

Article

Pharmacokinetic/Pharmacodynamic (PK/PD) Simulation for Dosage Optimization of Colistin Against Carbapenem-Resistant *Klebsiella pneumoniae* and Carbapenem-Resistant *Escherichia coli*

Kamonchanok Jitaree ¹, Korbtham Sathirakul ¹ , Jantana Houngsaitong ¹, Orarik Asuphon ², Weerayuth Saelim ³, Visanu Thamlikitkul ^{4,*} and Preecha Montakantikul ^{5,*}

¹ Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand

² Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok 65000, Thailand

³ Department of Pharmacy, Faculty of pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand

⁴ Division of Infectious Disease and Tropical Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

⁵ Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand

* Correspondence: visanu.tha@mahidol.ac.th (V.T.); preecha.mon@mahidol.ac.th (P.M.); Tel.: +66-2-419-7767-69 (V.T.); +66-2644-8694 (P.M.)

Received: 17 July 2019; Accepted: 16 August 2019; Published: 22 August 2019



Abstract: The purpose was to explore the optimal dosage regimen of colistin using Monte Carlo simulations, for the treatment of carbapenem-resistant *Klebsiella pneumoniae* and carbapenem-resistant *Escherichia coli* based on PK/PD targets in critically ill patients. A total of 116 carbapenem-resistant *K. pneumoniae* and *E. coli* were obtained from various clinical specimens at Siriraj Hospital in Bangkok, Thailand. Minimum inhibitory concentrations (MICs) of colistin were determined by broth microdilution method. Monte Carlo simulation was used to calculate the cumulative fraction of response (CFR) for European Medicine Agency (EMA), US-Food and Drug Administration (FDA), Nation et al., Siriraj Hospital and our study regimens. The targeted CFR was 90%. For colistin-susceptible *K. pneumoniae*, all of the dosage regimens achieved $\geq 90\%$ CFR in patients with creatinine clearance < 80 mL/min except the FDA-approved regimens for patients with creatinine clearance 51–79 and 11–29 mL/min, respectively. While, patients with creatinine clearance ≥ 80 mL/min, CFR $\geq 90\%$ was observed in Siriraj Hospital and our study regimen. For colistin-susceptible *E. coli*, all of the dosage regimens achieved $\geq 90\%$ CFR regardless of renal function. In contrast, the currently approved regimens achieved CFR target in only 10–50% for colistin-resistant isolates subgroup. These results suggest that currently approved regimens still recommended for colistin-susceptible CRE. For colistin-resistant CRE, alternative approaches such as high dose or combination therapy should be considered.

Keywords: colistin; Monte Carlo simulation; pharmacokinetics; pharmacodynamics; carbapenem-resistant *Klebsiella pneumoniae*; carbapenem-resistant *Escherichia coli*

1. Introduction

Worldwide emergence of carbapenem-resistant gram-negative bacteria, and particularly carbapenem-resistant Enterobacteriaceae (CRE) have become a major concern [1]. Specifically, carbapenem-resistant *Klebsiella pneumoniae* and carbapenem-resistant *Escherichia coli* which most commonly cause hospital acquired infections like intra-abdominal infections, urinary tract infections,

nosocomial pneumonia, and bloodstream infections with high mortality rate of 44% to 70% [2,3]. In Thailand, the prevalences of carbapenem-resistant *K. pneumoniae* as well as carbapenem-resistant *E. coli* were approximately 2–10% in 2017 and these had rapidly increased from 0.3–0.8% in 2010 [4–6]. Concomitantly, there has been a shortage of newer antibiotics to fight multidrug-resistant (MDR) bacteria development. This has led to re-emergence of previously used old antibiotics like colistin.

Colistin has been developed as a mainstay of treatment for patients infected by carbapenem-resistant Enterobacteriaceae [7,8]. Although, optimal dosage regimen for colistin has been unclear because accurate pharmacodynamic and pharmacokinetic information are lacking. However, recent studies have improved our understanding about the pharmacokinetic/pharmacodynamic (PK/PD) which has guided us to selecting suitable colistin dosage regimen to treat carbapenem-resistant Enterobacteriaceae infections [7–9]. Suitable dosing strategies has lead to maximize the clinical efficacy, and to reduce the developing bacterial resistance rate, morbidity and mortality.

This study aimed to explore the optimal dosage regimen of colistin using Monte Carlo simulations, for the treatment of carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli* based on PK/PD targets in critically ill patients.

2. Materials and Methods

2.1. Microbiology

Carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli* were obtained from various clinical specimens (sputum, urine, skin and soft tissue, blood, and pleural fluid) which were submitted for culture to the microbiological laboratory at the Faculty of Medicine at Siriraj Hospital in Bangkok, Thailand. The isolates were collected between June 2011 and September 2016. The Carbapenem-resistant Enterobacteriaceae (CRE) phenotype was identified for isolates expressing non-susceptible (intermediate or resistant) to any carbapenem antibiotics or documented to produce carbapenemase. Minimum inhibitory concentrations (MICs) of colistin were determined by the broth microdilution method in cation-adjusted Mueller-Hinton II broth (CA-MHBII) according to Clinical and Laboratory Standards Institute (CLSI) guidelines [10]. Colistin was tested over a range of dilutions from 0.25 mcg/mL to 128 mcg/mL. *Escherichia coli* ATCC 25922 was used as a control. Isolate preparation was performed following the Clinical and Laboratory Standards Institute protocol (CLSI) [10]. The MIC value was defined as the lowest drug concentration for which the well was optically clear. The breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (MIC $\leq$ 2 mcg/mL) were applied to interpret those for colistin [11].

2.2. Pharmacokinetic Model

The population pharmacokinetic model for colistimethate sodium (CMS) and colistin were two-compartment and one-compartment models, respectively. Pharmacokinetic data from Nation et al. [12] was retrieved from previously published studies concerning critically ill patients. Table 1 a set of parameters was randomly generated for each mean and standard deviation of the parameters. Equations (1)–(3) below represent the differential equations for the disposition of CMS and colistin.

$$\frac{d\text{CMS}_{\text{c}}}{dt} = R_1 - \text{CLD}_1 \times \left(\frac{\text{CMS}_{\text{c}}}{V_1} - \frac{\text{CMS}_{\text{p}}}{V_2} \right) - \left(\text{CLT}_{\text{cms}} \times \frac{\text{CMS}_{\text{c}}}{V_1} \right) \quad (1)$$

$$\frac{d\text{CMS}_{\text{p}}}{dt} = \text{CLD}_1 \times \left(\frac{\text{CMS}_{\text{c}}}{V_1} - \frac{\text{CMS}_{\text{p}}}{V_2} \right) \quad (2)$$

$$\frac{d\text{Colistin}}{dt} = \left(\text{CLNR}_{\text{cms}} \times \frac{\text{CMS}_{\text{c}}}{V_1} \right) - \left(\text{CLT}_{\text{c}} \times \frac{\text{Colistin}}{V_3} \right) \quad (3)$$

CMS_c = mass of CMS in the central compartment, CMS_p = mass of CMS in the peripheral compartment, Colistin = mass of colistin in the single compartment, V₁ = central volumes for CMS, V₂ = peripheral volumes for CMS, V₃ = volume of distribution for colistin, R (1) = infusion rate of CMS,

CLD1 = distributional clearance between the central and peripheral compartments for CMS. CLT_{cms} = total intrinsic clearance for CMS, CLT_c = total intrinsic clearance for colistin and CLNR_{cms} = nonrenal clearance for CMS.

Table 1. Population pharmacokinetic parameters.

Category	Parameter	Units	Estimate	%SE	%IIV
CMS	V1	L	12.9	-	40.4
	V2	L	16.1	-	70.9
	CLD1	L	9.57	10.5	80.1
	CLR	L/h/CrCL	0.0340	6.85	75.2
	CLNR _{CMS}	L/h	2.52	3.71	39.8
Colistin	V3	L	57.2	5.13	43.5
	CLT _C	L/h	3.59	-	37.9
	CLR _C	L/h/CrCL	0.00834	27.7	-
	CLNR _C	L/h	3.11	4.38	-

V1 = Central volume for CMS, V2 = Peripheral volume for CMS, CLD1 = Distributional clearance between the central and peripheral compartments for CMS, CLR = Renal clearance of CMS, CLNR_{CMS} = Non-renal clearance of CMS, V3 = Volume of distribution of formed colistin, CLT_C = Total clearance of colistin, CLR_C = Renal clearance of colistin, CLNR_C = Non-renally of colistin clearance, %SE = The standard error or the precision of the estimates, %IIV = The inter-individual variability in the population, CrCL = creatinine clearance.

2.3. Pharmacodynamic Model

The pharmacodynamic (PD) surrogate indices for colistin are characterized by area under the unbound colistin plasma concentration-time curve to the minimum inhibitory concentration (*f*AUC/MIC) [13,14]. PK/PD targets were defined as *f*AUC/MIC ≥ 25 [13]. The trapezoidal rule was used to calculate AUC, then *f*AUC was divided by the MIC to obtain the value for the desired PK/PD index. A colistin unbound fraction of 50% was used [15]. The regimen administrated using IV infusions (infused over 30 min) were simulated over a 24-h period at different levels of renal function. The ranges of creatinine clearance (CrCL) used were ≥ 80 , 51 to 79, 30 to 50, 11 to 29 and ≤ 10 mL/min.

The regimens were chosen by using European Medicine Agency (EMA), US-Food and Drug Administration (FDA), Nation et al., Siriraj Hospital and our study regimens Tables 2 and 3 [12,16–18].

Table 2. Colistin dosage regimens for Simulations.

Creatinine Clearance	Daily Dose (CBA)	
≥ 80 mL/min	150 mg every 8 h	Siriraj Hospital regimen
	180 mg every 12 h	Nation, et al. regimen
	150 mg every 12 h	EMA-approved regimen FDA-approved regimen
51 to 79 mL/min	150 mg every 12 h	EMA-approved regimen
		Siriraj Hospital regimen
	114 mg every 12 h	Nation, et al. regimen FDA-approved regimen
30 to 50 mL/min	125 mg every 12 h	EMA-approved regimen
	110 mg every 12 h	Nation, et al. regimen
	150 mg every 24 h	FDA-approved regimen
	100 mg every 12 h	Siriraj Hospital regimen
11 to 29 mL/min	180 mg every 24 h	Nation, et al. regimen
	150 mg every 24 h	EMA-approved regimen
	60 mg every 24 h	Siriraj Hospital regimen FDA-approved regimen
≤ 10 mL/min	150 mg every 24 h	Nation, et al. regimen
	120 mg every 24 h	EMA-approved regimen
	60 mg every 24 h	FDA-approved regimen

Table 3. Our study regimens for Simulations.

Creatinine Clearance	Daily Dose (CBA)
≥ 80 mL/min	180 mg every 8 h
51 to 79 mL/min	180 mg every 8 h
	150 mg every 8 h
	180 mg every 12 h
	100 mg every 8 h
30 to 50 mL/min	180 mg every 8 h
	150 mg every 8 h
	180 mg every 12 h
	150 mg every 12 h
	100 mg every 8 h
11 to 29 mL/min	180 mg every 8 h
	180 mg every 12 h
	150 mg every 12 h
	150 mg every 8 h
≤ 10 mL/min	180 mg every 8 h
	150 mg every 8 h
	100 mg every 8 h
	180 mg every 12 h
	150 mg every 12 h
	100 mg every 12 h
	180 mg every 24 h

CBA = colistin base activity, EMA = European Medicine Agency, FDA = US-Food and Drug Administration. All of regimens were infused over 30 min.

2.4. Monte Carlo Simulation

Monte Carlo Simulation (Crystal Ball version 2017; Decisioneering Inc., Denver, CO USA) was conducted to generate 10,000 subjects for IV dosage regimens of colistin based on the linear pharmacokinetic behavior. The $fAUC/MIC$ following multiple intravenous doses of various regimens was determined for the profile of each individual. Log-normal distributions were studied for between-patient variability. Probability of target attainment (PTA) was determined as the percentage of all 10,000 estimates which achieved or exceeded pharmacodynamics surrogate indices ($fAUC/MIC \geq 25$) with increasing MIC [13]. The cumulative fraction of response (CFR) was calculated as the proportion of %PTA of each MIC according to the MIC distribution. The PTA and CFR of 90% were considered successful.

3. Results

3.1. Microbiology

All clinical isolates of 116 CRE include carbapenem-resistant *K. pneumoniae* (n = 96) and carbapenem-resistant *E. coli* (n = 20) were used. Colistin MIC's ranged from 0.25- >128 mcg/mL. The overall colistin MIC₅₀ and MIC₉₀ were 1 and 16 mcg/mL, respectively. Among the carbapenem-resistant isolates, 91 of 116 isolates (78.44%) were susceptible to colistin (MIC ≤ 2 mcg/mL). Of the colistin-susceptible isolates, 74 were *K. pneumoniae* (74/91; 81.32%) and 17 were *E. coli* (17/91; 18.68%). Colistin-susceptible *K. pneumoniae* isolates had MIC₅₀ and MIC₉₀ of 0.5 and 2 mcg/mL, respectively. For colistin-susceptible *E. coli* isolates, they had MIC₅₀ and MIC₉₀ of 0.5 and 0.5 mcg/mL, respectively. While, 25 of 116 isolates (21.56%) were resistant to colistin, of which 22 were *K. pneumoniae* (22/25; 88%) and 3 were *E. coli* (3/25; 12%). Colistin-resistant *K. pneumoniae* isolates had MIC₅₀ and MIC₉₀ of 16 and 32 mcg/mL, respectively. For colistin-resistant *E. coli* isolates, they had MIC₅₀ and MIC₉₀ of 8 and 32 mcg/mL, respectively. Minimum inhibitory concentrations (MICs) values of the study isolates are shown in Table 4.

Table 4. Minimum inhibitory concentrations (MICs) distribution of colistin.

MIC (mcg/mL)	0.25	0.5	1	2	4	8	16	32	64	>128	MIC ₅₀ (mcg/mL)	MIC ₉₀ (mcg/mL)
All isolates (n = 116)	3	55	19	14	4	5	10	4	1	1	1	16
%	2.58	47.41	16.38	12.07	3.45	4.31	8.6	3.45	0.86	0.86		
Colistin-Susceptible Isolates (MIC ≤ 2 mcg/mL)												
<i>K. pneumoniae</i> (n = 74)	3	40	18	13	-	-	-	-	-	-	0.5	2
<i>E. coli</i> (n = 17)	-	15	1	1	-	-	-	-	-	-	0.5	0.5
Colistin-Resistant Isolates (MIC > 2 mcg/mL)												
<i>K. pneumoniae</i> (n = 22)	-	-	-	-	3	4	10	3	1	1	16	32
<i>E. coli</i> (n = 3)	-	-	-	-	1	1	-	1	-	-	8	32

3.2. Pharmacokinetic-Pharmacodynamic Simulations

3.2.1. Probability of Target Attainment

The PTA analyses of various colistin regimens and creatinine clearance to achieve 90% PTA against carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli* following the $fAUC/MIC \geq 25$ are shown in Figure 1A–E. This figures include the %PTA for the EMA-, FDA-, Nation et al., Siriraj Hospital together with our study regimens. None of the colistin dosing regimens achieved PTA target against the MIC₉₀ for colistin-resistant *K. pneumoniae* and colistin-resistant *E. coli* (32 mcg/mL) in all renal function groups. Similarly, none of the colistin dosing regimens achieved $\geq 90\%$ PTA against the MIC₅₀ for colistin-resistant *K. pneumoniae* (16 mcg/mL) in patients with creatinine clearance >10 mL/min. For patients with creatinine clearance ≤ 10 mL/min, attainment rate of 90% was observed only in our study regimen using 180 mg every 8 h. At the MIC₅₀ for colistin-resistant *E. coli* (8 mcg/mL), none of the colistin approved by EMA-, FDA-, Nation et al. as well as Siriraj Hospital achieved PTA target in all renal function groups. However, our study regimens with daily dose of at least 450 mg at creatinine clearance 11–29 mL/min and daily doses of at least 360 mg at creatinine clearance ≤ 10 mL/min could achieve 90% PTA.

At the MIC of 0.5 mcg/mL (MIC₅₀ for colistin-susceptible *K. pneumoniae* and MIC₅₀/MIC₉₀ for colistin-susceptible *E. coli*), all of the dosage regimens achieved $\geq 90\%$ PTA regardless of renal function. At the MIC of 2 mcg/mL (MIC₉₀ for colistin-susceptible *K. pneumoniae* and the current susceptibility breakpoint), none of the colistin dosing regimens achieved $\geq 90\%$ PTA in patients with creatinine clearance ≥ 80 mL/min. However, the EMA-, FDA-, Nation et al. and Siriraj Hospital approved regimens provided PTA of 64.41, 69.2 and 79.7%, respectively. For patients with creatinine clearance 11–79 mL/min, the EMA-, FDA-, Nation et al. as well as Siriraj Hospital provided PTA of 55–89%. However, our study regimens using daily doses of 540 mg at creatinine clearance 51–79 mL/min and daily doses of at least 300 mg at creatinine clearance 11–50 mL/min could provide an attainment rate >90%. Finally, in patients with creatinine clearance ≤ 10 mL/min, an attainment rate of 90% PTA was observed for all dosage regimens with daily doses of at least 120 mg except the FDA-approved regimens.

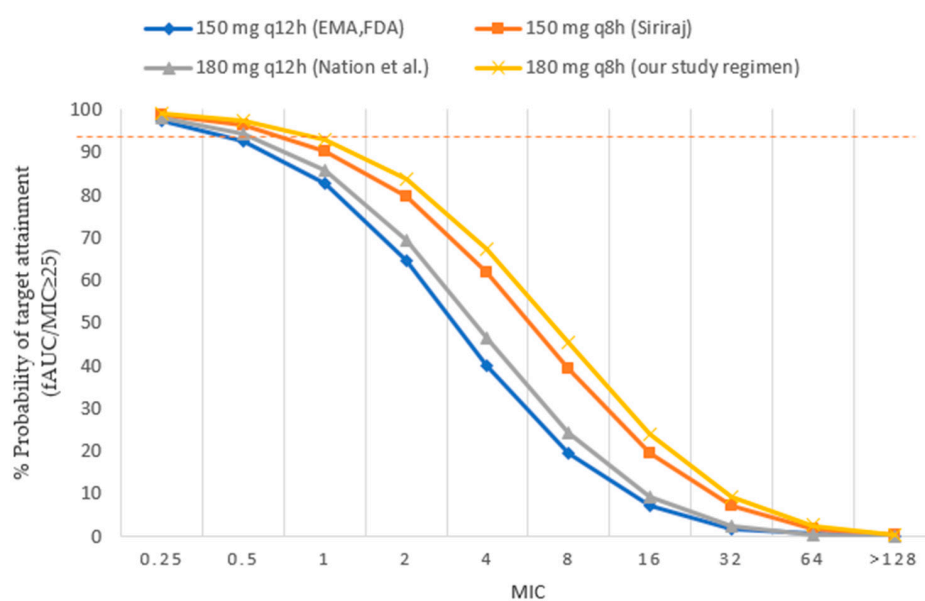
The recommended dose based on the ability to achieve PTA target at various MICs with each dosing regimen are shown in Tables 5 and 6.

3.2.2. Cumulative Fraction of Response

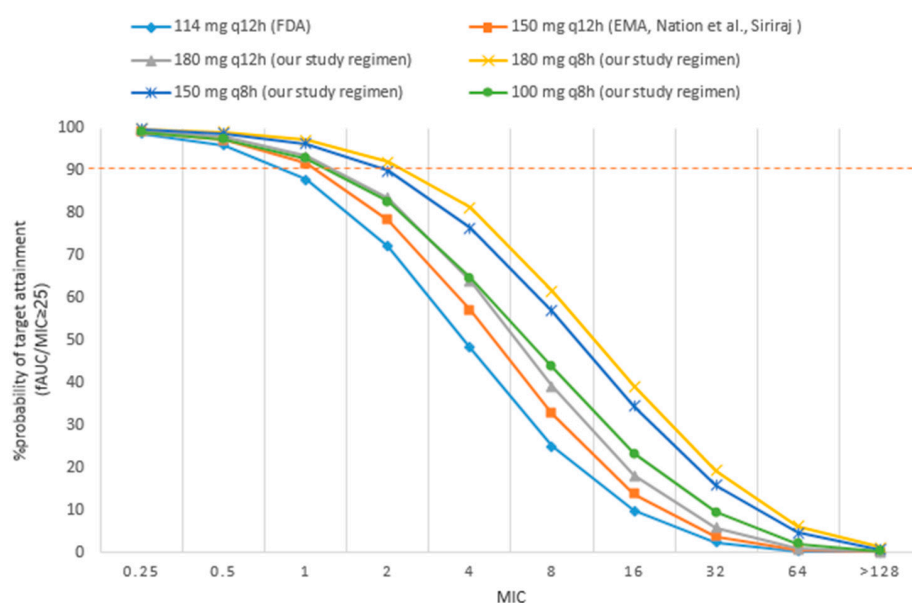
Tables 7 and 8 summarizes the cumulative fraction of response (CFR) for colistin against 116 carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli*. Overall, there was lower than 90% CFR for all of regimens in patients with creatinine clearance >50 mL/min. For patients with creatinine clearance ≤ 50 mL/min, higher doses of at least 450 mg per day in patients with creatinine clearance 30–50 mL/min, at least 300 mg per day in patients with creatinine clearance 11–29 mL/min and at least 200 mg per

day in patients with creatinine clearance ≤ 10 mL/min could achieve the CFR target. For colistin-resistant isolates subgroup, the currently approved regimens achieved CFR target in only 10–50%.

The CFR for colistin against colistin-susceptible *K. pneumoniae* and colistin-susceptible *E. coli* subgroup are shown in Tables 7 and 8. For colistin-susceptible *K. pneumoniae*, patients with creatinine clearance ≥ 80 mL/min, attainment rate of 90% was observed only in Siriraj Hospital and our study regimens (150 mg every 8 h and 180 mg every 8 h, respectively). While, attainment rates were higher than 90% with all dosage regimens in patients with creatinine clearance 30–50 and ≤ 10 mL/min. For patients with creatinine clearance 51–79 and 11–29 mL/min, all dosage regimens achieved the CFR target except the FDA-approved regimens. In contrast, for colistin-susceptible *E. coli*, all dosage regimens achieved $\geq 90\%$ CFR regardless of renal function.

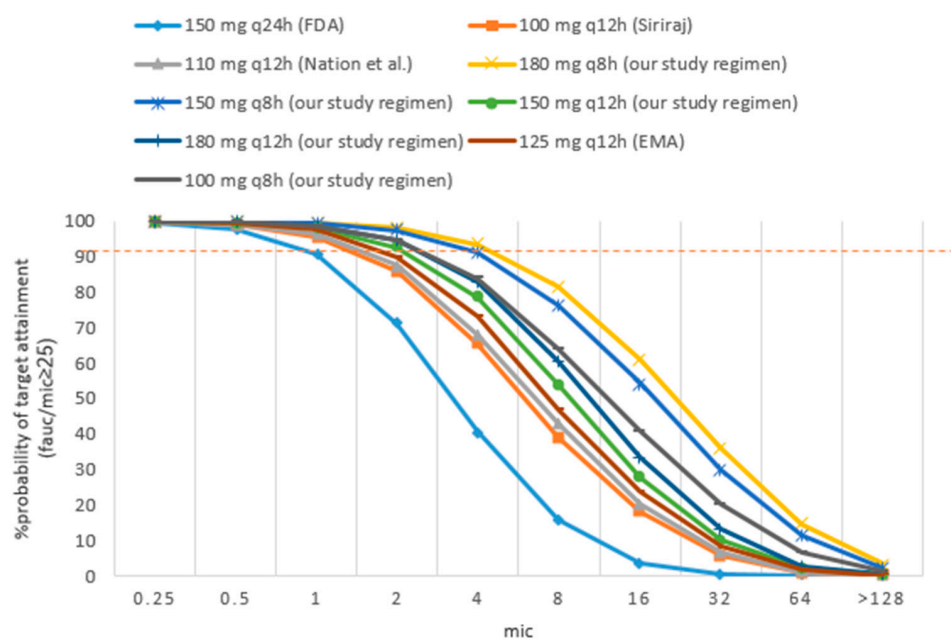


(A)

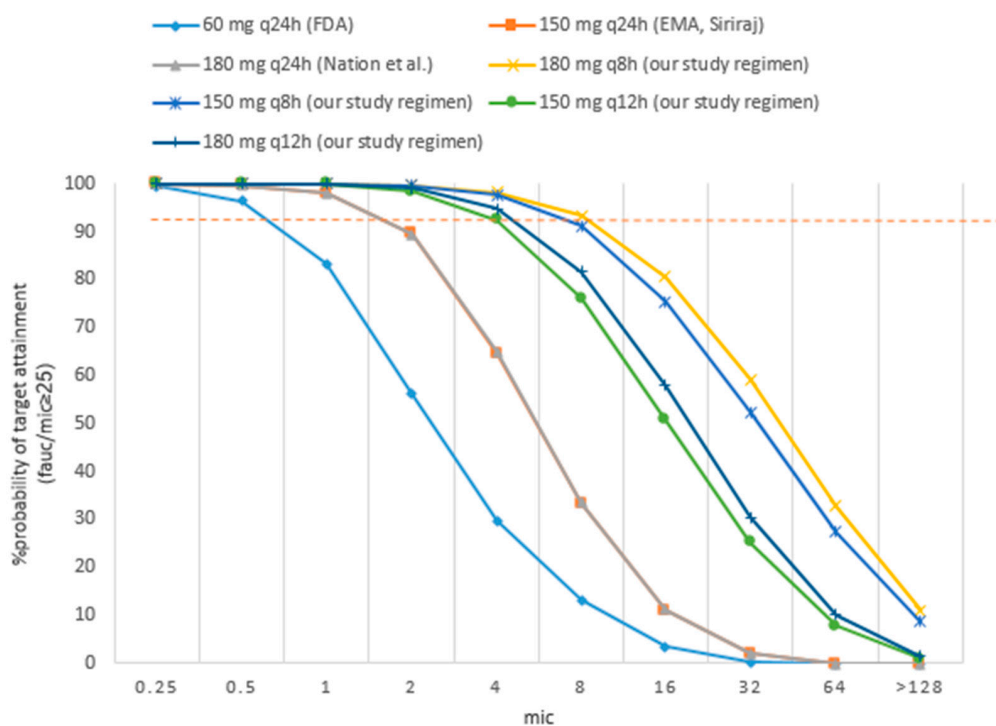


(B)

Figure 1. Cont.

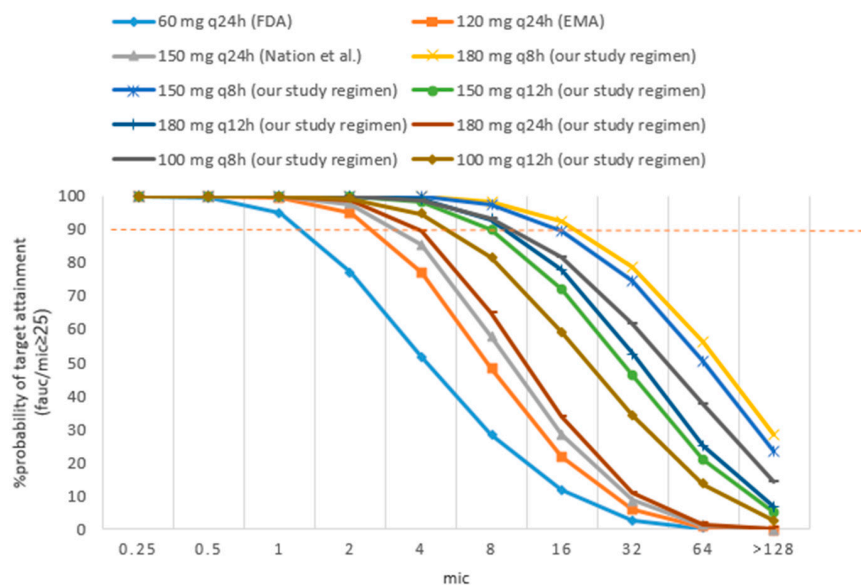


(C)



(D)

Figure 1. Cont.



(E)

Figure 1. (A) %PTA of colistin in patients with CrCl ≥ 80 (mL/min). (B) %PTA of colistin in patients with CrCl 51–79 (mL/min). (C) %PTA of colistin in patients with CrCl 30–50 (mL/min). (D) %PTA of colistin in patients with CrCl 11–29 (mL/min). (E) %PTA of colistin in patients with CrCl ≤ 10 (mL/min).

Table 5. The recommended dose based on the ability to achieve PTA target at various MICs.

Creatinine Clearance (mL/min)	MIC 0.5 mcg/mL Daily Dose (CBA)	MIC 2 mcg/mL Daily Dose (CBA)	MIC 8 mcg/mL Daily Dose (CBA)
≥ 80	150 mg every 12 h (EMA, FDA)	Not recommended	Not recommended
51–79	114 mg every 12 h (FDA)	180 mg every 8 h (our study)	Not recommended
30–50	150 mg every 24 h (FDA)	150 mg every 12 h (our study)	Not recommended
11–29	60 mg every 24 h (FDA)	150 mg every 12 h (our study)	150 mg every 8 h (our study)
≤ 10	60 mg every 24 h (FDA)	120 mg every 24 h (EMA)	180 mg every 12 h (our study)

Table 6. The recommended dose based on the ability to achieve PTA target at various MICs.

Creatinine Clearance (mL/min)	MIC 16 mcg/mL Daily Dose (CBA)	MIC 32 mcg/mL Daily Dose (CBA)
≥ 80	Not recommended	Not recommended
51–79	Not recommended	Not recommended
30–50	Not recommended	Not recommended
11–29	Not recommended	Not recommended
≤ 10	180 mg every 8 h (our study)	Not recommended

MICs = minimum inhibitory concentrations (mcg/mL), EMA = European Medicine Agency, FDA = US-Food and Drug Administration, CBA = colistin base activity.

Table 7. %PTA and %CFR for All isolates, Colistin-susceptible isolates subgroup and Colistin-resistant isolates subgroup.

MIC (mcg/mL)	All Isolates			Colistin-Susceptible Isolates							Colistin-Resistant Isolates							%CFR for all Resistant Isolates
	%PTA		%CFR	Colistin-Susceptible <i>K. pneumoniae</i> Subgroup			Colistin-Susceptible <i>E. coli</i> Subgroup			%CFR for all Sus-Ceptible Isolates	Colistin-Resistant <i>K. pneumoniae</i> Subgroup			Colistin-Resistant <i>E. coli</i> Subgroup				
				%PTA		%CFR	%PTA		%PTA		%CFR	%PTA		%PTA				
	MIC ₅₀	MIC ₉₀		MIC ₅₀	MIC ₉₀		MIC ₅₀	MIC ₉₀	MIC ₅₀			MIC ₉₀	MIC ₅₀	MIC ₉₀				
	1	16		0.5	2		0.5	0.5	16			32	8	32				
CrCl ≥80 mL/min																		
150 mg q12 h (EMA, FDA)	82.47	7.08	70.68	92.66	64.41	85.41	92.66	92.66	90.40	86.34	7.08	1.51	12.45	19.48	1.51	20.33	13.40	
180 mg q12 h (Nation et al.)	85.55	8.99	73.14	97.91	69.2	87.87	97.91	97.91	92.25	88.69	8.99	2.2	15.08	24.09	2.2	24.18	16.18	
150 mg q8 h (Siriraj)	90.07	19.48	78.56	98.68	79.7	92.02	98.68	98.68	95.06	92.58	19.48	7.02	25.45	39.3	7.02	35.99	26.71	
CrCl 51 to 79 mL/min																		
114 mg q12 h (FDA)	87.96	9.8	74.90	95.95	71.98	89.91	95.95	95.95	94.07	90.69	9.8	2.36	15.94	25.05	2.36	25.26	17.06	
150 mg q12 h (Siriraj, EMA, Nation et al)	91.66	13.73	77.96	97.26	78.32	92.65	97.26	97.26	95.82	93.24	13.73	3.8	20.53	32.72	3.8	31.22	21.81	
CrCl 30 to 50 mL/min																		
150 mg q24 h (FDA)	90.53	3.58	74.65	97.55	71.1	91.27	97.55	97.55	95.58	92.07	3.58	0.39	10.05	15.59	0.39	18.84	11.10	
100 mg q12 h (Siriraj)	95.34	18.09	81.26	98.89	85.65	95.74	98.89	98.89	97.90	96.14	18.09	5.58	25	38.9	5.58	36.58	26.39	
110 mg q12 h (Nation et al.)	96.29	20.03	82.17	99.03	87.43	96.35	99.03	99.03	98.19	96.70	20.03	6.41	27.05	42.66	6.41	39.01	28.48	
125 mg q12 h (EMA)	97.71	23.65	83.51	99.15	89.8	97.18	99.15	99.15	98.52	97.43	23.65	8.09	30.41	46.87	8.09	42.66	31.87	
CrCl 11 to 29 mL/min																		
60 mg q24 h (FDA)	83.41	3.57	70.63	96.33	56.2	86.26	96.33	96.33	97.91	87.56	3.57	0.42	8.11	13.11	0.42	14.41	8.87	
150 mg q24 h (EMA, Siriraj)	97.92	11.16	81.45	99.67	89.35	97.44	99.67	99.67	99.61	97.73	11.16	2.02	20.20	33.24	2.02	33.27	21.77	
180 mg q24 h (Nation et al.)	97.93	11.23	81.45	99.63	89.32	97.41	99.63	99.63	99.93	97.70	11.23	1.94	20.29	33.41	1.94	33.4	21.87	
CrCl ≤10 mL/min																		
60 mg q24 h (FDA)	94.94	11.81	78.82	99.5	77.09	94.47	99.5	99.5	99.99	95.11	11.81	2.61	17.88	28.19	2.61	27.44	19.03	
120 mg q24 h (EMA)	99.34	21.74	84.70	99.94	94.92	98.91	99.94	99.94	99.99	99.04	21.74	5.98	29.99	48.29	5.98	43.72	31.63	
150 mg q24 h (Nation et al.)	99.76	28.36	86.51	99.98	97.4	99.47	99.98	99.98	100	99.54	28.36	8.69	36.24	57.76	8.69	50.55	37.96	

MICs = minimum inhibitory concentrations (mcg/mL), PTA = Probability of target attainment, CFR = Cumulative fraction of response, CrCl = Creatinine clearance (ml/min), EMA = European Medicine Agency, FDA = US-Food and Drug Administration.

Table 8. %PTA and %CFR of our study regimens for All isolates, Colistin-susceptible isolates subgroup and Colistin-resistant isolates subgroup.

MIC (mcg/mL)	All Isolates			Colistin-Susceptible Isolates							Colistin-Resistant Isolates						
	%PTA		%CFR	Colistin-Susceptible <i>K. pneumoniae</i> Subgroup			Colistin-Susceptible <i>E. coli</i> Subgroup			%CFR for all Sus-CEPTible Isolates	Colistin-Resistant <i>K. pneumoniae</i> Subgroup			Colistin-Resistant <i>E. coli</i> Subgroup			%CFR for all Resistant Isolates
				%PTA		%CFR	%PTA		%PTA		%CFR	%PTA		%CFR			
	MIC ₅₀	MIC ₉₀		MIC ₅₀	MIC ₉₀		MIC ₅₀	MIC ₉₀	MIC ₅₀			MIC ₉₀	MIC ₅₀		MIC ₉₀		
	1	16		0.5	2		0.5	0.5	16			32	8		32		
CrCl ≥80 mL/min																	
180 mg q8h	92.88	23.74	80.80	97.19	83.61	93.83	97.19	97.19	96.14	92.58	23.74	9.17	29.55	45.2	9.17	40.54	30.87
CrCl 51 to 79 mL/min																	
100 mg q8 h	92.96	23.43	80.60	97.36	82.62	93.77	97.36	97.36	96.23	94.23	23.43	9.4	28.79	43.67	9.4	39.25	30.05
180 mg q12 h	93.43	18.04	80.15	97.82	83.54	94.31	97.82	97.82	96.72	94.76	18.04	5.7	24.88	39.23	5.7	36.31	26.25
150 mg q8 h	96.39	34.52	85.01	98.79	89.88	96.68	98.79	98.79	98.12	96.94	34.52	15.78	38.86	56.93	15.78	49.72	40.16
180 mg q8 h	97.13	39.07	86.51	99.15	92.05	97.44	99.15	99.15	98.61	97.65	39.07	19.36	43.05	61.77	19.36	54.16	44.38
CrCl 30 to 50 mL/min																	
100 mg q8 h	98.54	40.8	87.65	99.64	94.49	98.48	99.64	99.64	99.27	98.63	40.8	20.09	44.71	64.06	20.09	55.97	46.06
150 mg q12 h	97.9	27.61	84.91	99.41	92.44	97.84	99.41	99.41	98.91	98.04	27.61	9.97	34.47	53.71	9.97	47.36	36.01
180 mg q12 h	98.52	33.25	86.48	99.67	94.6	98.51	99.67	99.67	99.30	98.66	33.25	13.25	39.30	60.3	13.25	52.09	40.84
150 mg q8 h	99.33	54.13	90.59	99.76	97.29	99.23	99.76	99.76	99.59	99.30	54.13	29.89	55.53	76.01	29.89	65.64	56.75
180 mg q8 h	99.41	60.87	91.96	99.9	97.97	99.44	99.9	99.9	99.76	99.50	60.87	35.86	60.93	81.54	35.86	70.26	62.05
CrCl 11 to 29 mL/min																	
150 mg q12 h	99.76	50.76	90.39	99.91	98.35	99.60	99.91	99.91	99.81	99.64	50.76	25.25	53.34	76.03	25.25	64.55	54.68
180 mg q12 h	99.83	57.93	91.71	99.97	99.06	99.78	99.97	99.97	99.91	99.80	57.93	30.34	58.70	81.51	30.34	68.9	59.93
150 mg q8 h	99.91	75.28	94.91	99.96	99.57	99.88	99.96	99.96	99.93	99.89	75.28	52.4	72.87	91.10	52.4	80.38	73.77
180 mg q8 h	99.93	80.65	95.87	100	99.63	99.92	100	100	99.97	99.93	80.65	59.11	77.09	93.47	59.11	83.57	77.87
CrCl≤10 mL/min																	
180 mg q24 h	99.89	33.88	87.73	100	98.53	99.72	100	100	99.91	99.75	33.88	10.94	40.91	64.74	10.94	54.99	42.60
100 mg q12 h	99.93	59.11	92.02	99.98	99.18	99.83	99.98	99.98	99.93	99.85	59.11	34.22	59.95	81.32	34.22	70.5	61.16
100 mg q8 h	99.99	81.59	96.14	100	99.79	99.96	100	100	99.99	99.96	81.59	61.67	78.21	93.13	61.67	84.47	78.96
150 mg q12 h	99.98	71.94	94.13	100	99.84	99.98	100	100	99.99	99.97	71.94	46.32	69.86	89.74	46.32	78.00	70.84
180 mg q12 h	99.98	77.7	95.30	100	99.90	99.97	100	100	99.99	99.98	77.7	52.76	74.31	92.85	52.76	81.47	75.17
150 mg q8 h	99.99	89.51	97.76	100	99.97	99.99	100	100	100	99.99	89.51	74.47	85.46	97.26	74.47	90.46	86.06
180 mg q8 h	99.99	92.31	98.30	100	99.94	99.99	100	100	100	99.99	92.31	78.66	87.97	98.18	78.66	92.19	88.48

MICs = minimum inhibitory concentrations (mcg/mL), PTA = Probability of target attainment, CFR = Cumulative fraction of response, CrCl = Creatinine clearance (mL/min).

4. Discussion

In our study, the MICs of colistin for CRE isolates were within the range of 0.25–>128 mcg/mL. The overall colistin MIC₅₀ and MIC₉₀ were 1 and 16 mcg/mL, respectively. Our study showed MIC₅₀/MIC₉₀ of 1/16 and 0.5/4 mcg/mL for carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli*, respectively. In Thailand, a study which was performed at Siriraj Hospital [19] demonstrated MIC₅₀/MIC₉₀ of 32 /> 128 and 0.5/8 mcg/mL for carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli*, respectively. A Global Surveillance Program study (including isolates of Enterobacteriaceae in Thailand) [20] demonstrated values of MIC₅₀ and MIC₉₀ at ≤0.012 and ≥4 mcg/mL, respectively. The discrepancies in MIC results among the studies could be due to the difference in prevalence of colistin resistance isolates (21.56% in our study, 71.3% in study at Siriraj Hospital [19] and <10% Global Surveillance Program study [20], respectively) as well as the percentage of *K. pneumoniae* isolates (82.75% in our study, 88.32% in study at Siriraj Hospital [19] and <50% Global Surveillance Program study [20], respectively). Our study showed the frequency of colistin resistance in *K. pneumoniae* to be higher than the frequency of colistin resistance in *E. coli* (22.9% versus 15%, respectively). In addition, the MIC₅₀ and MIC₉₀ values of *K. pneumoniae* isolates were higher than *E. coli* isolates. This was consistent with previous studies which described the use of high MICs for colistin in *K. pneumoniae* [19,21]

This is the first study using Monte carlo simulation to determine effective dosage regimens for colistin against carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli*. When colistin was administered as monotherapy, all of colistin regimens approved by EMA-, FDA-, Nation et al., Siriraj Hospital would not be effective against MIC₉₀ of colistin-resistant *K. pneumoniae* and colistin-resistant *E. coli* (32 mcg/mL), MIC₅₀ of colistin-resistant *K. pneumoniae* (16 mcg/mL) and MIC₅₀ of colistin-resistant *E. coli* isolates (8 mcg/mL) as shown by the PTA falling below 90%.

For isolates with MIC ≤0.5 mcg/mL (MIC₅₀ for colistin-susceptible *K. pneumoniae* and MIC₅₀/MIC₉₀ for colistin-susceptible *E. coli*), all dosage regimens achieved ≥90% PTA regardless of renal function. This was consistent with a study by Tsala, et al. [13] which found >95% PTA to be effective against *K. pneumoniae* when the MIC were ≤0.5 mcg/mL by using colistin 300 mg CBA per day in patients with normal renal function. In contrast, there were lower success rates report with colistin against isolates with MIC of 2 mcg/mL (MIC₉₀ for colistin-susceptible *K. pneumoniae* and the current susceptibility breakpoint) using all of recommendations in patients who had creatinine clearance > 10 mL/min. However, the EMA-, FDA-, Nation et al. and Siriraj Hospital approved regimens achieved PTA target in approximately 65–89%. Interestingly, all the regimens with daily doses of at least 120 mg could achieve the target for patients with creatinine clearance of ≤10 mL/min. This was consistent with a study by Tsala, et al. [13] which showed lower success rates using colistin 300 mg CBA per day in patients who had normal renal function for isolates with MIC ≥2 mcg/mL.

Previous studies have shown that the EMA-, FDA- and Nation et al. approved regimens could achieve PTA target for patients with creatinine clearance <80 mL/min. Our results were in contrast to the above studies, and these results might be explained because previous studies used the average plasma concentration at steady state (C_{ss}, avg) of 2 mcg/mL which was a reasonable PK/PD target of colistin against gram negative organisms [12,16]. However, the PK/PD target of C_{ss}, avg of 2 mcg/mL was appropriate for pathogen with MIC ≤2 mcg/mL [12,16]. The prevalence of colistin resistance (MIC >2 mcg/mL) among isolates in our study was rather high (approximately 40%) and the MIC₅₀ and MIC₉₀ values were higher than other studies. For this reason, the PK/PD target of C_{ss}, avg of 2 mcg/mL was inappropriate to use in our study. The PK/PD targets $fAUC/MIC \geq 25$, which were used in this study, were determined using limited information [13]. However, several studies including in vitro studies as well as infection models which used neutropenic mice have confirmed the relation to clinical applications with these targets for colistin [13,14]. In addition, our study used higher PTA target compared with other studies (≥90% versus 80–90%).

The FDA-approved regimens have shown lower target attainment rates than other regimens. Similarly, the studies from Nation et al. [12,16] showed that FDA-approved regimens were substantially

lower than those approved by the EMA. The data has also shown that patients with renal impairment have a better chance to achieve PTA target compared with normal renal function. The findings of our study were consistent with previous analyses, the dosing suggestions of Nation et al. achieved 80–90% of patients in each of 3 groups of creatinine clearance patients (50 to <80, 30 to <50, <30 mL/min). At creatinine clearance ≥ 80 mL/min, the suggested doses only provided <40% PTA for plasma colistin C_{ss}, avg of 2 mcg/mL [12]. Additionally, renal function significantly impacts upon the proportion of colistimethate for conversion to colistin due to colistimethate being predominately renally excreted by with only small fraction of the dose converted to colistin [9,22,23].

Our results have suggested that current maintenance doses may not be effective against isolates with an MIC >0.5 mcg/mL. This is consistent with a study by Garonsik, et al. [9] and Tsala, et al. [13] which showed this MIC as the highest MIC offering reasonable PTA for current maintenance doses. Similarly, previous studies have reported that colistin monotherapy might be non-inferior when compared to combination therapy used for treating blood stream infections which are caused by carbapenem-resistant gram negative bacilli with the MIC for colistin as ≤ 0.5 mcg/mL (mortality rate 83 versus 79%, respectively) [24]. These results have suggested a susceptibility PK/PD breakpoint of ≤ 0.5 mcg/mL might be able to identify between isolates which are resistant and susceptible to colistin. This suggested breakpoint is less than the present breakpoints (EUCAST) value of ≤ 2 mcg/mL [11]. However, a prospective cohort clinical study did not find any differences in mortality compared with patients infected by colistin-susceptible and colistin-resistant CRE with 2 mcg/mL breakpoint [25]. Furthermore, clinical study by Choi, et al. [26] found that the 7-day and 14-day mortality rate in patients who were infected by colistin-susceptible *A. baumannii* (MIC < 2 mcg/mL) with high colistin MICs (≥ 1 mcg/mL) were statistically significant higher than ones with isolates with lower MICs (<1 mcg/mL) (38.2% versus 20.2%, $p = 0.025$ and 35.2% versus 19.1%, $p = 0.014$, respectively). Therefore, a revision of the current colistin susceptibility breakpoint for Enterobacteriaceae may be needed.

Based on a PK/PD target of $fAUC/MIC \geq 25$, CFR are lower than 90% for all regimens approved by EMA-, FDA-, Nation et al., Siriraj Hospital in all categories of creatinine clearance. Overall, they are approximately 70–86%. For colistin-resistant isolates, the currently approved regimens achieved CFR target in only 10–50%.

Our simulations were carried out on colistin-susceptible *K. pneumoniae* and colistin-susceptible *E. coli* subgroup. For colistin-susceptible *K. pneumoniae*, this study has shown an attainment rate of 90% CFR was observed in Siriraj Hospital as well as our study regimens in patients with creatinine clearance ≥ 80 mL/min. However, CFR targets are achieved for all dosage regimens of patients with creatinine clearance <80 mL/min except the FDA-approved regimens in patients with creatinine clearance 51–79 and 11–29 mL/min. While, all of dosage regimens achieved CFR target in all renal function groups for colistin-susceptible *E. coli* infection.

This data supports that colistin is still the mainstay treatment option against carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli* infections provided that: (i) the colistin MIC for the infecting organism is ≤ 0.5 mcg/mL (ii) high-dose regimens are administered to attain the PK/PD targets. However, high dose of colistin may have adverse effects such as nephrotoxicity and neurotoxicity [27–29]. It is necessary to be careful to balance between risks of toxicity and clinical benefit (iii) for combination of the colistin and other antibiotics, the MICs were markedly lower than the MICs of the antimicrobials in monotherapy and resulting MIC values of colistin ≤ 0.5 –1 mcg/mL.

The study has limitations as follows. First, the number of isolates evaluated was not very large and had only two species (*K. pneumoniae* ($n = 96$) and *E. coli* ($n = 20$)). The isolates came from a tertiary university hospital in Bangkok, which might be different from other hospitals or other countries. These are factors which affect the dosing regimen based on the CFR results. Second, we did not simulate about the drug level for patients using hemodialysis. Finally, the molecular characteristics of carbapenemase enzyme has not been performed in this study.

5. Conclusions

Our study is the first to determine effective and compare the colistin dosing regimens approved by the EMA-, FDA-, Nation, et al., Siriraj Hospital and our study against carbapenem-resistant *Klebsiella pneumoniae* and carbapenem-resistant *Escherichia coli*. It used differences between the regimens, especially for FDA- provided attainment rates which were lower than other approved regimens. The reduction in the CrCl improved attainment of %PTA and %CFR. Findings indicate the use of alternative dosing approaches allowing for higher daily doses or combination therapy are preferable for patients with CrCl ≥ 80 mL/min and if the MIC of colistin ≥ 0.5 mcg/mL.

Author Contributions: Conceptualization, K.J., P.M. and V.T.; methodology, K.J., P.M., V.T. and J.H.; software, K.J., P.M., K.S., J.H., O.A. and W.S.; validation, K.J., P.M. and K.S.; formal analysis, K.J.; investigation, K.J.; resources, K.J., P.M. and V.T.; data curation, K.J.; writing original draft preparation, K.J.; writing-review and editing, K.J., P.M. and V.T.; visualization, K.J.; supervision, P.M. and V.T.; project administration, K.J., P.M. and V.T.

Funding: This research received no external funding.

Acknowledgments: We would like to thank Stephen Pinder, Faculty of Medicine Ramathibodi Hospital, Mahidol University for his advice on English expression and comments that greatly improved this document.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Zarkotou, O.; Pournaras, S.; Tselioti, P.; Dragoumanos, V.; Pitiriga, V.; Ranellou, K.; Prekates, A.; Themeli-Digalaki, K.; Tsakris, A. Predictors of mortality in patients with bloodstream infections caused by KPC-producing *Klebsiella pneumoniae* and impact of appropriate antimicrobial treatment. *Clin. Microbiol. Infect.* **2011**, *17*, 1798–1803. [CrossRef] [PubMed]
2. Munoz-Price, L.S.; Poirel, L.; Bonomo, A.R.; Schwaber, M.J.; Daikos, G.L.; Cormican, M.; Cornaglia, G.; Garau, J.; Gniadkowski, M.; Hayden, M.K.; et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. *Lancet Infect. Dis.* **2013**, *13*, 785–796. [CrossRef]
3. Nordmann, P.; Naas, T.; Poirel, L. Global Spread of Carbapenemase-producing Enterobacteriaceae. *Emerg. Infect. Dis.* **2011**, *17*, 1791–1798. [CrossRef] [PubMed]
4. National Antimicrobial Resistance Surveillance Center, Thailand. Antibigrams. Available online: <http://narst.dmsc.moph.go.th/antibiograms.html>. (accessed on 20 July 2017).
5. Kazmierczak, K.M.; Rabine, S.; Hackel, M.; McLaughlin, R.E.; Biedenbach, D.J.; Bouchillon, S.K.; Sahm, D.F.; Bradford, P.A. Multiyear, Multinational Survey of the Incidence and Global Distribution of Metallo- β -Lactamase-Producing Enterobacteriaceae and *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* **2016**, *60*, 1067–1078. [CrossRef] [PubMed]
6. Hsu, L.Y.; Apisarnthanarak, A.; Khan, E.; Suwantararat, A.; Ghafur, A.; Tambyah, P.A. Carbapenem-Resistant *Acinetobacter baumannii* and Enterobacteriaceae in South and Southeast Asia. *Clin. Microbiol. Rev.* **2017**, *3*, 1–22. [CrossRef] [PubMed]
7. Li, J.; Nation, R.L.; Turnidge, J.D.; Milne, R.W.; Coulthard, K.; Rayner, C.R.; Paterson, D.L. Colistin: The re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect. Dis.* **2006**, *6*, 589–601. [CrossRef]
8. Lim, L.M.; Neang, L.Y.; Anderson, D.; Yang, J.C.; Macander, L.; Jarkowski III, A.; Forrest, A.; Bulitta, J.B.; Tsuji, B.T. Resurgence of Colistin: A Review of Resistance, Toxicity, Pharmacodynamics and Dosing. *Pharmacotherapy* **2010**, *30*, 1279–1291. [CrossRef] [PubMed]
9. Garonzik, S.M.; Li, J.; Thamlikitkul, V.; Paterson, D.L.; Shoham, S.; Jacob, J.; Silveira, F.P.; Forrest, A.; Nation, R.L. Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients. *Antimicrob. Agents Chemother.* **2011**, *55*, 3284–3294. [CrossRef]
10. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing. Twenty-Seven Informational Supplement. CLSI Document M100-Swayne*; CLSI: Wayne, PA, USA, 2017.
11. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Available online: http://www.eucast.org/clinical_breakpoints/ (accessed on 20 July 2017).

12. Nation, R.L.; Garonzik, S.M.; Thamlikitkul, V.; Giamarellos-Bourboulis, E.J.; Forrest, A.; Paterson, D.L. Dosing Guidance for Intravenous Colistin in Critically Ill Patients. *Clin. Infect. Dis.* **2017**, *64*, 565–571. [CrossRef]
13. Tsala, M.; Vourli, S.; Georgiou, P.C.; Pournaras, S.; Tsakris, A.; Daikos, G.L.; Mouton, J.W.; Meletiadis, J. Exploring colistin pharmacodynamics against *Klebsiella pneumoniae*: A need to revise current susceptibility breakpoints. *J. Antimicrob. Chemother.* **2018**, *73*, 953–961. [CrossRef]
14. Cheah, S.E.; Wang, J.; Nguyen, V.T.T.; Turnidge, J.D.; Li, J.; Nation, R.L. New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in mouse thigh and lung infection models: Smaller response in lung infection. *J. Antimicrob. Chemother.* **2015**, *70*, 3291–3297. [PubMed]
15. Jacobs, M.; Grégoire, N.; Mégarbane, B.; Gobin, P.; Balayn, D.; Marchand, S.; Mimoz, O.; Couet, W. Population Pharmacokinetics of Colistin Methanesulfonate and Colistin in Critically Ill Patients with Acute Renal Failure Requiring Intermittent Hemodialysis. *Antimicrob. Agents Chemother.* **2016**, *60*, 1788–1793. [CrossRef] [PubMed]
16. Nation, R.L.; Garonzik, S.M.; Li, J.; Thamlikitkul, V.; Giamarellos-Bourboulis, E.J.; Paterson, D.L.; Turnidge, J.D.; Forrest, A.; Silveira, F.P. Updated US and European Dose Recommendations for Intravenous Colistin: How Do They Perform? *Clin. Infect. Dis.* **2016**, *62*, 552–558. [CrossRef] [PubMed]
17. European Medicines Agency Completes Review of Polymyxin-based Medicines: Recommendations Issued for Safe Use in Patients with Serious Infections Resistant to Standard Antibiotics. Available online: https://www.ema.europa.eu/documents/press-release/european-medicines-agency-completes-review-polymyxin-based-medicines_en.pdf (accessed on 2 December 2017).
18. FDA Approved Drug Products. Label and Approval History for Coly-Mycin M, NDA 050108. Available online: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=050108> (accessed on 2 December 2017).
19. Eiamphungporn, W.; Yainoy, S.; Jumderm, C.; Tan-Arsuwongkul, R.; Tiengrim, S.; Thamlikitkul, V. Prevalence of the colistin resistance gene mcr-1 in colistin-resistant *Escherichia coli* and *Klebsiella pneumoniae* isolated from humans in Thailand. *J. Glob. Antimicrob. Resist.* **2018**, *15*, 32–35. [CrossRef] [PubMed]
20. Bradford, P.A.; Kazmierczak, K.M.; Biedenbach, D.J.; Wise, M.G.; Hackel, M.; Sahm, D.F. Correlation of β -Lactamase Production and Colistin Resistance among Enterobacteriaceae Isolates from a Global Surveillance Program. *Antimicrob. Agents Chemother.* **2016**, *60*, 1385–1392. [CrossRef] [PubMed]
21. Maalej, S.; Meziou, M.; Rhimi, F.; Hammami, A. Comparison of disc diffusion, Etest and agar dilution for susceptibility testing of colistin against Enterobacteriaceae. *Lett. Appl. Microbiol.* **2011**, *53*, 546–551. [CrossRef] [PubMed]
22. Nation, R.L.; Li, J.; Cars, O.; Couet, W.; Dudley, M.N.; Kaye, K.S.; Mouton, J.W.; Paterson, D.L.; Tam, V.H.; Theuretzbacher, U.; et al. Framework for optimisation of the clinical use of colistin and polymyxin B: The Prato polymyxin consensus. *Lancet Infect. Dis.* **2015**, *15*, 225–234. [CrossRef]
23. Nation, R.L.; Velkov, T.; Li, J. Colistin and polymyxin B: Peas in a pod, or chalk and cheese? *Clin. Infect. Dis.* **2014**, *59*, 88–94. [CrossRef]
24. Shah, P.G.; Shah, S.R. Treatment and Outcome of Carbapenem-Resistant Gram-Negative Bacilli Blood-Stream Infections in a Tertiary Care Hospital. *J. Assoc. Physicians India* **2015**, *63*, 14–18.
25. De Maio Carrilho, C.M.D.; de Oliveira, L.M.; Gaudereto, J.; Perozin, J.S.; Urbano, M.R.; Camargo, C.H.; Grion, C.M.C.; Levin, A.S.S.; Costa, S.F. A prospective study of treatment of carbapenem-resistant Enterobacteriaceae infections and risk factors associated with outcome. *BMC Infect. Dis.* **2016**, *16*, 629. [CrossRef]
26. Choi, I.S.; Lee, Y.J.; Wi, Y.M.; Kwan, B.S.; Jung, K.H.; Hong, W.P.; Kim, J.M. Predictors of mortality in patients with extensively drug-resistant *Acinetobacter baumannii* pneumonia receiving colistin therapy. *Int. J. Antimicrob. Agents* **2016**, *48*, 175–180. [CrossRef] [PubMed]
27. Sorli, L.; Luque, S.; Grau, S.; Berenguer, N.; Segura, C.; Montero, M.M.; Álvarez-Lerma, F.; Knobel, H.; Benito, N.; Horcajada, J.P. Trough colistin plasma level is an independent risk factor for nephrotoxicity: A prospective observational cohort study. *BMC Infect. Dis.* **2013**, *13*, 380. [CrossRef] [PubMed]

28. Horcajada, J.P.; Sorlí, L.; Luque, S.; Benito, N.; Segura, C.; Campillo, N.; Montero, M.; Esteve, E.; Mirelis, B.; Pomar, V.; et al. Validation of a colistin plasma concentration breakpoint as a predictor of nephrotoxicity in patients treated with colistin methanesulfonate. *Int. J. Antimicrob. Agents* **2016**, *48*, 725–727. [[CrossRef](#)] [[PubMed](#)]
29. Falagas, M.E.; Fragoulis, K.N.; Kasiakou, S.K.; Sermaidis, G.J.; Michalopoulos, A. Nephrotoxicity of intravenous colistin: A prospective evaluation. *Int. J. Antimicrob. Agents* **2005**, *26*, 504–507. [[CrossRef](#)] [[PubMed](#)]



© 2019 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).