Original Article

Factors Associated with Microbiological Outcomes to Colistin in Patients with Multidrug-resistant Gram-Negative Bacterial Infections

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Background: Multidrug-resistant (MDR) gram-negative bacterial infections continuously increases in prevalence, rate of ICU admission and mortality. Although, colistin has been used to treat MDR organisms, the controversial outcomes regarding its efficacy and safety were reported. Therefore, factors related with microbiological response to colistin should be determined.

Objective: To evaluate the rate and related factors of microbiological outcome in patients who received intravenous colistin for treatment of MDR gram-negative bacterial infections.

Materials and Methods: The retrospective cohort study was performed in adult patients between June 2015 and June 2017. Patient information, microbiology data, duration of colistin treatment and clinical outcomes were reviewed and analyzed. Microbiological responses were classified as either eradication or persistence of the initial MDR bacteria. Factors influencing microbiological response were determined by multiple logistic regression analysis.

Results: 303 colistin-given patients were enrolled with the mean age of 62.8±18.3 years. Pneumonia and soft tissue infections were the most two common sites of infection. Reports of culture revealed monomicrobial gram-negative bacteria 80.5%. *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were the major organisms accounting for 79.9% and 17.2%, respectively. Microbiological clearance rate of colistin was 66%. Multivariate analysis demonstrated the factors related with poor microbiological response were (a) AKI before colistin treatment associated with higher severity of AKI (b) presence of pneumonia, (c) infection with *P. aeruginosa* and (d) mixed gram-negative bacterial infections. The overall mortality rate was 39.3% with no significant differences of mortality rate and incidence of AKI after colistin administration between the eradication and persistence groups.

Conclusion: Colistin accomplished with rather good microbiological response in clearance of MDR gram-negative bacteria. AKI influenced the microbiological response therefore early and aggressive care to prevent AKI is mandatory. Additionally, because of high non-response rate in *P. aeruginosa* infection, combined antibiotics and surveillance may be crucial.

Keywords: Colistin; Microbiological response; Factors for good and poor outcomes

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Multidrug-resistant (MDR) gram-negative bacterial infection has been globally prevalent, particular in hospital-acquired infection[1]. These life-threatening pathogens leads to therapeutic challenge due to limitation of available effective antimicrobial agents. Emerging of carbapenem-resistant gram-negative bacilli including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae is the mainstay for revival use of polymyxin group of antibiotics, most commonly colistin. The efficacy and safety of colistin for treatment of these MDR microorganisms has been evaluated in several studies. The 30-day all-cause mortality, clinical, and microbiological responses were reported in 33 to 46%, 60 to 81%, and 43 to 95%, respectively for using colistin therapy in these MDR pathogens[2,3]. Nephrotoxicity was observed in 31 to 48%[2,3]. Factors associated with favorable outcomes of colistin treatment are limited information. Use of loading and high dose colistin is related to greater survival, clinical cure, and microbiological clearance; however, this is not without increase nephrotoxicity. The objective of this study was to evaluate the factors which related to microbiological response in adult patients who received intravenous colistin for treatment of MDR gram-negative bacterial infections.

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Materials and Methods

This retrospective cohort study was conducted in

Srinagarind Hospital, a 1,500-bed tertiary care university hospital, located in northeastern Thailand, between June 2015 and June 2017. The study protocol was reviewed and approved by the institutional review board of Khon Kaen University (approval number HE601148) and was performed in accordance with the Helsinki Declaration. Inclusion criteria was in-patient adults (aged >18 years) who received intravenous colistin for at least 48 hours for the treatment of MDR gram-negative bacilli infection. Patients were excluded if they had underlying chronic kidney disease (CKD) stage 5 regardless of receiving long-term renal replacement therapy, no microbiological confirmed MDR gram-negative bacterial infection, had colistin-resistant gram-negative bacilli infection, or had no available follow-up cultures after receiving colistin treatment. Only the first course of colistin treatment that met the inclusion and without exclusion criteria was included.

Patient information were reviewed and retrieved from the medical records and hospital computerized system. These data included demographic data, source of infection, biochemistry and microbiological laboratory data, dosage, and duration of colistin treatment, microbiological responses, acute kidney injury (AKI) after colistin treatment, length of hospital stay, and mortality outcome. Multidrug-resistant gram-negative bacteria was defined as a resistance to at least three of five drug classes of antibiotics as follows: piperacillin/tazobactam, ceftazidime or cefepime, carbapenems, aminoglycosides, and quinolones[4]. Microbiological responses at the end of colistin treatment were classified as eradication or persistence. Microbiological eradication defined as most recent cultures on or close to the end of colistin treatment from any site of baseline infection was negative for the initial MDR gram-negative bacteria. If initial MDR gram-negative bacteria was still detected on culture from any site of baseline infection, this was defined as microbiological persistence. Definition of AKI diagnosis and stages classification were based on the Kidney Disease Outcomes Quality Initiative (KDOGI) criteria[5]. Colistin (colistimethate sodium) was administered intravenously as a loading dose of 300 mg and then followed by 150 mg intravenously every 12 hours. The dose was adjusted according to the renal function (creatinine clearance calculated by using Cockcroft-Gault equation)[6]. The primary outcome was to determine the factors related to the microbiological eradication at the end of intravenous colistin therapy for MDR gram-negative bacterial infections.

VITEX®2 automated microbiology system (BioMerieux, France) was used for routine identification of all bacterial cultures. Antimicrobial susceptibility testing was performed using a disc diffusion method and determined following the recommendation of the Clinical Laboratory Standards Institute (CLSI)[7]. Colistin E-test strip (AB BIODISK®, Solna, Sweden) was used for susceptibility testing of MDR gram-negative bacteria to colistin. During the study period, strains were sensitive to colistin if their MIC was ≤2 µg/mL. This study was conducted prior to the recent criteria of CLSI in which no breakpoint interpretation of colistin susceptibility for *P. aeruginosa*, *A. baumannii*, and Enterobacteriaceae and all isolates which have MIC ≤ 2 µg/mL will be categorized as intermediate susceptible[8].

Statistical analysis

The sample size calculation was based on the objective of study to evaluate factors associated with microbiological persistence by using logistic regression analysis. A total sample size of 302 subjects would have a power of 80% and a targeted significance level of 0.05 to detect probabilities of non-response to treatment as 0.45 and 0.25 if presence and non-presence of risks, respectively by referring a prevalence of interested risk of 25% according to the study of Desai K, et al[9].

Statistical analyses comprised computing (a) frequency counts and percentages for categorical variables and (b) mean levels with standard deviation (SD) or medians with interquartile range (IQR) for continuous variables. The two-tailed t-test was used to compare continuous variables of the two groups. Categorical data were compared by the Chi-squared and Fisher's exact test as appropriate. Multivariate logistic regression analysis was performed by full model to determine the clinical factors significantly associated with microbiological response presented as odd ratio (OR) with 95% confidence interval (CI). The p-values <0.05 were considered statistically significant. All statistical analyses were performed using STATA version 14.2.

We set a priori target for an acceptable level of missing data as <5% and used the multiple imputation method for handling the missing data. These missing data were replaced with a set of predicted values imputed from the other variables in existing data which contain the natural variability and uncertainty of the right values then multiple imputed data set were combined and repeatedly analyzed to produce the final single overall analysis result.

Results

Of the 576 patients who received intravenous colistin from June 2015 to June 2017, 273 were excluded, due to age <18 years (n=8), CKD stage 5 (n=118), received intravenous colistin less than 48 hours of administration (n=21), no microbiological confirmed MDR gram-negative bacteria infection (n=73) and no available follow-up culture information (n=53). The total 303 patients were included to the study. Characteristics of the study population were as follows: 64.4% of male; mean (SD) age 62.8±18.3 years; mean sequential organ failure assessment (SOFA) score 5.07±3.64; baseline serum creatinine (Cr) and estimated glomerular filtration rate (eGFR) values before colistin administration 1.11±1.03 mg/dL and 83.5±39.1 ml/min/1.73 m^2; mean duration of colistin treatment 12.1±6.71 days [median duration 11 (7 to 14) days]; and mean hospital length stay 50.1±38.3 days [median hospital stay 41 (25 to 61) days]. Pneumonia and soft tissue infections were the two most common sites of infection. Monomicrobial infection with gram-negative bacteria was revealed in 80.5% of cultures

and the remaining 17.2% reported mixed gram-negative bacterial infection and 2.6% mixed with gram-positive organism. *A. baumannii* and *P. aeruginosa* were the major organisms accounting for 79.9% and 17.2%.

Table 1 shows the characteristics of patients with microbiological responses after colistin treatment; 200/303 (66%) achieved microbiological eradication. Among 103 cases who failed to eradicate the initial MDR gram-negative bacteria, the persistent pathogens were recognized as follows: *P. aeruginosa* (44.2%), *Klebsiella pneumoniae* (41.3%), *A. baumannii* (36.8%) and *Escherichia coli* (9.1%).

The patients in microbiological persistence group had a significantly higher SOFA score and higher proportion of the follows: male, AKI before initiation of colistin treatment, pneumonia, received mechanical ventilator, infections from *P. aeruginosa* and *K. pneumoniae*, and mixed gram-negative bacterial infection. Urinary tract infection and eGFR levels before colistin treatment were significantly higher in microbiological eradication group. No statistically significant differences were observed between patients who achieved microbiological cure and failed to eradicate the target pathogens regarding to a daily and total dosages of colistin, and proportion of cases received loading dose of colistin but the patients in microbiological persistence group had significantly received lower daily dose of colistin per body weight.

The 28-day and in-hospital mortality rate were 24.1% and 39.3%. No significant differences of mortality rate, hospital length stay and incidence of AKI after colistin administration were observed between both groups (Table 2).

The results of univariate logistic regression analysis are presented in Table 3. Factors related to microbiological persistence after colistin treatment were male sex, SOFA score >8, requiring mechanical ventilator, occurrence of coagulopathy, AKI developed before colistin usage, severity of AKI (stage 2 and 3), presence of pneumonia, infection with *P. aeruginosa*, *K. pneumoniae,* mixed gram-negative bacterial infection, and reduced daily colistin dose per body weight. Multivariate analysis demonstrated the independent factors associated with microbiological persistence were as follows: (a) AKI before colistin treatment which increased strength of an association with higher severity of AKI [AKI stage 1 (OR 1.33, 95% CI 0.63 to 2.81, p=0.46), AKI stage 2 (OR 2.66, 95% CI 1.09 to 6.49, p=0.032, AKI stage 3 (OR 2.89, 95% CI 1.11 to 7.52, p=0.03) vs. non AKI group], (b) pneumonia [OR 2.02, 95% CI 1.09 to 3.73, p=0.025], (c) infection with *P. aeruginosa* [OR 2.40, 95% CI 1.23 to 4.69, p=0.01 comparing with other gram-negative organisms], and (d) mixed gram-negative bacterial infections [OR 3.60, 95% CI 1.86 to 6.96, p<0.001].

Discussion

In this retrospective study evaluated 303 patients with MDR gram-negative bacilli infection, mainly *A. baumannii*, treated with parenteral colistin. The microbiological eradication rate was 66% and in-hospital mortality rate was 39.3%. These results were similar to the previous studies conducted in Thailand, with microbiological success and mortality rates ranging from 50 to 94.9% and 23.2 to 46.2%[3,6,10]. The independent factors related to poor microbiological response after colistin treatment were prior AKI, AKI severity, pneumonia, *P. aeruginosa* infection, and mixed gram-negative bacterial infection.

An emergence of MDR gram-negative bacilli, such as *P. aeruginosa*, *A. baumannii*, and carbapenem-resistant Enterobacteriaceae, triggered a reintroduction of colistin for treatment of these difficult-to-treat pathogens. Major concerns for using colistin are related to its adverse drug effect, particularly nephrotoxicity and neurotoxicity. Several previous studies reported favorable clinical outcomes (71.7 to 80.8%) of colistin in management of MDR gram-negative infections[3,6]. Apart from clinical efficacy, microbial persistence after treatment is one of major concerns because it can cause recurrent and intractable infections and can be a niche of resistant development[11]. In the present study, prior AKI and its severity before colistin use was one of independent factors associated with failure to microbial eradication after colistin treatment. Patients with AKI may at a high risk for colistin underdosing due to physician concerns of progressive renal impairment during colistin use. However, there is a conflicting evidence regarding to the relationship between colistin dose and treatment outcomes. Several previous studies revealed no significant association between clinical outcomes and giving a loading dose[10], high maintenance daily doses of colistin[12], and parenteral colistin administration (in treatment of lung infection)[13] whereas some demonstrated that systemic use of colistin with high loading and maintenance doses were significantly related to favorable clinical outcomes[14] and optimal plasma concentration for treating MDR gram-negative pathogens[15]. Recent meta-analysis study[16] showed that the administration of a colistin loading dose in patients receiving high maintenance dosage regimens was significantly associated with higher rates of microbiological response, but did not affect clinical cure, mortality or nephrotoxicity risk. However, the majority of previous studies were observational cohorts therefore there are the need for large-scale, randomized controlled trials to determine whether the loading and high maintenance doses of colistin for treatment of MDR gram-negative bacilli have benefit on treatment outcomes outweigh risk of drug adverse effects.

As shown in our study, pneumonia was previously reported to be another factor that link to poor microbiological outcome with colistin treatment for MDR gram-negative bacterial infection[17]. A poor lung penetration following intravenous colistin administration is an obstacle to reach adequate epithelial lining fluid drug concentration. Using nebulized colistin can achieve high lung tissue concentration that necessary for an effective treatment of pneumonia due to MDR gram-negative bacilli and several previous studies reported higher rate of microbiological clearance[18,19]. However, impact of nebulized colistin on clinical cure rate is still controversy. Nebulized colistin may be used as adjunctive

Table 1. Characteristics of patients with microbiological persistence and eradication after colistin treatment

Characteristics	Microbiological persistence n=103	Microbiological eradication n=200	p-value
Age (years), mean±SD	63.8±17.1	62.2±18.9	0.49
Sex, male, n (%)	76 (73.8)	119 (59.5)	0.014
BMI (kg/m^2), mean±SD	22.3±4.39	21.5±5.14	0.18
Underlying diseases, n (%)			
Hypertension	42 (40.8)	73 (36.5)	0.47
Diabetes mellitus	20 (19.4)	57 (28.5)	0.09
Coronary artery disease	14 (13.6)	21 (10.5)	0.43
Stroke	16 (15.5)	20 (10.0)	0.16
Cancer	12 (11.7)	29 (14.5)	0.49
CKD	29 (28.2)	42 (21.0)	0.16
SOFA score, mean±SD	5.81±3.93	4.69±3.44	0.014
SOFA score >8, n (%)	24 (23.3)	24 (12.0)	0.011
eGFR before colistin treatment (ml/min/1.73 m^2), mean±SD	77.4±40.9	86.7±37.8	0.049
Renal function statuses before colistin treatment, n (%)			0.019
Normal renal function	61 (59.2)	149 (74.5)	
AKI with underlying CKD	26 (25.2)	38 (19.0)	
AKI without underlying CKD	13 (12.6)	9 (4.5)	
CKD without AKI	3 (2.9)	4 (2.0)	
AKI staging before colistin treatment, %			0.014
AKI stage 1/2/3	13.6/12.6/11.7	13.0/6.0/4.5	
On mechanical ventilator, n (%)	70 (68.0)	108 (54.0)	0.019
Septic shock, n (%)	21 (20.4)	44 (22.0)	0.75
Serum albumin (g/dL), mean±SD	2.70±0.76	2.60±0.56	0.18
Site of infection, n (%)			
Pneumonia	82 (79.6)	121 (60.5)	0.001
Soft tissue infection	22 (21.4)	44 (22.0)	0.90
Urinary tract infection	5 (4.9)	24 (12.0)	0.045
Septicemia	7 (6.8)	23 (11.5)	0.19
Other sites*	7 (6.8)	8 (4.0)	0.29
Multiple sites of infection, n (%)	19 (18.4)	27 (13.5)	0.26
Type of MDR organisms treated with colistin, n (%)			
Acinetobactor baumannii	85 (82.5)	157 (78.5)	0.41
Pseudomonas aeruginosa	25 (24.3)	27 (13.5)	0.018
Klebsiella pneumoniae	22 (21.4)	24 (12.0)	0.032
Escherichia coli	4 (3.9)	7 (3.5)	1.00
Other gram-negative bacilli**	0 (0.0)	7 (3.5)	0.10
Mixed infection of MDR gram-negative organisms, n (%)	30 (29.1)	22 (11.0)	<0.001
Mixed infection with gram-positive bacteria, n (%)***	1 (0.97)	7 (3.5)	0.27

* Other sites; ascites, bile, septic arthritis, empyema thoracis
** Other gram-negative bacilli; *Acinetobactor lwoffii*, *Enterobactor spp*, *Klebsiella oxytoca*, *Moraxella catarrhalis*
*** Gram positive bacteria; Methicillin-resistant *Staphylococcus aureus*, *Enterococcus faecium*, *Corynebacterium spp.*
BMI = body mass index; SOFA = sequential organ failure assessment; eGFR = estimated glomerular filtration rate; AKI = acute kidney injury; CKD = chronic kidney disease; SD = standard deviation; MDR = multidrug-resistant

Table 1. Cont.

Characteristics	Microbiological persistence n=103	Microbiological eradication n=200	p-value
Dosage of colistin			
% of patients receiving loading dose, n (%)	97 (94.2)	177 (88.5)	0.11
Daily dose (mg/day), mean±SD	255±78	260±74	0.56
Daily dose per body weight (mg/kg), mean±SD	4.47±1.74	4.88±1.71	0.047
Total dose (mg), mean±SD	3,284±2,116	3,186±1,788	0.67
Total dose per body weight (mg/kg), mean±SD	58.0±37.4	59.5±33.3	0.73
Duration of colistin used (days), mean±SD	12.8±7.75	11.8±6.09	0.19
Combined vancomycin	39 (37.9)	71 (35.5)	0.69
Empirical treatment	38 (36.2)	64 (32.3)	0.39
Specific treatment	1 (0.95)	7 (3.5)	0.27
Combined aminoglycoside	3 (2.9)	3 (1.5)	0.41

* Other sites; ascites, bile, septic arthritis, empyema thoracis
** Other gram-negative bacilli; *Acinetobactor lwoffii*, *Enterobactor spp*, *Klebsiella oxytoca*, *Moraxella catarrhalis*
*** Gram positive bacteria; Methicillin-resistant *Staphylococcus aureus*, *Enterococcus faecium*, *Corynebacterium spp.*
BMI = body mass index; SOFA = sequential organ failure assessment; eGFR = estimated glomerular filtration rate; AKI = acute kidney injury; CKD = chronic kidney disease; SD = standard deviation; MDR = multidrug-resistant

Table 2. Length of hospital stay, drug-induced acute kidney injury and mortality outcomes between patients with microbiological persistence and eradication after colistin treatment

Outcomes	Microbiological persistence n=103	Microbiological eradication n=200	p-value
Hospital length stay (days), median (IQR)	41 (24 to 65)	42 (26 to 60)	0.91
AKI after colistin use, n (%)*	47/61 (77.1)	95/149 (63.8)	0.06
28-day mortality after admission, n (%)	31 (30.1)	42 (21.0)	0.08
Mortality rate, n (%)	47 (45.6)	72 (36.0)	0.10

* AKI in participants who had normal renal function before colistin usage
IQR = interquartile range; AKI = acute kidney injury

therapy in non-responders to systemic colistin due to MDR gram-negative bacilli susceptible only to colistin. *P. aeruginosa* infection was found as the risk factor of unfavorable clinical and microbiological clearance from the infected sites, this might be related to an ability of this organism to produce biofilms in many environments leading to ineffective clearance by antibiotics[20]. Furthermore, lipopolysaccharides, a common component of gram-negative bacilli, showed a potent colistin-inhibitory activity which was more potent in *P. aeruginosa* than *E. coli* and *A. baumannii*[21].

Regarding to colistin-induced nephrotoxicity, a recent systematic review and meta-analysis of observational studies revealed that the prevalence of nephrotoxicity was 26.7% (0 to 76.1%)[22]; however the prevalence of this concern colistin adverse effect in the present study was rather high, up to 67.6%. Risk factors of colistin-induced nephrotoxicity include dose and duration of colistin therapy, co-administration with other nephrotoxic drugs, and patients factors such as advanced age, underlying diseases and severity of illness[23]. The reasons underlined extremely high colistin nephrotoxicity in the present study could be multiple factors included elder population, patients' severity, high proportion of combined vancomycin and loading dose administration with long duration of colistin treatment. Therefore, close monitoring of renal function in patients at high risk for colistin nephrotoxicity and colistin dosage adjustment in patients with renal impairment are essential.

Table 3. Univariate and multivariate logistic regression analyses of factors related to microbiological persistence after colistin treatment which the odd ratios (OR) compare between presence and absent of the variables

Variables	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Sex		0.015		0.054
Female	1.0		1.0	
Male	1.92 (1.14 to 3.23)		1.73 (0.99 to 3.01)	
SOFA score >8	2.23 (1.19 to 4.16)	0.012	1.58 (0.77 to 3.25)	0.22
On mechanical ventilator	1.81 (1.10 to 2.98)	0.020	Not included*	
Coagulopathy	2.51 (1.04 to 6.01)	0.040	2.03 (0.76 to 5.41)	0.16
AKI before colistin use	1.98 (1.19 to 3.32)	0.009	Not included*	
Staging of AKI before colistin use				
No AKI	1.0		1.0	
AKI stage 1	1.29 (0.63 to 2.62)	0.487	1.33 (0.63 to 2.81)	0.46
AKI stage 2	2.59 (1.12 to 5.98)	0.026	2.66 (1.09 to 6.49)	0.032
AKI stage 3	3.19 (1.28 to 7.94)	0.013	2.89 (1.11 to 7.52)	0.030
Pneumonia	2.55 (1.46 to 4.45)	0.001	2.02 (1.09 to 3.73)	0.025
Urinary tract infection	0.37 (0.14 to 1.01)	0.053	0.40 (0.13 to 1.22)	0.11
Pseudomonas aeruginosa infection	2.05 (1.12 to 3.77)	0.020	2.40 (1.23 to 4.69)	0.01
Klebsiella pneumoniae infection	1.99 (1.05 to 3.76)	0.034	1.95 (0.99 to 3.84)	0.052
Mixed MDR gram-negative bacterial infection	3.33 (1.80 to 6.14)	<0.001	3.60 (1.86 to 6.96)	<0.001
Daily colistin dose/BW (every increase of 1 mg/kg)	0.87 (0.75 to 0.999)	0.048	0.88 (0.75 to 1.02)	0.09

* Variables were not included in the final model of multivariate analysis
OR = Odds ratio; CI = confidence interval; SOFA = sequential organ failure assessment; AKI = acute kidney injury

This study has several limitations. Due to the nature of a retrospective study design, there may be some missing information that could lead to a selection bias and unaccounted for the confounder such as proportion of participants who had immunocompromised status. Second, we included the patients who received either colistin monotherapy or in combination with other gram-negative bacteria coverage antibiotic, however we did not evaluate the effect of colistin-based combination therapy that could affect the higher microbiological response than colistin monotherapy[24]. Finally, no information on minimal inhibitory concentration of the pathogens and plasma colistin level therefore we cannot determine the effect of these factors that might affect the clinical and microbiological responses with colistin treatment. The strength of our study was enough study subjects to find the factors related with microbiological response outcome and can be referred as external generalization.

Conclusion

Use of colistin for treatment of MDR gram-negative bacilli, particular *A. baumannii* and *P. aeruginosa*, achieved fair microbiological clearance. Factors were related to poor microbiological outcome after colistin therapy for these difficult-to-treat pathogens were prior AKI with its severity, presence of pneumonia, *P. aeruginosa* infection, and mixed gram-negative bacterial infection. Further studies are needed to find new strategies to improve this outcome without increasing drug adverse effects. Colistin induced nephrotoxicity is commonly occur especially in high-risk group therefore closely monitoring renal function and dosage colistin adjustment should be performed.

What is already known on this topic?

Emerging of MDR gram-negative bacterial infection has been ongoing prevalence globally. Although few newly antibiotics were approved and could help for flighting with these pathogens, there are several limitations; therefore, colistin is still a choice of antimicrobial agent for treatment of MDR gram-negative bacterial infection in most countries. Colistin is effective for the treatment but not without risks, particularly nephrotoxicity. Optimal systemic colistin dosing that related to favorable treatment outcomes and less drug adverse effects, is still controversy. Factors that significantly associated with clinical response to colistin use are as follows: use of colistin loading dose and higher colistin dosages, severity of comorbidity, severity of diseases in critically ill patients, severity of sepsis, nephrotoxicity due to colistin therapy. Regard to microbiological outcome, there are evidence that use of parenteral colistin loading dose, colistin-based combination treatment, and inhaled colistin for lung infection

are associated with favorable microbiological outcome but colistin is less effective for microbiological clearance in pneumonia compared to the bacteremia and skin and soft tissue infection.

What this study adds?

The present study demonstrated significantly less likelihood of the microbiological clearance after colistin treatment for infections caused by MDR gram-negative bacteria in patients with having AKI prior to colistin use, pneumonia, infection with *P. aeruginosa*, and mixed gram-negative bacterial infection. Colistin nephrotoxicity is high, especially in high-risk patients. Additionally, this study enrolled more subjects with multiple infectious characteristics than several previous studies, therefore, risk factors of microbiological persistence were assessed in various aspects that can be referred as external generalization.

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Potential conflicts of interest

The authors declare no conflict of interest.

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