Original Article

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Investigation on colistin use at the University Medical Center Hochiminh City

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ABSTRACT

The upsurge of multi-resistant gram-negative pathogen highlights the role of colistin as the last-line antimicrobial agent in the treatment of severe infections all over the world. Recently, the increase of colistin use at University Medical Center Hochiminh City (UMC) has raised the concern about the potential resistance of microbes against this antibiotic. The aim of this study is to evaluate rational colistin indication and to identify factors which may be attributed to nephrotoxicity. One hundred and two in-patients indicated with colistin for 72 hours or more from January to December 2016 were enrolled in a descriptive cross-sectional study at University Medical Center HCMC. Medical records of patients were reviewed for data analysis. Risk, Injury, Failure, Loss of kidney function, and End-stage kidney diseases (RIFLE) criteria was used to evaluate nephrotoxicity during treatment. The median age of the study population was 77.5, 64.7% were male and 63 patients (61.8%) were treated in the ICU. The most common comorbidities were cardiovascular diseases (70.6%). *Acinetobacter baumannii* accounted for 35.76% of 4 common pathogens but no resistance to colistin was found during the study period. The average daily colistin dose per kilogram was 97.26 ± 35.21 IU and the average duration of intravenous colistin was 13.05 ± 6.67 days. Rational use of colistin was observed in only 32.8% of the study population. Twelve patients (11.76%) experienced nephrotoxicity after the course of treatment using RIFLE criteria. Logistic regression analysis showed that age (OR = 1.059; 95% CI 1.020-1.087, p = 0.004), respiratory diseases (OR = 0.139; 95% CI 0.024-0.804, p = 0.028), concomitant use with furosemide (OR = 6,215; 95% CI 1.002-38.565, p = 0.049) or amphotericin B (OR = 29.995; 95% CI 2.638-341.007, p = 0.006) were significantly associated with nephrotoxicity.

1. INTRODUCTION

Antibiotic resistance has turned into a global crisis, with pathogens being less susceptible or even resistant to last-resort antibiotics. In 2010, Lim LM estimated that no new antibiotics with activity against multidrug-resistant (MDR) gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumanii* and *Klebsiella pneumoniae* are expected to be released within the next five years[1]. This high lights the role of colistin, an old-class antibiotic that still remains the last-line therapy in clinical settings.

The spread of colistin use has recently raised concerns about resistance to this antibiotic.

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In May 2016, the first case of colistin-resistant *Escherichia coli* (mcr-1) infection was found in the USA, revealing the possibility of the emergence of truly-pan drug resistance[2]. Furthermore, the overuse of colistin in animal led to the release of a recommendation from European Medicines Ageney to set a goal of 65% reduction in colistin use in agriculture[3]. In the University Medical Center HCMC, the total colistin consumption in 2016 increased dramatically compared to the year 2015. This study was thus conducted to investigate colistin use, to evaluate rational colistin indication and to identify potential risk factors for colistin-induced nephrotoxicity.

2. MATERIAL AND METHODS

2.1 Study population

Data was obtained from all in-patients who were indicated colistin for 72 hours or more from January 1st 2016 to December 31st 2016. If a patient received more than one course of colistin therapy, data was only collected from the first course. One hundred and two medical profiles met the criteria were enrolled in this study. The study protocol was scrutinized and approved by ethical committee of UMC prior to data collection.

2.2 Methods

A descriptive cross-sectional study was conducted to provide information on demographics, causative organisms, antimicrobial treatment, outcome and nephrotoxicity. Colistin use is determined as "rational" when all these criteria are met:

- Gram-negative bacteria from collected sample were isolated before colistin indication[4*].
- The organisms was susceptible only to colistin*.
- If intravenous colistin was indicated, another antibiotic or inhaled colistin should be concurrently indicated[5,6].
- Inhaled colistin monotherapy was determined as irrational use. Inhaled colistin should be combined with intravenous colistin[4,6].
- Rational dosing using FDA recommendation[7,8].

* University Medical Center HCMC regulation

Nephrotoxicity was determined as kidney injury according to RIFLE criteria[9] during course of treatment with colistin. Multivariable logistic regression was used to identify factors statistically associated with colistin rational use and nephrotoxicity. Logistic regression was used to analyzed: (1) Association between rational colistin indication and factors including age, gender, clinical department, infectious disease diagnosed, type of comorbidity, number of comorbidities and length of stay; (2) Association between nephrotoxicity and factors including age, gender, body weight, type of comorbidity, number of comorbidities, site of infection, daily dose per kilogram, duration of colistin treatment and concomitant nephrotoxic agents. A *p*-value of less than 0.05 was considered as statistically significant difference. All data analysis was performed using SPSS 20.0 software package and Microsoft Excel 2013.

3. RESULTS

3.1 Characteristics of the study population

The median age of the study population was 77.5. Patients aged above 75 constituted more than half (53.9%) and 64.7% of the population was male. The mean body weight of the study population was 48.2 ± 19.5 kg, ranging from 3.5 to 85 kg. The ICU (61.8%), respiratory department (14.8%) and cardiac surgery department (12.7%) accounted for the most cases of colistin use. Cardiovascular diseases (70.6%) were the most common comorbid disease and 90.2% of patients experienced at least one comorbid disease. Endotracheal intubation (72.5%) was the most popular invasive procedure performed prior to colistin indication. The average length of hospital stay observed was 45.1 ± 31.3 days, ranging from 9 to 213. Pneumonia (77.5%) was the most common cause of colistin indication. The characteristics of the study population were presented in Table 1.

3.2 Microbiologic characteristics

3.2.1 Bacterial pathogens

Of 102 medical records collected, microbial testing was performed in 98 cases

(96.1%). Of 164 specimens analyzed, 151 specimens (89.9%) were found with positive test results, including sputum (66.9%), blood (11.9%), urine (8.6%) and others (12.6%).

Acinetobacter baumanii was the most frequently isolated bacteria (35.8%), followed by *Klebsiella pneumoniae* (20.5%), *Pseudomonas* spp. (16.6%) and *Escherichia coli* (9.9%). Distribution of bacterial pathogens isolated by specimens was presented in figure 1.

Table 1. Baseline characteristics of the study population (N = 102)

Age (year) (median)	77.5
< 18 (%)	9.8
18 – 59 (%)	15.7
60 – 75 (%)	20.6
> 75 (%)	53.9
Male (%)	64.7
Body weight (kg) (mean)	48.2 ± 18.5
ICU admission (%)	61.8
Comorbidities	
Hypertension (%)	44.1
Diabetes (%)	25.5
Respiratory diseases (%)	21.6
Chronic kidney disease (%)	10.8
Invasive procedures	
Endotracheal intubation (%)	72.5
Mechanical ventilation (%)	34.3
Catheterization (%)	52.0
Invasive blood pressure (%)	29.4
Length of stay (days) (mean)	45.1 ± 34.3

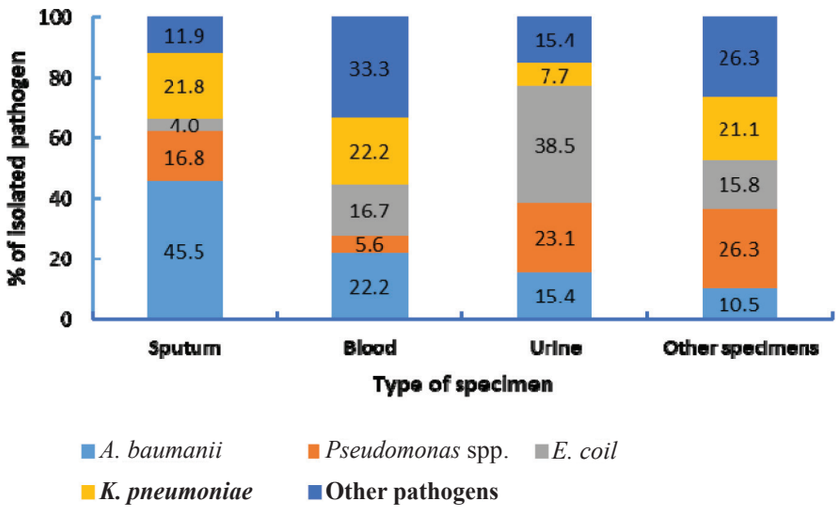
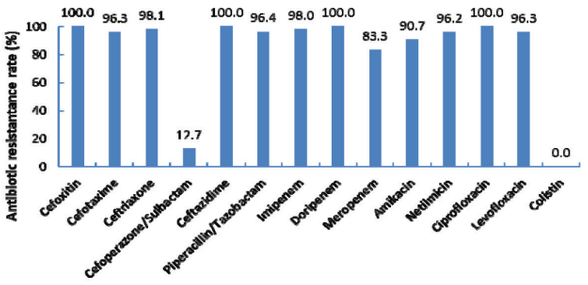


Figure 1. Distribution of bacterial pathogens isolated from the study population by specimens

3.2.2. Antibiotic resistance

Results from antibiograms showed that antibiotic resistance varied among different microbes, but no colistin-resistant pathogen was found in the study population. More than 80% of the multi-resistant bacteria isolated were resistant to all second and third-generation cephalosporin (except cefoperazone/sulbactam), carbapenem, netilmicin and fluoroquinolones. *A. baumanii* was resistant at a low rate to cefoperazone/sulbactam (12.7%) while piperacillin/tazobactam showed a low resistance proportion in *Pseudomonas* (34.8%). Amikacin and cefoperazone/sulbactam remained highly effective to *K. pneumoniae* and *E. coli*. Resistance to antibiotics tested of the multi-resistant bacteria isolated was illustrated in Figure 2.

2A



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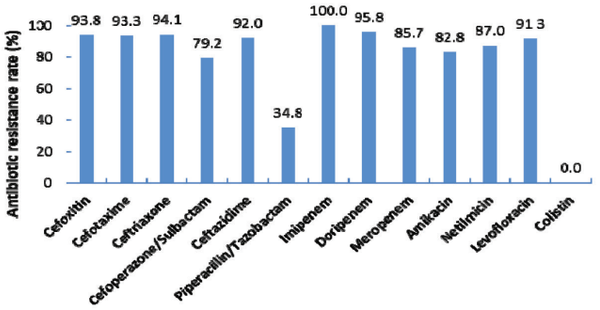

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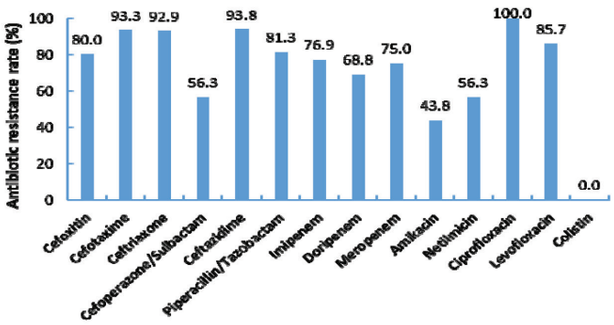

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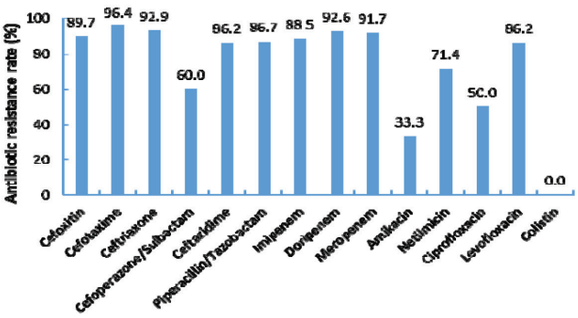

Figure 2. Resistance rate to antibiotics tested of the multi-resistant bacteria isolated *Acinetobacter baumannii* (A), *Pseudomonas* spp. (B); *E. coli* (C); *Klebsiella* spp. (D); in the study population

3.3 Antibiotic therapy

3.3.1 Empiric antibiotic before colistin use

Within 10 days prior to colistin therapy, 97.1% patients in the study population received at least one antibiotic orally or intravenously. Meropenem (21.8%), levofloxacin (15.3%) and teicoplanin (10.2%) were the most frequently antibiotic empirically prescribed.

3.3.2 Concurrent antibiotic use

The combination of two antibiotics, three antibiotics and four antibiotics was observed in 43.1%, 34.9% and 9.8% of the study population, respectively. Colistin plus cefoperazone/sulbactam was the most frequently combination administered (37.0%), followed by meropenem (23.0%), piperacillin/tazobactam (6.7%) and teicoplanin (6,7%).

3.3.3 Colistin use

The combination of inhaled and intravenous colistin was indicated in 56.8% of the study population. Intravenous colistin monotherapy and inhaled colistin monotherapy was indicated in 32.4 and 8.8% of the study population, respectively. Only two patients received intrathecal colistin (2.0%).

Loading dose was observed in 9 cases (8.8%). The average cumulative colistin dose during the course of treatment was 54.8 ± 34.4 MIU and patients received 97.26 ± 35.21 IU colistin intravenously on average. The mean duration of colistin therapy was 13.1 ± 6.7 days, ranging from 3 to 40 days.

When compared to FDA guidelines, it is shown that among patients with clearance creatinine greater than 80 mL per minute, colistin dose was rationally indicated (100%). However, the rationality decreased to 45.2% in patients with clearance creatinine between 50 and 80 mL per minute and 4.2% in patients with clearance creatinine less than 50 mL per minute (Table 2).

Table 2. Comparison of actual colistin dose and dose recommendation from FDA

	CrCl > 80 mL/min (n=15)	CrCl 50-80 mL/min (n=31)	CrCl 30-50 mL/min (n=27)	CrCl 10-30 mL/min (n=14)	CrCl < 10 mL/min (n=1)
Recommended dose (IU/kg/day)	75,000 – 150,000	75,000 – 114,000	75,000	30,000	NA
Average dose observed (IU/kg/day)	99,340 ± 12,243	99,885 ± 31,179	107,804 ± 38,072	71,786 ± 34,829	33,333
Dose analysis					
Higher than recommended (n (%))	0 (0%)	9 (29.0%)	19 (79.2%)	14 (100%)	
Within recommended dose range (n (%))	15 (100%)	14 (45.2%)	1 (4.2%)	0 (0%)	
Lower than recommended (n (%))	0 (0%)	8 (25.8%)	4 (16.7%)	0 (0%)	

NA: not available

3.3.4 Rationality of colistin indication

Only 32.8% of cases was found to be rationally indicated. Cases estimated as "irrational use" were classified as followed: (1) Colistin was not the last resort antibiotic in the antibiogram (52.0%); (2) No microbial testing was performed before colistin administration (9.8%); (3) Inhaled colistin monotherapy (8.8%); (4) Intravenous colistin monotherapy (12.7%).

Multivariable logistic regression showed that no significantly statistical association was found between rational colistin use and age, gender, clinical department, infectious disease diagnosed, type of comorbidity, number of comorbidities and length of stay.

3.3.5 Treatment outcome

At hospital discharge, only 2% of the study population was recovered, 47.5% was reported as "improved", 15.9% remained unchanged and deterioration was seen in 35.6% of the study population.

3.4 Nephrotoxicity

After the course of treatment, there was a significant decrease in the average clearance creatinine. ($p < 0.05$). Twenty one patients (22.8%) had preexisting renal failure prior to the administration of colistin, defined by serum creatinine (SCr) above 1.2 mg/dL (Table 3). Nephrotoxicity during colistin treatment was observed in 33 patients (35.5%) using RIFLE criteria.

3.4.1 Factors associated with nephrotoxicity

Multivariable logistic regression was used to analyze the association between nephrotoxicity and other risk factors including age, gender, body weight, type of comorbidity, number of comorbidities, site of infection, daily dose per kilogram, duration of colistin treatment and concomitant nephrotoxic agents (ACEi/ARB, vancomycin, furosemide, amphotericin B). The analysis showed that age (OR = 1.059; 95% CI 1.020-1.087, $p = 0.004$), respiratory diseases (OR = 0.139; 95% CI 0.024-0.804, $p = 0.028$), concomitant use with furosemide (OR = 6.215; 95% CI 1.002-38.565, $p = 0.049$) or amphotericin B (OR = 29.995; 95% CI 2.638-341.007, $p = 0.006$) were significantly associated with nephrotoxicity.

Table 3. Renal function and nephrotoxicity among patients in the study population

Variable	Before treatment with colistin	After treatment with colistin	*p*
SCr (mg/dL)	1.17 ± 1.01	1.55 ± 1.13	< 0.05
CrCl (mL/minute)	54.50 ± 34.52	46.70 ± 37.88	< 0.05
Kidney injury (n (%))	21 (22.8%)	33 (35.5%)	< 0.05
Hemodialysis (n (%))	11 (10.8%)	12 (11.8%)	> 0.05

4. DISCUSSION

The length of stay observed in this study varied widely from 9 to 213 days. This can be explained by the fact that a majority of the population with multiple comorbidities was admitted to Intensive Care Unit. Moreover, late onset hospital-acquired infections could be associated with multi-drug resistant organisms and empiric antibiotic could be ineffective, leading to prolonged hospital stay.

Results from our study showed a considerably high proportion of irrational colistin use in the study population. Although no case of resistance to colistin was observed during the study period, such high proportion of irrational use might lead to the development of resistance to colistin through adaptation. Guidelines for colistin use should be established and strictly followed to prevent resistance to this last-resort antibiotic.

The dose recommendations for colistin differ among guidelines, especially FDA and EMA-approved recommendations. In this study, we compared daily dose per kilogram to the FDA-approved dose recommendations since the EMA-approved doses were considerably higher than those recorded from our study. However, a study conducted by Nation RL showed that average steady state concentrations could only be achieved by EMA - approved regimen and the other regimens did not provide adequate concentration[7]. Further studies need to be conducted to assess the efficacy and toxicity of different dosing regimens to establish a standard dose recommendation for UMC as well as other hospitals in Vietnam.

Microbial testing was performed in only 39.2% patients after 5 days using colistin. Microbiological outcome, therefore, was not reported in the study.

Nephrotoxicity was observed in 35.5% of the study population using RIFLE criteria, which was comparable to previous studies. The previously reported incidences of nephrotoxicity varied widely from 0 to 76%[9]. Four contributing factors to nephroxicity included age, respiratory diseases, concomitant use with furosemide or amphotericin B. These findings were also similar to the results from previous reports. According to Koksal I, age was positively correlated with nephrotoxicity[10]. The majority of patients in this study population aged 60 or over and nephrotoxicity was observed in 41.8% of patients in this group while only 19.2% of patients under-60 experienced the event. The study by Montero M. concluded that respiratory diseases were attributable to nephrotoxicity[11]. Although results from this study showed that the presence of asthma, COPD or other respiratory diseases decreased the risk of renal injury, findings from the study by Montero M revealed the opposite. No statistical association was found between colistin dose and nephrotoxicity was observed in this study though it was found in previous study by Deryke CA.[12] Concurrent use with other nephrotoxic agents such as furosemide and amphotericin B was reported in previous studies by Deryke and Sorli L[12,13]. In patients with multiple comorbidities, the use of these agents sometimes is unavoidable. Thus, all these factors should be taken into consideration when colistin is indicated and renal function should be frequently monitored.

5. ACKNOWLEDGEMENT

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