ORIGINAL ARTICLE

Colistin-associated nephrotoxicity among patients in intensive care units (ICU) of hospitals in Selangor

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ABSTRACT

Introduction: The increasing trend of extensively drug-resistant gram negative bacteria responsible for nosocomial infections has prompted resurgence colistin usage. Colistin-induced nephrotoxicity is a concern with disparity in the reported rates between previous studies. This study aims to evaluate colistin-induced nephrotoxicity among Malaysian population.

Methods: The medical records of ICU patients receiving colistin therapy in Hospital Serdang and Hospital Sungai Buloh from 2010 to 2012 were retrospectively reviewed. Demographics data, treatment characteristic as well as culture result and creatinine level were documented. Nephrotoxicity was determined based on RIFLE criteria.

Results: A total of 100 patients were included. Median daily dose, cumulative dose and duration of colistin therapy were 3.0 MIU (IQR: 4, range 1-12), 17.8 MIU (IQR: 31.5, range 2-180) and seven days (IQR: 4, range 1-30). Nephrotoxicity was found in 23% of the study population. All cases were reversible but marginally associated with higher mortality. No statistical association exist between age, gender and race as well as administration routes with nephrotoxicity by univariable analysis. The association of dose and duration with nephrotoxicity was also not significant by univariable analysis. After adjustment for confounders, statistical association between the independent variables and dependent variable remains not significant.

Conclusion: Lower dose and shorter duration in local settings contribute to lack of association between colistin therapy and nephrotoxicity in this study. Higher dosing regimen with loading dose application has been introduced in the latest National Antibiotic Guideline. Further evaluation of colistin-induced nephrotoxicity and potential risk factors is therefore warranted.

KEY WORDS:
Colistin, Intensive care units, acute kidney injury, Acinetobacter baumannii, retrospective studies

INTRODUCTION

The emergence of extensively drug-resistant bacterial strain is a challenge in infectious disease therapy. Particularly alarming are gram negatives specifically the extensively drug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* as well as carbapenem resistant enterobactericeae (CRE).[1,2] An international survey of infections in Intensive care units (ICUs) recently reported the overall predominance of gram negatives bacteria among ICU isolates. Significant association between higher risk of mortality and infection with *Acinetobacter species* was also highlighted in the survey.[3] In the meantime, the surveillance of antibiotic resistance by Ministry of Health Malaysia reported more than 50% resistance rate of *Acinetobacter species* against carbapenems in two consecutive years 2013 and 2014.[4] This report indicates that the extensively drug-resistant Acinetobacter species are circulating with considerably high proportion in the country and appropriate treatment strategy is warranted.

Drying of new antibiotic pipeline which is effective against gram negative bacteria has prompted the resurgence usage of older antibiotic group polymyxins.[5] Polymyxins are fermentation product of bacteria *Bacillus polymyxa* consisting five agents with different chemical structure namely polymyxin A, B, C, D and E. Based on efficacy and toxicity profiles, only polymyxin B and E (colistin) are used in clinical practice.[6] Both the antibiotics show excellent and identical in vitro activity against gram negative bacteria.[7] However, they tend to accumulate in renal tissue and cause nephrotoxicity. This adverse effect is due to the ability of the antibiotic to interact electrostatically with membrane cell of the tubular epithelial cell causing disruption of the membrane integrity. Consequently, causes increase in the membrane permeability and influx of cations, anions as well as water followed by cell lysis.[8] Contemporary report relates polymyxin-induced nephrotoxicity with other pathway such as apoptosis of renal tubular cells but the exact mechanism remain uncertain.[9]

Recently, the National Antibiotic Guideline stated that colistin usage by mean DDD/1000 patient days in Malaysian hospitals is higher than polymyxin B and the usage shows gradual increase from year 2011 to 2013.[10] This report is consistent with a global survey on polymyxins usage conducted in 2011 which also reported the use of colistin by majority of respondents.[11] In line with increasing usage, the association between colistin therapy and nephrotoxicity continue to be a major topic in many studies with conflicting findings. Differences in study design and sample size, dosing strategy, patient's comorbidities, patients care and

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monitoring as well as co-administration with other antibiotics and nephrotoxic agents contributed to variability between these study reports.[12]

Due to a narrow therapeutic index, the efficacy and nephrotoxicity of colistin significantly overlapped. However, to improve patient outcome, higher dosing regimen based on pharmacokinetics and pharmacodynamics evaluation is recommended without compromising with the nephrotoxicity effect.[13] As such, this study aims to describe the association between colistin administration and nephrotoxicity among ICU patients in Malaysian hospitals. The intention is to signify whether dosing strategy of colistin currently applied in Malaysian settings predicts the incidence of nephrotoxicity. It is essential to produce the current report of colistin-induced nephrotoxicity as a platform to support the implementation of newly developed dosing standard outlined in the latest National Antibiotic Guideline.[10]

MATERIALS AND METHODS

A retrospective cohort study was conducted in two tertiary hospitals in Selangor, Malaysia (Hospital Serdang and Hospital Sungai Buloh). Simple random sampling method was used and the largest sample size was obtained using Pocok's formula as in the following.

$$n = \frac{p_1(1 - p_1) + p_o(1 - p_o) \times (z\alpha + z\beta)^2}{(p_1 - p_o)^2}$$

n = required sample size
p_1 = expected proportion of colistin usage among patients with nephrotoxicity (expert opinion)[12]
p_o = proportion of colistin usage amongst general population (reported data of year 2009)[14]
$z\alpha$ = confidence level at 95% (standard value of 1.96)
$z\beta$ = 80% power of study (standard value of 0.84)

The sample size calculation:

$$n = \frac{0.10(1 - 0.10) + 0.00095(1- 0.00095)}{(0.10 - 0.00095)^2} \times (1.96 + 0.84)^2$$

$$= \frac{0.09 + 0.00095}{0.0098} \times (2.8)^2$$

$$= 9.28 \times 7.84 = 73$$

Approximately 88 patients were targeted to cater for potential 20% dropout.

73 + (0.2 x 73) = 88

In total, the sample size for patients on colistin to be sampled was:

88 x 2 = 176

Patients admitted to ICU and received colistin therapy from 2010 to 2012 were identified from medical records database. Patient demographic including age, gender and race were documented as well as culture result and serum creatinine level. Reviewed data on colistin treatment includes indication for use, route of administration, duration and dosage. Colistin was dosed as pro-drug colistimethate sodium (CMS) in million international unit (MIU) whereby 1 MIU equals to approximately 80 mg CMS or 30 mg colistin base activity (CBA).[15] Nephrotoxicity in the form of acute kidney injury was defined by comparing peak creatinine level to its baseline value and classification was done based on RIFLE (Risk, Injury and Failure; and Loss; and End-stage kidney disease) criteria. Baseline creatinine is serum creatinine level in mmol/L on admission before starting colistin therapy whereas peak creatinine is the highest serum creatinine level documented during therapy. Serum creatinine level at four weeks and three months after colistin initiation were also recorded. A patient was considered to have nephrotoxicity when he or she had an increase in peak serum creatinine by 1.5 times from baseline (defined as Risk) or doubled (defined as Injury) or had a three times increase (defined as Failure). 'Loss' and 'End-Stage Kidney Disease (ESKD)' were defined as the persistent of acute renal failure for more than four weeks and three months respectively.[16] This study was initially reviewed and approved by the Medical Research Ethical Committee, Ministry of Health (MOH), Malaysia and the Ethical Committee of Faculty of Medicine and Health Sciences, Universiti Putra Malaysia to ensure its conformity to strict research ethics guidelines. The approval letters were dated 11th July 2013 (reference number KKM/NIHSEC/800-2/2/2 Jld2.P13-584(2)) and 18th June 2013 (reference number UPM/TNCP1/RMC/1.4.18.1 (JKEUPM)/F1) respectively.

STATISTICAL ANALYSIS

Appropriate descriptive statistics were used to explore and present variables. Numerical variables were screened for normality of distribution graphically and statistically. The relationship between nephrotoxicity and mortality was analysed by using Pearson's Chi-square. Simple logistic regression was used to determine univariable relationship between each independent variables and dependent variable (nephrotoxicity). Potential factors which might contribute to nephrotoxicity were further analysed using multivariable analysis (multiple logistic regression). Statistical analyses were performed using IBM-SPSS Statistic version 20.0. Significance level is 0.05 and all tests were two-tailed.

RESULTS

A total number of 100 patients fulfilled the inclusion criteria during the study period. Pneumonia was the most common type of infection (47%), followed by sepsis (36%). The main pathogens involved were *A. baumannii* and *P. aeruginosa,* isolated in 71% and 10% of patients respectively. Seventy percent of the isolate from positive culture were sensitive to colistin while the remaining 30% were not tested.

Colistin was administered with mean 3.8 MIU (SD 2.1) and median 3.0 MIU (IQR: 4, range 1-12 MIU) for total daily dose. Mean and median for cumulative dose were 24.7 MIU (SD 26) and 17.8 MIU (IQR: 31.5, range 2-180 MIU), respectively. Meanwhile, mean and median duration were six days (SD 4) and seven days (IQR: 4, range 1-30), respectively. Data distribution is not normal for daily and cumulative dose as well as duration of therapy therefore median is used to express the data.

Table I: Patients' demographic between nephrotoxicity and non-nephrotoxicity groups (n=100 respondents)

Patients' demographic	Nephrotoxicity [n (%)]		Total respondents [n (%)]
	Present	Absent	
Age[a]	48.17 (21.32)	44.69 (19.08)	45.49 (19.56)
Gender			
Female	6 (20.7)	23 (79.3)	29 (29.0)
Male	17 (23.9)	54 (76.1)	71 (71.0)
Race			
Malay	17 (27.0)	46 (73.0)	63 (63.0)
Chinese	1 (10.0)	9 (90.0)	10 (10.0)
Indian	4 (19.0)	17 (81.0)	21 (21.0)
Others	1 (16.7)	5 (83.3)	6 (6.0)

Data are presented as number (%) unless otherwise indicated.
[a] Mean (SD), age in years

Table II: Distribution of treatment characteristics of colistin between nephrotoxicity and non-nephrotoxicity (n=100 respondents)

Treatment Characteristics	Nephrotoxicity [n (%)]		Total respondents [n (%)]
	Present	Absent	
Administration routes			
Intravenous	21 (25.6)	61 (74.4)	82 (82.0)
Nebulized	2 (11.1)	16 (88.9)	18 (18.0)
Dosage, mIU[a]			
Daily dose	3.0 (2.0)	3.0 (4.0)	3.0 (4.0)
Cumulative dose	17.6 (22.0)	18.0 (34.0)	17.8 (31.5)
Duration, days[a]	5.0 (7.0)	7.0 (4.0)	7.0 (4.0)

Data are presented as number (%) unless otherwise indicated.
[a] Median (IQR)

Table III: Associated factors of nephrotoxicity among patients on colistin (n=100 respondents) by simple and multiple logistic regression.

Variables	Univariable analysis[a]			Multivariable analysis[b]		
	Regression coefficient, b	Crude OR (95% CI)	p value	Regression coefficient, b	Adjusted OR (95% CI)	p value
Age	0.009	1.01 (0.99, 1.03)	0.452			
Gender						
Male	-	-	-			
Female	-0.188	0.829 (0.29, 2.37)	0.726			
Race						
Malay	-	-	-			
Chinese	-1.202	0.30 (0.04, 2.55)	0.271			
Indian	-0.451	0.64 (0.19, 2.16)	0.469			
Others	-0.614	0.54 (0.06,4.97)	0.587			
Daily dose	-0.145	0.87 (0.68, 1.11)	0.251	No statistically significant variable even after adjustment for confounders		
Cumulative dose	-0.02	0.99 (0.98, 1.02)	0.811			
Duration	0.031	1.03 (0.93, 1.15)	0.563			
Dosing interval						
OD	-	-	-			
BD	-0.29	0.75 (0.22, 2.52)	0.642			
TDS	-0.26	0.77 (0.26, 2.32)	0.646			
Administration route						
Nebulized	-	-				
Intravenous	1.01	2.75 (0.58, 12.99)	0.201			

[a] Simple Logistic Regression was applied.
[b] Variable selection using Backward, Forward and Stepwise method of multiple logistic regression produced no statistically significant variables.

Nephrotoxicity, as defined per RIFLE criteria, occurred in 23% of patients. They were in the Risk (18%), Injury (3%) and Failure (2%) categories. No patients had long-term kidney failure (Loss and ESKD criteria). Age was sufficiently normally distributed for each nephrotoxicity and non-nephrotoxicity group with equal variance between the groups. There is statistical association between nephrotoxicity and mortality whereby the proportion of deceased in nephrotoxicity group is marginally higher than the proportion of deceased in non-nephrotoxicity group by Pearson's Chi-square test (52.2% vs 29.9%, χ^2= 3.873, p-value= 0.039).

In univariable analysis utilising simple logistic regression, age, gender, race, dose, duration, dosing interval and administration route were analysed as potential contributing variables for nephrotoxicity. However, no statistical significant was established to proof the statistical association. After confounder adjustment in multivariable analysis by multiple logistic regression, significant association remains non-established. Related data are presented in table I to table III.

DISCUSSION

In this retrospective cohort study of 100 patients, colistin dosing in median (IQR) were 3.0 MIU (4) for total daily dose, 17.8 MIU (31.5) for cumulative dose and seven days (4) for duration. The nephrotoxicity rate among the studied population was 23% by RIFLE criteria with all cases that were reversible (no patients develop Loss and ESKD) but marginally associated with higher mortality.

The objective of this study is to observe if colistin dosing regimen predicts the occurrence of nephrotoxicity among the studied population. From the univariable analysis, age, gender, race of patient and administration routes (IV or inhalation) does not significantly associated with nephrotoxicity. Likewise, association of nephrotoxicity with total daily and cumulative dose as well as duration of therapy was not significant by univariable analysis. After adjustment for confounder in multivariable analysis, statistical association between the independent variables (age, gender, race and dosing regimen) and dependent variable (nephrotoxicity) remains not significant.

During the study period, colistin dosing is based on the Malaysian National Antibiotic Guideline 2008. The guideline recommends 3-6 MIU daily dose given 8-hourly with interval adjustment up to 36-hourly for renal impairment.[17] Since Malaysian local hospitals are following this recommendation, total daily and cumulative dose as well as duration of colistin therapy in the current study were significantly lower compared to studies from other countries. This consequently led to lack of association between dosing regimen and nephrotoxicity in our studied population. In the following paragraph, the studies that utilised higher dosing regimen and reported significant association between colistin therapy and nephrotoxicity are briefly reviewed.

A prospective cohort study conducted in Greece involving 21 patients who received intravenous colistin therapy reported increased rate of nephrotoxicity associated with colistin cumulative dose.[18] Colistin was administered with significantly higher dose and longer duration in this study (median daily dose, cumulative dose and duration of 6.0 MIU, 72.0 MIU and 15 days respectively) compare to our study (comparison by one sample sign test: k=6, p-value=0.001, k=5, p-value=0.001 and k=2, p-value=0.001 respectively).

Meanwhile, a study in Florida described the association of excessive colistin dosing with increased rates of nephrotoxicity among 30 patients. The excessive dosing in the study was approximately 19.5 MIU and 10.8 MIU total daily dose for creatinine clearance >80 mL/min and 30-80 mL/min respectively with 65 kg ideal body weight.[19] Relatively, dosing regimen in our study is significantly lower (maximum daily dose is 12 MIU and overall data point was statistically lower than 10.8 MIU, k=1, p-value=0.001 by one sample sign test).

In the meantime, the United States outlined a standard dosing regimen of 5.0 mg/kg CBA daily dose which in a 65 kg patient equal to 10.8 MIU. In a retrospective cohort study conducted in USA, colistin dose-dependent nephrotoxicity with significantly higher daily doses among patients who develop nephrotoxicity was described (median daily dose 11.9 vs 8.3 MIU for patient with body weight 65 kg).[20] Again, colistin total daily dose in our study is significantly lower compare to this study (nephrotoxicity group: median 3.0 vs 11.9 MIU, k=0, p-value=0.001 and non-nephrotoxicity group: median 3.0 vs 8.3 MIU, k=5, p-value=0.001 by one sample sign test).

Another study conducted in Thailand also reported significantly higher daily dose (median 6.7 vs 5.0 MIU, p-value=0.001) and longer duration (median 14.0 vs 6.5 days, p-value=0.001) between nephrotoxicity and non-nephrotoxicity group among 139 subjects with IV colistin.[21] Colistin duration in the non-nephrotoxicity group of this study is not significantly different from our study (median 7.0 vs 6.5 days, k=37, p-value=0.821). However, daily dose among non-nephrotoxicity and nephrotoxicity as well as duration in nephrotoxicity group are significantly lower in our study (3.0 vs 5.0 MIU, k=24, p-value=0.001; 3.0 vs 6.7 MIU, k=0, p-value=0.001 and 5.0 vs 14.0 days, k=1, p-value=0.001, respectively) by one sample sign test.

Upon benchmarking with the above mentioned studies, we concluded that colistin was administered in a considerably lower dose and shorter duration in Malaysian settings during this study period. As such, dosing regimen does not present as risk factor for nephrotoxicity among the studied population. This fact is further supported by a study conducted in Israel involving mean total daily dose 6.1 MIU and median treatment duration 10 days with no significant of colistin-associated nephrotoxicity.[22] Our total daily dose and treatment duration are significantly lower when compare to this study (k=6, p-value=0.001 and k=11, p-value=0.001 respectively by one sample sign test) suggesting that colistin-associated nephrotoxicity is similarly unlikely with our treatment regimens.

However, other factors including patient's comorbidities and concomitant use of other nephrotoxic agents are also potential confounders predicting nephrotoxicity. In a retrospective study involving 49 critically ill ICU patients from Ohio, hypertension and chronic kidney disease were described as significant risk factors contributing to nephrotoxicity during colistin therapy. In addition, higher risk of nephrotoxicity with concomitant use of intravenous contrast material during colistin therapy was also reported. Meanwhile, concomitant use of at least two additional nephrotoxic agents significantly increased the odds ratio to 6.5 times chance of developing colistin-induced nephrotoxicity.[23] Regrettably, data on patient comorbidities and concomitant use of other nephrotoxic agents were not collected in this study, thus their confounding effect was not evaluated. Due to the disparity in regards to dosing regimen between the current study and studies from other countries, contribution of other risk factors in predicting nephrotoxicity among our studied population is probable. As such, related data should be included in future study.

Nevertheless, higher dosing regimen has been outlined in the latest Malaysian National Antibiotic Guideline suggesting the application of a loading dose of 7-9 MIU followed by 9 MIU daily maintenance dose.[10] The intention is to enhance efficacy of colistin by rapid attainment of steady state level and to prevent the emergence of bacterial resistance.[24-26] This is based on theoretical back ground that the older dosing regimen is associated with suboptimal serum concentration of colistin, poor treatment outcome and development of resistant bacterial strains.[27,28] However, the newly introduced dosing strategy raises concerns of colistin-induced nephrotoxicity and warrant further evaluation on it prevalence and severity.

Among the limitations of our study include its retrospective nature with higher tendency of getting missing data. In addition, confounders such as patient's comorbidities and concomitant use of other nephrotoxic agents were not included which result in potential information bias. Finally, the power of study achieved with the collected sample size is 62% only instead of 80% based on post hoc power analysis. Follow up study utilising larger sample size is therefore recommended.

CONCLUSION

This study described no significant relationship between colistin dosing regimen and incidence of nephrotoxicity in Malaysian local hospitals. Lower dose and shorter duration of the treatment applied in local settings might contribute to the finding which inconsistent with reports from other countries. Latest updates of the Malaysian National Antibiotic Guideline has suggested higher dosing regimen with loading dose application. Further evaluation of colistin-induced nephrotoxicity among Malaysian population with larger sample size is necessary with the implementation of the new dosing regimen. Other possible factors that may influence the outcome should also be considered in future study.

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