International Journal of Infectious Diseases 35 (2015) 18–23

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

The efficacy and nephrotoxicity associated with colistin use in an intensive care unit in Vietnam: Use of colistin in a population of lower body weight

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ARTICLE INFO

Article history:
Received 11 March 2015
Received in revised form 21 March 2015
Accepted 26 March 2015

Keywords:
Colistin
Hospital acquired infection
ICU
Nephrotoxicity
Asia
Lower body weight

SUMMARY

Background: There has been a growing need for colistin as a key drug for the treatment of MDR-GNB infection. Information on colistin use in Asian population is limited.
Methods: A retrospective observational study was conducted to assess the efficacy and nephrotoxicity in critically ill adult patients who received intravenous colistin for MDR-GNB infection in the intensive care unit (ICU) at Bach Mai Hospital in Hanoi, Vietnam. Colistin was administered according to the dosing guideline that was based on pharmacokinetic, pharmacodynamic and toxicodynamic principles, adjusted by body weight and creatinine clearance.
Results: Twenty-eight eligible patients were included. The mean patient age was 60 ± 20.4 years. The mean body weight was 53 ± 8.6 kg. The mean daily dose of colistin was 4.1 ± 1.6 MIU, and the mean cumulative dose of colistin was 48.2 ± 22.8 MIU. Colistin therapies were classified as clinically effective in 19 (67.9%) cases. Six (21.4%) patients developed nephrotoxicity during the study period according to RIFLE criteria.
Conclusion: A personalized dosing protocol of colistin was effective, with low nephrotoxicity, among critically ill Vietnamese patients with low body weight. Further studies are warranted for assessing the efficacy and toxicity in a larger cohort.

1. Introduction

Multi-drug resistant gram-negative bacteria, such as MDR-*Acinetobacter baumannii*, carbapenemase-producing *Enterobacteriaceae*, MDR-*Pseudomonas aeruginosa* have spread rapidly worldwide, including Asia.[1] Colistin, which is produced *in vivo* after hydrolyzation of its prodrug colistimethate sodium, has been increasingly employed for over a decade as a key drug for the treatment of these MDR-GNB.[2] Colistin is known for its nephrotoxicity which initially resulted in abundance of its clinical use in 1970s.[2] Majority of recent studies on the clinical use of colistin were conducted in Europe or North America, and there has been debate on the appropriate dosing and its relation to the efficacy and nephrotoxicity of colistin.[2] Information on colistin use pertaining to the Asian population is limited. Recently, the interim guideline to administer colistin in critically ill patients based on pharmacokinetic, pharmacodynamic, and toxicodynamic principles

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http://dx.doi.org/10.1016/j.ijid.2015.03.020

has been proposed.[3] The efficacy and toxicity of such "personalized" administration of colistin has not been well evaluated worldwide, even less so in Asian countries where people tend to have lower body weight than in Europe or North America. In this study, we evaluated the efficacy and nephrotoxicity of personalized administration of colistin in critically-ill patients admitted to ICU in Vietnam.

2. Methods

2.1. Study Design and Patient Population

This was a retrospective observational study to assess the efficacy and nephrotoxicity in critically ill patients who received intravenous colistin at Bach Mai Hospital (BMH) between August 15, 2013 and January 15 2014. BMH has 2000 beds and serves as a tertiary care hospital in Hanoi, Vietnam. The study was approved by Bach Mai Hospital institutional review board. Adult patients aged greater than 18 years were included in the study if they were admitted to the intensive care unit (ICU) and received intravenous colistin for hospital acquired infection due to MDR-GNB with positive microbiological culture. Hospital acquired infection (HAI) was determined according to CDC/NHSN definitions[4] and according to multiple physicians' evaluation. Patients were excluded if they were pregnant or breast-feeding or were receiving renal replacement therapy (intermittent hemodialysis or continuous renal replacement therapy) before the initiation of colistin. Patients were excluded if they received colistin for less than five days, to ensure adequate exposure to the drug.

2.2. Microbiology

BMH has a single centralized microbiology laboratory. Standard identification and susceptibility testing of clinical isolates were performed in accordance with the Clinical and Laboratory Standards Institute (CLSI) criteria.[5] The minimum inhibitory concentrations (MICs) of collistin were determined by E-test (Sysmex-bioMerieux, Tokyo, Japan) according to the manufacturer's instructions.

2.3. Colistin administration

The colistin product used in this study was Coly-Mycin® produced by Sanofi-Aventis. Dosing of intravenous colistin was prospectively reviewed by clinical pharmacists. The institutional guideline for colistin dosing was as follows[3]:

Loading dose (Colistin Base Activity [CBA], mg) = C-Target × 2 × Total actual body weight (kg).

Maintenance dose (CBA, mg) = C-target × (1.5 × CrCl [Creatinine clearance, mL/min] + 30).

Maintenance dose was initiated 24 hours after loading dose infusion. C-target was calculated as follows. C-target was equal to the identified colistin MIC for the causative organism of HAI. The doses calculated based on CBA (mg) were divided by 33.3 to convert them to MIU (million international units). The total daily dosage was divided into two doses for twice-daily administration.

Each bottle of colistin was dissolved in 50 mL of normal saline solution (0.9% NaCl) and was infused immediately over 30 minutes to 2 hours following its dissolution. Clinical pharmacists rechecked and recalculated the maintaining colistin dose according to the patient's measured renal function during colistin therapy. Body weights and CrCl were measured within 2 days of colistin administration. Nebulized colistin was not used throughout the study period.

2.4. Data Collection

The following parameters were retrieved from the medical records of patients in the study: age, sex, weight, underlying diseases, baseline serum creatinine concentration, Charlson's score,[6] Acute Physiology and Chronic Health Evaluation (APACHE) II score,[7] Clinical Pulmonary Infection Score (CPIS),[8] and Sequential Organ Failure Assessment (SOFA) score on ICU admission.[9] The information on the use of other nephrotoxic drugs (NSAIDs, furosemide, contrast agent, angiotensin-converting enzyme inhibitors) was also collected.

2.5. Clinical assessment

Clinical assessments were conducted at 3 time points: the first was prior to using colistin; the second was after day 5 of colistin treatment; the last point was after discontinuing colistin. Multiple physicians involved in the patients' care evaluated the clinical effectiveness of colistin therapy at each time point, based on the resolution, persistence or worsening of symptoms and signs of infection.

2.6. Microbiological assessment

Microbiological culture samples were collected at two time points, the first was prior to administering colistin and the second was after day 5 of colistin treatment. Samples were transferred to the microbiology department, and sample culture result and MICs were determined. Microbiological efficacy was evaluated based on the comparison of two consecutive culture results; i.e., if the second culture was negative, then it was evaluated as microbiologically effective.

2.7. Nephrotoxicity assessment

Daily serum creatinine level was recorded from the first day of colistin therapy until discharge or death. Nephrotoxicity was defined based on the increase in the serum creatinine concentration of $\geq$50 percent as per RIFLE (risk, injury, failure, loss, and end-stage kidney disease) criteria.[10]

2.8. Statistical Analysis

All analyses were performed using SPSS 20. Bivariate analyses were performed using the Fisher's exact test or the Chi-square test for categorical variables and the t-test or the Mann-Whitney U test for continuous variables. All P-values were two-sided, a p value of less than 0.05 was considered to indicate a statistically significant difference. Throughout the text, the percentages displayed are the "valid percent", which indicates the percent excluding the missing data from the denominator.

3. Results

During the study period, 28 eligible patients were identified. The mean age was 60 (±20.4; range: 19-88) years, and 18 (64%) were male (Table 1). The mean body weight of the study cohort was 53 (±8.6; range: 35.5-75) kg. Eight (28.6%) patients had preexisting renal failure prior to the administration of colistin, which was defined by a serum creatinine (Scr) value > 1.2 mg/dl. The majority (n = 26, 92.9%) of patients had ventilator-associated pneumonia (VAP), and 2 (7.1%) patients had blood-stream infections.

Acinetobacter baumannii were most frequently isolated (n = 24 [85.7%]; 23 from sputum, 1 from blood), followed by *Pseudomonas aeruginosa* (n = 3 [10.7%]; 3 from sputum), and *Klebsiella pneumonia* (n = 3 [10.7%]; 2 from sputum and 1 from

Table 1
Patient characteristics based on the clinical response to intravenous colistin therapy (n = 28)

Characteristics	Whole cohort (n = 28)	Clinically effective (n = 19, 68%)	Clinically ineffective (n = 9, 32%)	P value (Effective group vs ineffective-treatment group)
Demographics				
Age (years), mean ± SD	60.0 ± 20.4	51.8 ± 19.6	74 ± 12.8	0.01
Male, n (%)	18 (64.3%)	14 (73.7%)	4 (44.4%)	0.21
Body weight (kg), median (IQR), [mean ± SD]	53.5 (45.5-58.5) [53 ± 8.6]	57 (51-59) [54.5 ± 6.8]	49.5 (41.5-54.3) [49.8 ± 11.4]	0.05
Charlson comorbidity index, median (IQR)	3 (2-5)	3 (1-4)	5 (3-6)	0.03
SOFA score, median (IQR)	8 (4.3-9)	6 (4-8)	8 (8-10)	0.02
APACHE II score, median (IQR)	14 (10-17)	12 (8-17)	14 (13-17)	0.41
CPIS, median (IQR)	6 (6-8)	6 (5-7)	8 (6-8)	0.01
Length of ICU stay prior to colistin therapy (days), median (IQR)	6 (3-11)	6 (3-9)	6 (1-16)	0.96
Severity of illness				
Severe sepsis, n (%)	19 (67.9%)	11 (57.9%)	8 (88.9%)	0.20
Septic shock, n (%)	6 (21.4%)	5 (26.3%)	1 (11.1%)	0.63
Site of Infection				
VAP, n (%)	26 (92.9%)	17 (89.5%)	9 (100%)	>0.99
BSI, n (%)	2 (7.1%)	2 (10.5%)	0	>0.99
Microbiology				
Acinetobacter baumannii, n (%)	24 (85.7%)	17 (89.5%)	7 (77.8%)	0.57
Pseudomonas aeruginosa, n (%)	3 (10.7%)	2 (10.5%)	1 (11.1%)	>0.99
Klebsiella pneumonia, n (%)	3 (10.7%)	2 (10.5%)	1 (11.1%)	>0.99
Colistin MIC of *Acinetobacter baumannii*, mg/L, median (IQR)	0.13 (0.13-0.30)	0.13 (0.09-0.16)	0.38 (0.13-0.50)	0.02
Colistin therapy				
Average daily dose (MIU), median (IQR), [mean ± SD]	4.0 (2.7-5.6) [4.1 ± 1.6]	4.4 (3.1-6.2) [4.4 ± 1.7]	3.2 (2.6-4.1) [3.5 ± 1.0]	0.12
Average daily dose per kg (MIU), median (IQR), [mean ± SD]	0.08 (0.05-0.11) [0.08 ± 0.03]	0.09 (0.06-0.11) [0.08 ± 0.03]	0.08 (0.05-0.11) [0.07 ± 0.03]	0.50
Total cumulative dose (MIU), median (IQR), [mean ± SD]	39 (33-57) [48.2 ± 22.8]	50 (33-72) [54.1 ± 24.2]	37.5 (26.5-43.5) [35.7 ± 13.1]	0.12
Total cumulative dose per kg (MIU), median (IQR), [mean ± SD]	0.84 (0.64-1.17) [0.91 ± 0.38]	0.86 (0.67-1.33) [0.98 ± 0.38]	0.80 (0.4-1.13) [0.76 ± 0.35]	0.27
Duration of colistin therapy (days), median (IQR)	11 (8-16)	13 (9-17)	10 (8-16)	0.26
Combination therapy with carbapenem, n (%)	25 (89.3%)	17 (89.5%)	8 (88.9%)	>0.99
Use of concomitant nephrotoxic agents				
Any nephrotoxic agent	11 (39.3%)	8 (42.1%)	3 (33.3%)	>0.99
ACEI	1 (3.6%)	1 (5.3%)	0	>0.99
Furosemide	10 (35.7%)	7 (36.8%)	3 (33.3%)	>0.99
Renal function				
Pre-existing renal failure (Scr > 1.2 mg/dl), n (%)	8 (28.6%)	5 (26.3%)	3 (33.3%)	>0.99
Scr, prior to colistin therapy, mg/dl, median (IQR), [mean ± SD]	0.8 (0.8-1.43) [1.2 ± 0.9]	0.9 (0.8-1.2) [1.1 ± 0.6]	0.8 (0.65-2.45) [1.5 ± 1.4]	0.63
Scr, worst during therapy, mg/dl, median (IQR), [mean ± SD]	1.05 (0.8-2.25) [1.7 ± 1.4]	1.2 (0.8-2.3) [1.5 ± 0.9]	0.9 (0.75-3.85) [2.1 ± 2.2]	0.73
Scr, upon discharge from ICU, mg/dl, median (IQR), [mean ± SD]	0.9 (0.7-1.5) [1.4 ± 1.3]	0.9 (0.7-1.4) [1.2 ± 0.7]	0.8 (0.6-3.7) [1.9 ± 2.1]	0.79
CrCl, prior to colistin therapy, ml/min, median (IQR), [mean ± SD]	62.3 (34.8-76.1) [62.6 ± 37.8]	67.6 (51.7-83.5) [80 ± 40.5]	50 (21.1-66.2) [44.9 ± 24.8]	0.06
CrCl, worst during therapy, ml/min, median (IQR), [mean ± SD]	52 (25.5-70) [53.7 ± 30]	61 (34-79) [60.4 ± 31.5]	48 (16-57.5) [39.4 ± 21.9]	0.09
CrCl, upon discharge from ICU, ml/min, median (IQR), [mean ± SD]	60 (35.8-87.3) [63.5 ± 34.1]	64 (47-99) [71 ± 33.6]	55 (16.5-74) [47.7 ± 31.2]	0.08
Renal failure upon discharge (Scr > 1.2 mg/dl), n (%)	9 (32.1%)	6 (31.6%)	3 (33.3%)	>0.99
Outcome				
Total ICU length of stay (days), median (IQR)	22 (17-30)	22 (19-30)	21 (14-30)	0.40
Microbiologically effective, n (%)	15 (62.5%)	13 (81.2%)	2 (25%)	0.02
Nephrotoxicity during colistin therapy per RIFLE criteria[a], n (%)	6 (21.4%)	5 (26.3%)	1 (11.1%)	0.63
Increase of Scr > 150% as compared to baseline upon discharge, n (%)	3 (10.7%)	2 (10.5%)	1 (11.1%)	>0.99
In-hospital mortality, n (%)	5 (17.9%)	0	5 (55.6%)	<0.01
14-day mortality, n (%)	8 (28.6%)	2 (10.5%)	6 (66.7%)	<0.01

Abbreviations. ACEI, Angiotensin-converting enzyme inhibitors; APACHE, Acute Physiology and Chronic Health Evaluation; BSI, blood stream infection; CBA, colistin base activity; CrCl, Creatinine clearance; CPIS, Clinical Pulmonary Infection Score; ICU, intensive care unit; IQR, interquartile range; MIU, Million International Units; Scr, serum creatinine; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; VAP, ventilator associated pneumonia.

[a] RIFLE criteria.[10]

blood). The colistin MIC_{50} and MIC_{90} of *A. baumannii* were 0.125 mg/L, and 0.5 mg/L, respectively, and MIC ranged from 0.064-0.75 mg/L.

The mean daily dose of colistin used in the whole cohort was 4.1 ± 1.6 MIU (136.5 ± 53.3 mg CBA; median: 4.0 MIU [133.2 mg CBA], IQR [interquartile range]: 2.7-5.6 MIU [89.9-186.5 mg CBA]). The mean daily dose of colistin per kg was 0.08 ± 0.03 MIU/kg (2.66 ± 1.0 mg CBA/kg; median: 0.08 MIU/kg [2.66 mg CBA/kg], IQR: 0.05-0.11 MIU/kg [IQR: 1.67-3.66 mg CBA/kg]). The mean duration of colistin therapy was 12.5 ± 5.2 days (range: 5-23 days), and the mean cumulative colistin dose was 48.2 ± 22.8 MIU [1605.1 ± 759.2 mg CBA)] (median: 39 MIU [1298.7 mg CBA], IQR: 33-57 MIU [1098.9-1898.1 mg CBA]). The mean cumulative colistin dose per kg was 0.91 ± 0.38 MIU/kg [30.3 ± 12.65 mg CBA/kg] (median: 0.84 MIU [27.97 mg CBA/kg], IQR: 0.64-1.17 MIU/kg [21.31-38.96 mg CBA/kg]). In all cases, colistin was used as combination therapy and most frequently combined with carbapenem in 25 (89.3%) cases.

Nephrotoxicity during colistin therapy was identified in 6 (21.4%) patients according to the RIFLE criteria. All six patients identified as AKI per RIFLE criteria were categorized as "risk" under RIFLE criteria. Among 8 patients with pre-existing renal failure, 3 (37.5%) developed AKI per RIFLE criteria. Among 20 patients without pre-existing renal failure, 3 (15%) developed AKI according to RIFLE criteria.

Concomitant nephrotoxicity agents were used in 11 (39.3%) patients: 1 patient received angiotensin converting enzyme inhibitor, and 10 patients received furosemide. Other nephrotoxic agents, such as non-steroidal anti-inflammatory drug, vancomycin, aminoglycoside, or contrast agent was not used concurrently with colistin in any patient.

3.1. Comparison between the clinically effective-treatment group and the ineffective-treatment group

Colistin therapies were evaluated as clinically effective in 19 cases (68%) and clinically ineffective in 9 (32%) cases. The patients' characteristics based on the clinical response to intravenous colistin therapy, were summarized in Table 1. The patients of the clinically effective-treatment group were younger than patients without response (mean age 51.8 ± 19.6 vs 74 ± 12.8, p = 0.01). The patients of the ineffective-treatment group comprised the population that showed a greater incidence of comorbidities with higher median Charlson comorbidity index (3 [IQR: 1-4] vs 5 [IQR: 3-6], p = 0.03) and had more organ dysfunction indicated by higher median SOFA score (6 [IQR: 4-8] vs 8 [IQR: 8-10], p = 0.02). The median CPIS score was significantly lower in the clinically effective-treatment group than in the ineffective-treatment group (6 [IQR: 5-7] vs 8 [IQR: 6-8], p = 0.01). The patients in clinically effective-treatment group had marginally higher median body weight than the ineffective-treatment group (57 [IQR: 51-59] vs. 49.5 [41.5-54.3], p = 0.05). The median MIC of *A. baumannii* is lower in clinically effective-treatment group than in ineffective-treatment group (0.13 [0.09-0.16] vs. 0.38 [0.13-0.50], p = 0.02). The other variables, including patients' demographics (e.g. sex, APACHE II score, length of ICU stay prior to colistin use), severity of illness (e.g. severe sepsis, septic shock), site of infection, and colistin therapy (daily doses, duration, cumulative dose), and concomitant nephrotoxic agent use were similar between two groups. The prevalence of pre-existing renal failure defined as Scr >1.2 mg/dl prior to colistin therapy were similar between two groups. The frequencies of the development of nephrotoxicity, which were defined by RIFLE criteria, were similar between the two groups. No deaths were observed in the clinically effective-treatment group during the study period; however, 5 (55.6%) patients without response died ($p < 0.01$). The 14-day mortality was higher in the clinically ineffective-treatment group than the effective treatment group (6 [66.7%] vs. 2 [10.5%], $P < 0.01$).

3.2. Comparison between nephrotoxicity and non-nephrotoxicity group

Characteristics of patients who developed nephrotoxicity and who did not develop nephrotoxicity during colistin therapy based on RIFLE criteria were also compared (Table 2). Patients with nephrotoxicity had higher median body weight than patients without nephrotoxicity (57.8 [IQR: 53.8-65.3] vs. 51.3 [IQR: 43.8-58.1], p = 0.05). However, the colistin doses were similar between 2 groups because of decreased CrCl in the nephrotoxicity group. Duration of colistin therapy did not differ between the two groups. Other characteristics such as age, sex, severity of illness, site of infections were similar between the two groups. The prevalence of pre-existing renal failure was similar between the two groups. Outcome parameters such as microbiological and clinical effectiveness, in-hospital and 14-day mortality did not differ between the two groups.

4. Discussion

To our knowledge, this is the first study to describe the details of clinical experiences of colistin use in Vietnam. The vast majority of reports regarding colistin use in clinical settings have been published from Europe and North America, and the data on the clinical use of colistin in Asia is scarce.

The previously reported incidences of nephrotoxicity during colistin therapy vary from 6% to 55%,[2] and depend on various factors such as dosing, population differences (e.g. comorbidity, severity, clinical setting), and definition of nephrotoxicity. In this study, we used RIFLE criteria to identify nephrotoxicity, which was validated to correlate with prognosis.[11] We used only Scr changes for applying the RIFLE criteria without reference to GFR, because previous reports suggested that the changes in Scr concentrations do not correlate with the percent decreases in GFR in the RIFLE classification.[12] The incidence of nephrotoxicity in this study (21.4%) was lower than the incidence reported in previous studies (range: 31-54.6%) that have evaluated nephrotoxicity during colistin therapy using RIFLE criteria.[13] Patients received relatively lower dose of colistin in our study than the previous studies,[14–17] even if their actual body weights are considered. The mortality and prevalence of non-responding patients were not higher in our study,[14,17,18] even though Charlson comorbidity index scores, SOFA scores, and patients' ages in our study were apparently not lower than previous studies.[14,17,18] We used actual body weight in place of ideal body weight since there were no obese patients in our study cohort, in whom the dissociation between actual and ideal body weight could be significant.

We excluded patients if they received colistin for less than five days to ensure adequate exposure to the drug. In our study, no patient developed nephrotoxicity within 5 days after starting colistin therapy. However, previous studies reported the development of nephrotoxicity of various incidences (15.5%-100%) within 7 days of colistin administration,[15,18] and used inclusion criteria of receiving colistin longer than 48 to 72 hours.[14–18] There was no patient who died within 5 days after starting colistin therapy.

In this study, we used a dosing strategy including the loading dose and maintenance dose, which was suggested by a recent study by Garonzik et al.[3] The report of Garonzik et al included patients from Thailand; however, it also included patients from the U.S., and thus the range was much wider than our study (median body weight 59.1 kg [range: 30.0–106.4] vs. 53.5 kg [35.5-75]). We

Table 2
Patient characteristics based on nephrotoxicity to intravenous colistin therapy (n = 28)

Characteristics	Nephrotoxicity group[a] (n = 6, 21%)	Non-nephrotoxicity group (n = 22, 79%)	P value (Nephrotoxicity group vs non-nephrotoxicity group)
Demographics			
Age (years), mean ± SD	50.2 ± 26.4	61.4 ± 18.4	0.29
Male, n (%)	5 (83.3%)	13 (59.1%)	0.38
Body weight (kg), median (IQR), [mean ± SD]	57.8 (53.8-65.3) [59.9 ± 8.1]	51.3 (43.8-58.1) [51.1 ± 8.0]	0.05
Charlson comorbidity index, median (IQR)	3 (0-5)	3 (2-5)	0.59
SOFA score, median (IQR)	11 (6-13)	8 (4-8)	0.09
APACHE II score, median (IQR)	13 (15-20)	14 (12-16)	0.84
CPIS, median (IQR)	6 (3-7)	6 (6-8)	0.16
Length of ICU stay prior to colistin therapy (days), median (IQR)	4 (1-7)	6 (4-12)	0.14
Severity of illness			
Severe sepsis, n (%)	2 (33.3%)	17 (77.3%)	0.06
Septic shock, n (%)	3 (50%)	3 (13.6%)	0.09
Site of Infection			
VAP, n (%)	5 (83.3%)	21 (95.5%)	0.39
BSI, n (%)	1 (16.7%)	1 (4.5%)	0.39
Microbiology			
Acinetobacter baumannii, n (%)	4 (66.7%)	20 (90.9%)	0.19
Pseudomonas aeruginosa, n (%)	1 (16.7%)	2 (9.1%)	0.53
Klebsiella pneumonia, n (%)	2 (33.3%)	1 (4.5%)	0.11
Colistin MIC of *Acinetobacter baumannii*, mg/L, median (IQR)	0.13 (0.03-0.17)	0.13 (0.13-0.37)	0.31
Colistin therapy			
Average daily dose (MIU), median (IQR), [mean ± SD]	3.3 (2.2-5.8) [3.8 ± 1.8]	4 (3-5.5) [4.2 ± 1.5]	0.43
Average daily dose per kg (MIU), median (IQR), [mean ± SD]	0.07 (0.04-0.1) [0.07 ± 0.03]	0.09 (0.06-0.11) [0.08 ± 0.03]	0.22
Total cumulative dose (MIU), median (IQR), [mean ± SD]	42 (32-89.3) [57.2 ± 33.3]	39 (33-57) [45.7 ± 19.3]	0.70
Total cumulative dose per kg (MIU), median (IQR), [mean ± SD]	0.76 (0.56-1.5) [0.96 ± 0.54]	0.85 (0.7-1.16) [0.9 ± 0.34]	0.96
Duration of colistin therapy (days), median (IQR)	16 (12-18)	11 (8-15)	0.11
Combination therapy (with carbapenem), n (%)	5 (83.3%)	20 (90.9%)	0.53
Use of concomitant nephrotoxicity agents			
Any nephrotoxicity agent	2 (33.3%)	9 (40.9%)	>0.99
ACEI	0	1 (4.5%)	>0.99
Furosemide	2 (33.3%)	8 (36.4%)	>0.99
Renal function			
Pre-existing renal failure (Scr > 1.2 mg/dl), n (%)	3 (50%)	5 (22.7%)	0.31
Scr, prior to colistin therapy, median (IQR)	1.2 (0.8-2.0) [1.5 ± 1.0]	0.8 (0.7-1.3) [1.2 ± 0.9]	0.26
Scr, worst during therapy, median (IQR)	2.7 (1.3-3.7) [2.7 ± 1.7]	1.0 (0.8-1.4) [1.4 ± 1.2]	0.03
Scr, upon discharge from ICU, median (IQR)	1.9 (1.2-3.7) [2.4 ± 1.8]	0.8 (0.7-1.1) [1.1 ± 1.0]	0.02
CrCl, prior to colistin therapy, median (IQR)	62.2 (25.4-119.7) [77.4 ± 66.6]	62.3 (37.9-76) [58.6 ± 26.4]	0.80
CrCl, worst during therapy, median (IQR)	28.5 (13.3-89) [46.7 ± 43.2]	54 (44.3-68) [55.6 ± 26.4]	0.40
CrCl, upon discharge from ICU, median (IQR)	42 (17.8-81) [52.2 ± 46.1]	61.5 (44.8-90.3) [66.6 ± 30.7]	0.31
Renal failure upon discharge (Scr > 1.2 mg/dl), n (%)	5 (83.3%)	4 (18.2%)	0.01
Outcomes			
Total ICU length of stay (days), median (IQR)	23 (19-33)	21 (16-29)	0.40
Microbiologically effective, n (%)	5 (83.3%)	10 (55.6%)	0.35
Clinically effective, n (%)	5 (83.3%)	14 (63.6%)	0.63
In-hospital mortality, n (%)	1 (16.7%)	4 (18.2%)	>0.99
14-day mortality, n (%)	2 (33.3%)	6 (27.3%)	>0.99

Abbreviations. ACEI, Angiotensin-converting enzyme inhibitors; APACHE, Acute Physiology and Chronic Health Evaluation; BSI, blood stream infection; CrCl, Creatinine clearance; CPIS, Clinical Pulmonary Infection Score; ICU, intensive care unit; IQR, interquartile range; MIU, Million International Units; Scr, serum creatinine; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; VAP, ventilator associated pneumonia.

[a] Nephrotoxicity was defined according to RIFLE criteria.[10]

evaluated the efficacy and safety of a colistin dosing strategy, including the loading dose and the maintenance dose,[3] which was adjusted by both body weight and CrCl, in Asian population with lower body mass. Further studies are warranted to assess the efficacy and toxicity in a larger cohort. Due to the worldwide spread of multi-drug resistant pathogens, a personalized approach is crucial for the appropriate use and evaluation of efficacy and safety of colistin therapy in clinical settings.

Acknowledgments

This work was supported by the J-GRID (Japan Initiative for Global Research Network on Infectious Diseases), MEXT Japan.

Conflict of interest statement: No conflicts of interest to declare.

The study was approved by Bach Mai Hospital institutional review board. (Approval No. 38).

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