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* clones in patients with ventilator-associated pneumonia in an adult intensive care unit at a university hospital. Braz J Infect Dis 2015; 19(4): 350-7.
5. Khalifehzadeh A, Parizade A, Hosseini A and Yousefi H: The effects of an oral care practice on incidence of pneumonia among ventilator patients in ICUs of selected hospitals in Isfahan, 2010. Iran J Nurs Midwifery Res. 2012; 17(3): 216-9.
6. Kiabi FH, Alipour A, Darvishi-Khezri H, Aliasgharian A and Zeydi AE: Zinc supplementation in adult mechanically ventilated trauma patients is associated with decreased occurrence of ventilator-associated pneumonia: A secondary analysis of a prospective, observational study. Indian J Crit Care Med2017; 21(1): 34-39.
7. Salehi H: The most common bacterial agents and their antibiotic sensitivity in ICU patients of AL-Zahra Hospital in Isfahan. Journal of Research in Medical Sciences2004; 9(4): 178-81.
8. Khorvash F, Abbasi S, Meidani M, Shakeri M. Prevalence and antimicrobial susceptibility pattern of isolated microorganisms from central venous catheters in ICU patients. Adv Biomed Res 2014; 3: 102.
9. Tahanasab Z, Mobasherizadeh S, Moghadampour M, Rezaei A, Maleki N and Faghri J: High prevalence of Multiple Drug Resistance among ESBLs-Producing Klebsiella pneumoniae isolated from hospitalized patients in Isfahan, Iran. Journal of Medical Bacteriology 2017; 5(5-6): 29-38.
10. Tulli G, Messori A, Trippoli S and Marinai C. Non-inferiority of colistin compared with standard care for the treatment of ventilator-associated pneumonia. Int J Antimicrob Agents 2017; 49(5): 638-41.
11. Kim YK, Lee JH, Lee HK, Chung BC, Yu SJ, Lee HY, *et al*., Efficacy of nebulized colistin-based therapy without concurrent intravenous colistin for ventilator-associated pneumonia caused by carbapenem-resistant Acinetobacter baumannii. J Thorac Dis 2017; 9(3): 555-67.
12. Gutiérrez-Pizarraya A, Amaya-Villar R and Garnacho-Montero J: Nebulized colistin in ventilator-associated

pneumonia: Should we trust it? J Crit Care 2017; 41: 328-329.
13. Zalts R, Neuberger A, Hussein K, Raz-Pasteur A, Geffen Y, Mashiach T, *et al*., Treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia: retrospective comparison between intravenous colistin and intravenous ampicillin-sulbactam. Am J Ther 2016; 23(1): e78-e85.
14. Peng YT and Chuang YT: Comparison of the effectiveness and safety of inhaled colistin to intravenous colistin in eradication of respiratory carbapenem-resistant Acinetobacter baumannii-a tertiary medical center experience in Taiwan. Pharmacotherapy 2016; 36(12): e244-e5.
15. Park SY, Park MS, Chung CR, Kim JS, Park SJ and Lee HB: Clinical effectiveness and nephrotoxicity of aerosolized colistin treatment in multidrug-resistant gram-negative pneumonia. The Korean Journal of Critical Care Medicine 2016; 31(3): 208-20.
16. Parchem N, Bauer K, Cook C, Mangino J, Jones C, Porter K: Colistin combination therapy improves microbiologic cure in critically ill patients with multi-drug resistant gram-negative pneumonia. Eur J Clin Microbiol Infect Dis 2016; 35(9): 1433-9.
17. Rello J, Solé-Lleonart C, Rouby JJ, Chastre J, Blot S, Poulakou G, *et al*., Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. Clin Microbiol Infect 2017; 23(9): 629-639.
18. Hsieh TC, Chen FL, Ou TY, Jean SS and Lee WS: Role of aerosolized colistin methane sulfonate therapy for extensively-drug-resistant Acinetobacter baumannii complex pneumonia and airway colonization. J Microbiol Immunol Infect 2016; 49(4): 523-30.
19. Valachis A, Samonis G and Kofteridis DP: The role of aerosolized colistin in the treatment of ventilator-associated pneumonia: a systematic review and metaanalysis. Crit Care Med 2015; 43(3): 527-33.
20. 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.
21. Vardakas KZ, Voulgaris GL, Samonis G and Falagas ME: Inhaled colistin monotherapy for respiratory tract infections in adults without cystic fibrosis: a systematic review and meta-analysis. Int J Antimicrob Agents 2017. pii: S0924-8579(17)30232-7.
22. Jang JY, Kwon HY, Choi EH, Lee W-Y, Shim H and Bae KS: Efficacy and toxicity of high-dose nebulized colistin for critically ill surgical patients with ventilator-associated pneumonia caused by multidrug-resistant Acinetobacter baumannii. J Crit Care 2017; 40: 251-6.

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