TREATMENT AND CLINICAL OUTCOME OF COLISTIN-RESISTANT *KLEBSIELLA PNEUMONIAE* BACTEREMIA PATIENTS

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Abstract. In recent years, emergence of carbapenem-resistant (CR*KP*) and colistin-resistant *Klebsiella pneumoniae* (CoR*KP*) has become one of the leading causes of nosocomial infection worldwide and is a public health concern due to few available treatment options and high mortality. Here, 14-day and in-hospital mortalities of patients infected with CR*KP* and CoR*KP* were investigated as well as treatment regimen for salvage therapy and risk factors of in-hospital bacteremia mortality from 1 January 2016 to 31 December 2018. Patients (n = 96) with bacteremia were classified into three groups, namely, those with non-CR*KP* (n = 58), CR*KP* (n = 10) and CoR*KP* (n = 28). The 14-day mortality rate of patients infected with non-CR*KP*, CR*KP* and CoR*KP* was 12, 40 and 61%, respectively and in-hospital mortality 24, 70 and 82%, respectively, with statistically significant difference between non-CR*KP* and the drug-resistant groups (p-value < 0.05). The treatment regimen associated with a favorable outcome on the 14-day survival rate in bacteremia patients due to CoR*KP* was gentamicin or amikacin combined with fosfomycin with or without tigecycline. Chronic kidney disease, admission to intensive care unit and Pitt score ≥4 were associated with in-hospital mortality among CoR*KP* patients. In conclusion, patients infected with CoR*KP* were of the highest mortality. However, the aminoglycosides/fosfomycin combination with or without tigecycline appeared to be a desirable clinical outcome for bacteremia patients due to CoR*KP*.

Keywords: *Klebsiella pneumoniae*, bacteremia, carbapenem resistance, colistin-resistance, clinical outcome

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INTRODUCTION

In recent years, the emergence of colistin-resistant *Klebsiella pneumoniae* (CoR*KP*) has become one of the leading causes of nosocomial infection worldwide (Jayol *et al*, 2018). Infection with

K. pneumoniae is a public health problem in many regions of the world due to difficulty of treating this infection (Machuca et al, 2017). Colistin is the antibiotic of last resort to treat multidrug-resistant Gram-negative bacterial infections and emergence of resistance to colistin leaves clinicians with few therapeutic options of treatment resulting in high mortality (Capone *et al*, 2013; Rossi *et al*, 2016). To date, the data regarding CoR*KP* salvage therapy are limited (Machuca *et al*, 2017).

This study investigated the situation of CoR*KP* problem in a hospital in Bangkok, Thailand by collecting data regarding 14-day and in-hospital mortality, treatment regimens for salvage therapy in CoR*KP*-infected patients and risk factors for in-hospital mortality. The results of this study would raise the healthcare workers' awareness of CoR*KP*-infected patients leading to the regimens to improve a clinical outcome and decrease patient mortality.

MATERIALS AND METHODS

Participants' recruitment

This was a single center retrospective cohort study conducted from 1 January 2016 to 31 December 2018. Patients (n = 96) with *K. pneumoniae* bacteremia at Phramongkutklao Hospital, Bangkok, Thailand were classified into three groups, namely, those infected with CoR*KP*, those infected with carbapenem-resistant *K. pneumoniae* (CR*KP*) and those infected with non-carbapenem-resistant *K. pneumoniae* (non-CR*KP*).

Data collection

Clinical information was gathered of infected patients regarding age, sex, Charlson Comorbidity Index, diagnosis, admitting ward, shock, appropriate empirical therapy, treatment regimen, duration of antibiotic treatment, and 14-day mortality. Empirical therapy is defined as treatment administered within the first 24 hours following result of blood culture and prior to determination of antibiotic susceptibility. Treatment was considered appropriate when isolate was susceptible *in vitro* to at least one of the prescribed antibiotics. Treatment regimen, 14-day mortality and in-hospital mortality (mortality during hospitalization) were reviewed and compared. Treatment regimens associated with 14-day survival rate in patients with CoR*KP* bacteremia and factors associated with in-hospital mortality were subjected to univariate and multivariate statistical analysis.

This study was reviewed and approved by Ethics Committee of the Royal Thai Army Medical Department with the Certificate of Ethical Approval No. Q023b/61.

RESULTS

During the study period, 96 bacteremia patients due to *K. pneumoniae* were observed, of which 58, 10 and 28 were due to non-CR*KP*, CR*KP* and CoR*KP* strains, respectively. Most of patients were men, the median of age was 66 years, source of bacteremia initiated from primary bacteremia and catheter-related infection. The number of ICU admission, Pitt bacteremia score (indicated for severity during bloodstream infection), Charlson Comorbidity Index score, septic shock and inappropriate empirical antibiotic in CoR*KP*-infected groups were higher than CR*KP*- or non-CR*KP*-infected groups. The general characteristic of bacteremia patients infected with CoR*KP* were presented in Table 1. In-hospital and 14-day mortality rates of patients infected with CoR*KP* or CR*KP* are significantly

Table 1
Profile of patients with *Klebsiella pneumoniae* bacteremia at Phramongkutklao Hospital, Bangkok, Thailand (1 January 2016 to 31 December 2018).

Characteristic/antibiotic therapy	non-CR*KP* ($n = 58$)	CR*KP* ($n = 10$)	CoR*KP* ($n = 28$)
Age, median (IQR), years	65 (57-81)	62 (52-76)	66 (61-79)
Male *n* (%)	40 (69)	4 (40)	18 (64)
Source of bacteremia *n* (%)			
Urinary tract	4 (7)	1 (10)	0 (0)
Intra-abdominal	9 (15)	0 (0)	2 (7)
Vascular catheter-related infection	8 (14)	1 (10)	9 (32)
Pneumonia	7 (12)	0 (0)	4 (14)
Skin and soft tissue	3 (5)	0 (0)	1 (3)
Unknown	26 (45)	8 (80)	12 (43)
Others	1 (2)	0 (0)	0 (0)
Surgery within past 7 days *n* (%)	0 (0)	1 (10)	2 (7)
ICU admission *n* (%)	17 (29)	5 (50)	19 (67)
Charlson Comorbidity Index score, median (IQR)	2.0 (1.0-4.0)	2.5 (1.8-4.0)	3 (1.3-4)
Chronic kidney disease *n* (%)	9 (15)	2 (20)	7 (40)
Pitt bacteremia score, median (IQR)	1.0 (0.0-5.0)	3.5 (1.8-5.0)	5.0 (4.2-6.7)
Neutropenia *n* (%)	5 (9)	1 (10)	4 (14)
Septic shock *n* (%)	24 (41)	5 (50)	22 (78)
Inappropriate empirical antibiotic prescription *n* (%)	10 (17)	5 (50)	23 (82)
Prior antibiotic use *n* (%)			
Fluoroquinolones	1 (2)	1 (10)	5 (18)
Cephalosporins	14 (24)	3 (30)	18 (64)
Carbapenems	2 (3)	6 (60)	26 (93)
Colistin	1 (2)	1 (10)	15 (53)
Monotherapy *n* (%)	58 (100)	-	-
Combination therapy *n* (%)	-	10 (100)	28 (100)
Plus colistin	3 (5)	9 (90)	11 (39)
Minus colistin	-	-	17 (61)
Fluoroquinolone-based	2 (3)	-	1 (3)
Cephalosporin-based	34 (59)	-	-
β-lactam/β-lactamase inhibitor-based	3 (5)	-	-
Carbapenem-based	16 (27)	-	-
AG-based	-	1 (10)	8 (28)
AG + FOF	-	-	3 (11)
AG + TGC	-	-	3 (11)
AG + FOF + TGC	-	-	2 (7)
AG + others*			
Treatment duration, median (IQR), days	14 (8-17)	11 (7-14)	11 (4-16)

* Sulbactam + ciprofloxacin or imipenem; AG: aminoglycoside; CoR*KP*: colistin-resistant *K. pneumoniae*; CR*KP*: carbapenem-resistant *K. Pneumonia*; FOF: fosfomycin; IQR: interquartile range; TGC: tigecycline.

higher than those of non-CR*KP*-infected patients, but not different between CoR*KP*- and CR*KP*-infected groups (Table 2); however, only microbiological failure is significantly higher in CoR*KP*-compared to non-CR*KP*-infected patients. Patients with bacteremia due to CoR*KP* have significantly better 14-day survival rate when treated with antibiotic combination therapy without colistin than those with colistin-containing drug therapy (Table 3). It is worth pointing out patients were treated empirically by the attending physician prior to knowledge of the antibiogram profile of the infecting *K. pneumoniae* isolate. The small number of patients precluded any statistical analysis of the efficacy among the antibiotic combination therapy prescribed. Multivariate analysis revealed only chronic kidney disease, admission to intensive care unit and Pitt bacteremia score (≥4) were significant independent parameters associated with in-hospital mortality of CoR*KP*-infected patients (Table 4).

Table 2
Clinical outcome of patients with *Klebsiella pneumoniae* bacteremia at Phramongkutklao Hospital, Bangkok, Thailand (1 January 2016 to 31 December 2018).

Clinical outcome	Number (%)			*p*-value		
	Non-CR*KP* ($n = 58$)	CR*KP* ($n = 10$)	CoR*KP* ($n = 28$)	Non-CR*KP* *vs* CR*KP*	Non-CR*KP* *vs* CoR*KP*	CR*KP* *vs* CoR*KP*
14-day mortality	7 (12)	4 (40)	17 (61)	0.049	<0.05	0.293
In-hospital mortality	14 (24)	7 (70)	23 (82)	0.007	<0.05	0.411
Microbiological failure*	2 (6)	2 (33)	9 (53)	0.104	<0.05	0.640

* The number of patients available for evaluating microbiological failure in Non-CR*KP*, CR*KP* and CoR*KP* were 33, 6 and 17, respectively.
CoR*KP*: colistin-resistant *K. pneumoniae*; CR*KP*: carbapenem-resistant *K. pneumoniae*.

DISCUSSION

The study clearly showed 14-day survival rate of patients with bacteremia from CoR*KP* infection was significant poorer when placed on a colistin-containing combination antibiotic regimen. As the decision as to the type of drug combination prescribed was made prior to knowledge of the colistin resistance status of the infecting organism, intravenous treatment should be switched to a non-colistin-containing drug regimen once informed. Treatment with colistin-based regimen has a potential for nephrotoxicity and neurotoxicity (Spapen *et al*, 2011). In a hospital outbreak of colistin-resistant, NDM-1- and OXA-

Table 3
Antibiotic regimen and 14-day survival of patients with colistin-resistant *Klebsiella pneumoniae* (CoR*KP*) bacteremia at Phramongkutklao Hospital, Bangkok, Thailand (1 January 2016 to 31 December 2018).

Antibiotic regimen	14-day survival rate (%)	*p*-value
Combination with colistin	1/11 (9)	< 0.05*
Combination without colistin	10/17 (59)	
- Fluoroquinolone-based combination	1/1 (100)	
- AG-based combination	9/16 (56)	
AG + FOF	3/8 (37)	
AG + TGC	1/3 (33)	
AG + FOF + TGC	3/3 (100)	
AG + others#	2/2 (100)	

* *p*-value <0.05 when compared between combination with and without colistin
# Sulbactam + ciprofloxacin or imipenem
AG: aminoglycoside; FOF: fosfomycin; TGC: tigecycline.

Table 4
Multivariate analysis of factors associated with in-hospital mortality of patients with *Klebsiella pneumoniae* bacteremia at Phramongkutklao Hospital, Bangkok, Thailand (1 January 2016 to 31 December 2018).

Factor	Unstandardized Coefficient	Multivariate analysis		
		p-value*	OR	95% CI
Age	-0.039	0.180	0.961	0.907-1.018
Source of infection	-0.181	0.532	0.835	0.474-1.471
Type of infection	1.100	0.559	3.004	0.075-120.3
Chronic kidney disease	-3.160	0.022	0.042	0.003-0.639
ICU admission	-2.148	0.037	0.117	0.015-0.879
Pitt bacteremia score	-0.636	0.006	0.529	0.337-0.830
Neutropenia	-2.318	0.267	0.098	0.002-5.911
Septic shock	-1.539	0.199	0.215	0.020-2.247
Inappropriate empirical antibiotic treatment	-0.694	0.597	0.500	0.038-6.545
Prior antibiotic use	0.257	0.556	1.293	0.550-3.040
Pattern of antibiotic treatment	-5.598	0.091	0.004	0.000-2.461
Duration of antibiotic treatment	-0.014	0.766	0.986	0.897-1.083

* Significance at $p < 0.05$.

48-producing *K. pneumoniae*, there is 100% mortality in infected-patients treated with meropenem (Guducuoglu *et al*, 2018). An analysis of a randomized clinical trial among patients with colistin-resistant isolates indicated colistin monotherapy is associated with a better outcome compared to colistin-meropenem

combination therapy, possibly owing to meropenem-associated gene expression of the organism leading to increased virulence and elevated resistance to colistin (Dickstein *et al*, 2019). In patients with CoR*KP* and high meropenem resistance treatment a combination of tigecycline and fosfomycin or gentamicin resulted in a mortality of 30% compared to 44% with monotherapy (Machuca *et al*, 2017). A patient with CoR*KP* ventilator-associated pneumonia treated with a high dose tigecycline plus fosfomycin and colistin shows improvement after none days and treatment is discontinued 15 days later (Viaggi *et al*, 2015).

These findings as well as those in the present study indicate therapy for CoR*KP* infection should be combination of antibiotics rather than monotherapy. The suggested appropriate regimen is a combination of fosfomycin and an aminoglycoside (amikacin or gentamicin depending on the organism susceptibility status) with or without tigecycline as they demonstrate (*in vitro*) synergistic activity (Prawang *et al*, 2019) and achieve clinically desirable outcome compared to other regimens. Machuca *et al* (2017) reported lowest mortality rate using a combination of tigecycline, gentamicin and fosfomycin in treating CoR*KP* bacteremia. A combination therapy provides a new hope to treat infection with colistin-resistant bacteria when new antibiotics are not yet available for multi-drug resistant pathogens that continue to cause dramatic public health problems worldwide.

The daily dose of fosfomycin used in the study ranged from 8-16 mg iv q8-12H. Although synergism of tigecycline and gentamicin in the previous study was limited in extent, no antagonistic activity is observed (Prawang *et al*, 2019). Clinically desirable outcome achieved using this drug combination in CoR*KP*-infected patient might be beneficial in settings where fosfomycin is not available or with few therapeutic options. However, pharmacokinetics/pharmacodynamics (PK/PD) of high dose tigecycline (100 mg iv q12H) in bacteremia and pneumonia should be performed because of low tigecycline blood levels in these situations (De Pascale *et al*, 2014). In addition, therapeutic drug monitoring should be performed when aminoglycosides are administered to patients to obtain optimal PK/PD profiles yielding improved outcome (Wong *et al*, 2014).

Chronic kidney disease, admission to intensive care unit (ICU) and Pitt score ≥4 were factors associated with in-hospital mortality among bacteremia patients infected with CoR*KP*. ICU admission is observed as a risk factor for 30-day mortality of the patients infected with CoR*KP* bacteremia (Machuca *et al*, 2017). ICU admission and chronic kidney disease were the risk factors for in-hospital mortality in bacteremia patients due to CoR*KP* because both of them always play a pivotal role in the development of bacterial severe infection (Giacobbe *et al*, 2015).

In summary, the study demonstrates a combination of fosfomycin with an aminoglycoside, such gentamicin, with or without tigecycline appeared to be an acceptable regimen for patients infected with colistin-resistant *K. pneumoniae* bacteremia resulting in reduced 14-day mortality rate. Chronic kidney disease, ICU admission and Pitt score ≥4 were risk factors associated with in-hospital mortality in colistin-resistant *K. pneumoniae*-infected patients. Thus, restricting colistin treatment and promoting rationale antimicrobial should

be encouraged in clinical practice to decrease incidence of CoR*KP* bacteremia.

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REFERENCES

Capone A, Giannella M, Fortini D, *et al*. High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality. *Clin Microbiol Infect* 2013; 19: E23-30.

De Pascale G, Montini L, Pennisi M, *et al*. High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria. *Critical Care* 2014; 18: R90.

Dickstein Y, Lellouche J, Ben Dalak Amar M, *et al*. Treatment outcomes of colistin and carbapenem-resistant *Acinetobacter baumannii* infections: an exploratory subgroup analysis of randomized clinical trial. *Clin Infec Dis* 2019; 69: 769-76.

Giacobbe DR, Del Bono V, Trecarichi EM, et al. Risk factors for bloodstream infections due to colistin-resistant KPC-producing *Klebsiella pneumoniae*: results from a multicenter case-control-control study. *Clin Microbiol Infect* 2015; 21: 1106.e1-8.

Guducuoglu H, Gursoy N, Yakupogullari Y, *et al*. Hospital outbreak of a colistin-resistant, NDM-1- and OXA-48-producing *Klebsiella neumoniae*: high mortality from pandrug resistance. *Microbial Drug Resist* 2018; 24: 966-72.

Jayol A, Nordmann P, Poirel L, Dubois V. Ceftazidime/avibactam alone or in combination with aztreonam against colistin-resistant and carbapenemase-producing *Klebsiella pneumoniae*. *J Antimicrob Chemother* 2018; 73: 542-4.

Machuca I, Gutierrez-Gutiérrez B, Gracia-Ahufinger I, *et al*. Mortality associated with bacteremia due to colistin-resistant *Klebsiella pneumoniae* with high-level meropenem resistance: importance of combination therapy without colistin and carbapenems. *Antimicrob Agents Chemother* 2017; 61. pii: e00406-17.

Prawang A, Santimaleeworagun W, Changpradub D, Thunyaharn S, Puttilerpong C. *In vitro* antibiotic synergy colistin-resistant *Klebsiella pneumoniae*. *Southeast Asean J Trop Med Public Health* 2019; 50: 703-7.

Rossi G, Ferreira M, Araujo B, *et al*. Outbreaks of colistin-resistant and colistin-susceptible KPC-producing *Klebsiella pneumoniae* in a Brazilian intensive care unit. *J Hosp Infect* 2016; 94: 322-9.

Spapen H, Jacobs R, Van Gorp V, Troubleyn J, Honoré PM. Renal and neurological side effects of colistin in critically ill patients. *Ann Intensive Care* 2011; 1: 14.

Viaggi B, Sbrana F, Malacarne P, Tascini C. Ventilator-associated pneumonia caused by colistin-resistant KPC-producing *Klebsiella pneumoniae*: a case report and literature review. *Respir Investig* 2015; 53: 124-8.

Wong G, Sime FB, Lipman J, Roberts JA. How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients? *BMC Infect Dis* 2014; 14: 288.