

Inhaled colistin for treatment of pneumonia due to multidrug-resistant gram-negative bacteria at a tertiary hospital, in Vietnam

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ABSTRACT

Background: There is a return of colistin as the treatment of last resort for multi-resistant bacteria. However, due to the limited penetration in the lung parenchyma and the renal side effects, the effectiveness of intravenous (IV) colistin therapy has been questioned. Colistin inhalation therapy is deemed tolerable, safe, and could be a beneficial therapy. However, the efficacy and safety of colistin monotherapy is still unclear. Therefore, this study aimed to describe the use of inhaled colistin in patients with drug-resistant bacterial pneumonia at a tertiary hospital in Vietnam from July 2021 to September 2022. **Methods:** A descriptive retrospective study was conducted using medical records of all inpatients who were treated with inhaled colistin at a tertiary hospital in Vietnam, from July 2021 to September 2022. **Results:** This study included 12 hospital pneumonia patients, aged 81.5±13.5, equivalent to 21 inhaled colistin treatment courses. The disease mainly causes *Acinetobacter baumannii* (100%), *Klebsiella pneumoniae* (47.62%), and *Pseudomonas aeruginosa* (38.09%). 100% of patients were taken an aerosol colistin dose of 4 million IU every 8h of aerosol for 30 minutes from 7 to 14 days. The success of clinical efficacy was 95.23% while the success of microbiological efficacy was just 42.86%. 5/12 patients have recurrent infection, and 1 patient used 6 courses of aerosol colistin treatment in 1 hospitalization. Changes in kidney function before and after the use of colistin aerosol are negligible. **Conclusion:** Colistin inhalation therapy has been shown effective in treating multidrug-resistant pneumonia without causing kidney toxicity. However, the rate of recurrent infection in the study was quite high, so a prospective study with a larger sample size should be conducted to further evaluate the efficacy and toxicity of inhaled colistin therapy.

Keywords: colistin inhalation, multidrug-resistant pneumonia (MDR).

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INTRODUCTION

Recently, increasing antibiotic resistance in multidrug-resistant (MDR) Gram-

negative bacteria (MDR-GNB) presents significant health problems worldwide. The vital available and effective antibiotics, including broad-spectrum penicillines,

fluoroquinolones, aminoglycosides, and β -lactams often fail to fight MDR Gram-negative pathogens, and the absence of new antibiotics that can defeat these “superbugs”. All of these have prompted the re-emerged of Colistin as a last-hope treatment in the mid-1990s against MDR Gram-negative pathogens [1]. In addition, due to inadequate penetration in the lung parenchyma and the renal side effect, the effectiveness of intravenous (IV) colistin therapy for pneumonia has been questioned [2]. Meanwhile, Colistin inhalation therapy is deemed tolerable and safe and could be beneficial as an adjective therapy for the management of pneumonia due to *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [3]. In the tertiary hospital, inhaled colistin has been administrated for critically ill patients in intensive care units (ICU) instead of IV colistin since July 2021. However, up to now, there have not been any specific reports related to the therapeutic effects and side effects of inhaled colistin in patients to support doctors consider prescribing inhaled colistin instead of IV colistin for the treatment of respiratory tract infections caused by MDR or colistin-only susceptible Gram-negative bacteria at this

hospital. Therefore, the aim of this study is to describe the use of inhaled colistin in patients with drug-resistant bacterial pneumonia in A tertiary hospital from July 2021 to September 2022.

OBJECTS AND METHODS

Research subject

Inclusion criteria

Medical records of inpatients treated with inhaled colistin at a tertiary hospital in Vietnam from July 2021 to September 2022.

Exclusion criteria

Medical records of patients taking inhaled colistin for less than 48 hours.

Research Methodology

Research design: A descriptive retrospective study

Method of data collection: From the hospital's electronic medical record software (E-Hospital), a list of inpatients who were prescribed inhaled colistin drugs during the study period was extracted. From there, filter out the list of electronic medical records that satisfy the selection requirements.

RESULTS

Demographic and clinical characteristics of patients

Table 1: Baseline features of patients

Patient characteristics	Number (%) or median (range)
Patients	12
Treatments	21
Sex	
Male	9 (75%)

Female	3 (25%)
Age (min; max)	81.6±6.8
Body mass index (kg/m²)	
Median	21.86
Underweight	4 (33,33%)
Normal	5 (41,67%)
Overweight	0
Obese	3 (25%)
Intensive Care Unit (ICU)	12 (100%)
Hospitalization (days) (min; max)	87.8±101.6
Courses of inhaled colistin treatment (days) (Min; max)	11.7±2.3

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The research included 12 patients who were treated by inhaled colistin therapy in A tertiary hospital, which is equivalent to 21 cases reported. Regarding hospitalization, it appears that all medical records in the study sample belong to patients who were hospitalized for a long period of treatment in the ICU and were charged after more than 12 weeks (87 days). The longest hospitalization lasted 389 days, which was about 19 times longer than the shortest.

Table 2: The features of background diseases (n=12)

Characteristics	Number
	n (%)
Number of background diseases	
≥ 2	12 (100%)
Background diseases	
Cardiovascular pathology ¹	9 (75%)
Hyperglycemia	4 (33.33%)
Respiratory disease ²	2 (16.67%)
Musculoskeletal disease ³	4 (33.33%)
Digestive disease ⁴	1 (8.33%)
Urinary disease ⁵	1 (8.33%)
Neuropathy ⁶	2 (16.67%)

Note: ¹Hypertension, Congestive heart failure, ²Asthma, Bronchospasm, Chronic obstructive pulmonary disease (COPD), ³Gout, Hip arthroplasty, Osteoarthritis, ⁴Increased liver enzymes, ⁵Renal failures, ⁶Alzheimer's disease, Parkinson's disease, Cerebrovascular accident

Table 2 illustrates that all patients in the study sample had more than two other diseases besides the main infectious disease, and Cardiovascular pathology accounted for the largest number of 9 patients (75%).

The diagnosis of infection is recorded in the consultation report just before the medication is administered. The characteristics of the patient's infection are studied in the article, including the proportion of isolated/combined infections and the proportion of each type of infection. In the study, 90% of patients prescribed inhaled colistin were currently in a state of combined infection.

Table 3: The rates of infections at the time of inhaled colistin prescription (n=21)

Classification of infections	Number (n = 21, %)
Hospital-acquired pneumonia	21 (100%)
Skin and soft tissue infection	3 (14.28%)
Bacteremia	6 (28.57%)
Urinary infections	5 (23.81%)

All 21 patients receiving inhaled colistin therapy had hospital-acquired infections, specifically hospital-acquired pneumonia.

Table 4: Characteristics of interventional procedures on patients (n=12)

Characteristics	Number n (%)
Number of interventional procedures	
Median (min; max)	3,42 (0; 5)
Types of interventional procedures	
Ventilator	9 (75%)
Endotracheal intubation	3 (25%)
Tracheostomy	4 (33.33%)
Implant a central venous catheter	3 (25%)
Nasogastric intubation	5 (41.67%)
Urinary catheterization	2 (16.67%)

According to data from the above table, an average of a patient in the study had undergone more than 3 interventional procedures. 75% of patients were involved in mechanical ventilation, while intubation and tracheostomy accounted for 25% and 33.33%, respectively.

The study conducted a survey on the renal function characteristics of patients based on their GFR characteristics immediately prior to the administration of colistin inhalation as

recommended by KDIGO. All 21 studied cases were instructed to undergo serum creatinine quantification testing before using colistin inhalation.

Table 5: Renal functional characteristics (n=21)

Category	GFR (ml/min/1.73 m ²)	Terms	Number n (%)
G1	≥ 90	Normal or high	8 (38.09%)
G2	60 – 89	Mildly decreased	5 (23.81%)
G3a	45 – 59	Mildly to moderately decreased	1 (4.76%)
G3b	30 – 44	Moderately to severely decreased	4 (19.05%)
G4	15 – 29	Severely decreased	3 (14.29%)
G5	< 15	Kidney failure	0

Microbiological characteristics

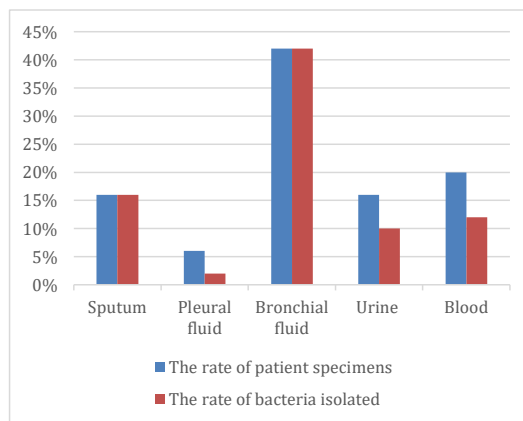


Figure 1: The positive rate of each type of specimen (n=21)

All patients in the research undergo microbiological testing immediately before using inhaled colistin. The positive rate of sputum and bronchial fluid was 100% while the remaining groups of specimens had a low positive culture rate, approximately 40% to 50%.

Table 6: The percentage of bacteria isolated in patients indicated inhaled colistin (n=21)

Bacterial strains isolated	Number n (%)
<i>Acinetobacter baumannii</i>	21 (100%)
<i>Pseudomonas aeruginosa</i>	8 (38.09%)
<i>Klebsiella pneumoniae</i>	10 (47.62%)
<i>Elizabethkingia meningosepticum</i>	3 (14.29%)
<i>Chryseobacterium indologenes</i>	2 (9.52%)

100% of patients in the study were administered colistin inhalation therapy when infected with *Acinetobacter baumannii*, followed by *Klebsiella pneumoniae* (47.62%) and *Pseudomonas aeruginosa* (38.09%).

Features of using inhaled colistin

Table 7: Characteristics of inhaled colistin indications (n=21)

Characteristics	Number n (%)
Indicated type	
Empiric treatment	0 (0%)
Targeted treatment	21 (100%)
Regiment type	
Single treatment regimen	0 (0%)
Combination therapy regimen	21 (100%)
Number of antibiotics used in combination with inhaled colistin	
1	12 (57.14%)
2	8 (38.1%)
3	1 (4.76%)
IV antibiotics combined with inhaled colistin	
Carbapenem ¹	11 (52.38%)
Levofloxacin ²	1 (4.76%)
Levofloxacin ² + Piperacillin/Tazobactam	2 (9.52%)
Piperacillin/Tazobactam	1 (4.76%)
Carbapenem ³ + Fosfomycin	1 (4.76%)
Carbapenem ⁴ + Clindamycin	1 (4.76%)
Carbapenem ⁴ + Piperacillin/Tazobactam	1 (4.76%)
Carbapenem ⁴ + Piperacillin/Tazobactam + Linezolid	1 (4.76%)
Ciprofloxacin + Ceftazidim	1 (4.76%)
Cefepim	1 (4.76%)
Other medications used before inhaled colistin	
Ipratropium + Salbutamol	21 (100%)
Bambuterol	3 (14.29%)
Dosage	
4 million IU every 8 hours	21 (100%)

Note: ¹Meropenem and Imipenem+cilastatin, ²Dropping into the trachea after suctioning phlegm, ³Imipenem+cilastatin, ⁴Meropenem

Most antibiotics used in combination with nebulized colistin are injectable antibiotics, except for Levofloxacin which was used as a drip in the endotracheal tube. Carbapenem was the most popular combined antibiotic group. During colistin inhalation therapy, all patients were given bronchodilators (Ipratropium + Salbutamol or/and Bambuterol) 30 minutes before inhalation. Afterward, patients proceeded with inhalation therapy with colistin at a dose of 4 million IU every 8 hours.

Description of treatment results

In 21 cases, 3 cases did not have microbiological results after treatment, therefore the

study evaluated the microbiological results of 19 cases.

Table 8: Treatment outcomes of inhaled colistin therapy

Microbiological outcomes (n=19)	Number (%)	Time for negative results after taking inhaled colistin (days) (median (range))	Length of inhaled colistin treatment (days) (median (range))	Length of hospital stay (days) (Median (range))
Eradication	9 (47.37)	6.89 (5 – 14)	10.67 (8 – 14)	63.33 (21 – 123)
Colonization	1 (5.26)		10	389
Recurrence	9 (47.37)	9.22 (5 – 14)	12.11 (10 – 15)	278.63 (73 – 389)

Regarding microbiologic outcomes in Table 9, there were 9 cases in which patients used colistin inhalation to eradicate the pathogen (47,37%), followed by 9 cases of recurrence (47,37%), and 1 case of colonization. To compare with eradication, the cases of recurrent infection or colonization had a longer time to achieve negative microbiological results, patients tended to use medication for a longer period, and had a significantly longer hospital stay.

Table 9: Changes in laboratory test values of a patient's characteristics

Characteristics	Median (min-max)		p-value
	Before	After	
Temperature (n=7)	37.67 (36,5 – 38,6)	37 (36 – 37,5)	0.061
WBC (n=21)	16.02 (4.0 – 24.6)	13.86 (5.8 – 24.1)	0.903
CRP (n=12)	101.22 (11.3 – 389.9)	93.87 (32.8 – 192.8)	0.136
Procalcitonin (n=11)	12.11 (0.045 – 100)	0.43 (0.064 – 0.928)	0.01

The evaluated indicators include Temperature, WBC, CRP, and Procalcitonin. The observed results showed a difference in the value of Procalcitonin before and after the patient completed the treatment with colistin inhalation (p=0.01), while the changes in the other infection indicators were not significant.

Features of recurrent infection

The cases referred to as **recurrent infection** in the study are a group of patients who were prescribed aerosolized colistin for two or more rounds during the same hospitalization period.

Table 10: Features of recurrent infection

Characteristics	Number n(%)
Number of patients experiencing recurrent infection (n = 12)	5 (41.67%)
The total number of recurrent infection (n = 21)	9 (42.85%)
recurrent infection rate/patient (min; max)	2.8 (1; 5)
Time to recurrent infection (days) (min; max) ¹	31.78 (8; 52)

Note: ¹ The period of time from the last date of using colistin inhalation from the previous treatment cycle to the start date of colistin inhalation for the next treatment cycle.

The survey found that over 40% of patients reused colistin inhalation. Specifically, 1 patient received six courses of colistin treatment during the same ICU stay, while the remaining four patients had two courses of colistin inhalation during their hospitalization. On average, these patients were reinfected after 31 days and as early as 8 days after using colistin again.

The current situation of toxicity to the kidneys in patients treated with inhaled colistin

The study compared the change in kidney function of patients by comparing the changes in blood creatinine levels before and after colistin inhalation therapy using a Wilcoxon matched pairs test – the non-parametric alternative to the paired t-test (Null hypothesis: no difference in median). The result obtained $p=0.091$, indicating that the change in creatinine level before and after medication use was not significant.

Table 11: The incidence of renal toxicity based on RIFLE criteria

Class	GFR	Number (n = 21, %)
Normal		17 (80.95%)
R – Risk	Increase SCr 1.5 times or decrease GFR >25%	3 (14.29%)
I – Injury	Increase SCr 2 times or decrease GFR >50%	1 (4.76%)
F – Failure	Increase SCr 3 times or decrease GFR >75% or if baseline SCr $\geq 353.6 \mu\text{mol/L}$ ($\geq 4 \text{ mg/dL}$) increase SCr $>44.2 \mu\text{mol/L}$ ($>0.5 \text{ mg/dL}$)	0

In most cases of treatment with colistin inhalation therapy, patients did not experience acute kidney toxicity (80,95%). However, there were 3 cases where kidney toxicity was observed at the R level (risk), 1 case at the I level (Injury), and no cases of higher severity were reported. Acute renal toxicity began on the 7th day of treatment. 4 out of 4 patients recovered renal function after stopping medication for 5-8 days.

DISCUSSIONS

The sample size of the study is much smaller than previous studies. However, this is the total number of patients designated for monotherapy with colistin inhalation in the treatment of gram-negative bacterial pneumonia in Hai Phong during the study period. Therefore, in terms of significance, the data collected in this study still holds valuable meaning, representing the population using colistin inhalation therapy in Hai Phong. This sample size is also equivalent to a study conducted at a university hospital in Wonju, South Korea

(2014) [3]. At the time of colistin inhalation prescription the patients in the study were severely ill and had multiple diseases, so patients had to take more medication, which led to the risk of drug interactions, increased toxicity to the kidneys, and/or reduced treatment efficacy. Therefore, monitoring the patient's condition, and balancing benefits - risks to have an appropriate medication regimen and treatment is necessary.

The most common bacterial pathogen in the study is consistent with the first global survey using colistin conducted by Heiman Wertheim [4] and the study on the prevalence

of three common pathogens isolated from 15 ICUs in Vietnam [5]. Specialized studies on colistin inhalation have also indicated that multidrug-resistant gram-negative bacteria are the main reasons for colistin inhalation indication [3,6-8].

One of the limitations of this research is that there is not enough data on patients as well as the relatively small population to fully assess the effectiveness of drugs on patients. According to the collected data, patients will stop taking the medication and evaluate the end of treatment as "successful" when the patient has a negative microbiological result with previously pathogenic bacteria instead of relying on clinical signs. When assessing the effectiveness of microbiology throughout the entire hospitalization of patients, in 19 out of 21 cases, the percentage of elimination of microorganisms was 47,37%, which is lower compared to the studies by A.S. Michalopoulos [9] and H.K. Choi [3] with elimination rates of 83.3% and 50%, respectively. This difference may be due to differences in patient characteristics, infection management, and epidemiology in each region. In addition, the fact that patients only used inhaled colistin alone and not combined with intravenous colistin like previous treatment methods in studies may also be a cause of incomplete elimination of bacteria.

A notable point of this study compared to existing ones is that in addition to evaluating treatment effectiveness through clinical response and microbiological efficacy, the study also conducted a survey of the number of colistin treatment courses that patients received during hospitalization. The recurrent infection rate of patients treated with colistin in the study is dramatically high (41.67%). Patients with re-infection all had a very long ICU stay (ranging from 68 to 389

days), underwent many procedures, used multiple antibiotic groups, and experienced severe multiple infections. This can be considered a major cause of treatment failure and the reason why patients suffer from recurrent infections many times.

The aerosol therapy was well tolerated. Changes in kidney function of the study participants were not significant. There were 4 cases (19.05%) of acute kidney toxicity, but all occurred in patients with pre-existing conditions such as hypertension, diabetes, or renal insufficiency, who were also using other nephrotoxic medications such as carbapenem antibiotics, penicillin/β-lactam, furosemide, or muscle relaxants. This result is much lower compared to the use of intravenous colistin [10].

CONCLUSIONS AND RECOMMENDATION

Colistin inhalation therapy has been shown to be effective in treating multidrug-resistant pneumonia without causing kidney toxicity. However, the rate of re-infection in the study was quite high, so a prospective study with a larger sample size should be conducted to further evaluate the efficacy and toxicity of inhaled colistin therapy.

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