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Original Article

Colistin plus Sulbactam or Fosfomycin against Carbapenem-Resistant *Acinetobacter baumannii*: Improved Efficacy or Decreased Risk of Nephrotoxicity?

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ABSTRACT

Background: *Acinetobacter baumannii* has been recognized as a cause of nosocomial infection. To date, polymyxins, the last-resort therapeutic agents for carbapenem-resistant *A. baumannii* (CRAB). Thus, the small number of effective antibiotic options against CRAB represents a challenge to human health. This study examined the appropriate dosage regimens of colistin alone or in combination with sulbactam or fosfomycin using Monte Carlo simulation with the aims of improving efficacy and reducing the risk of nephrotoxicity.
Materials and Methods: Clinical CRAB isolates were obtained from patients admitted to Phramongkutklao Hospital in 2014 and 2015. The minimum inhibitory concentration (MIC) of colistin for each CRAB isolate was determined using the broth dilution method, whereas those of sulbactam and fosfomycin were determined using the agar dilution method. Each drug regimen was simulated using the Monte Carlo technique to calculate the probability of target attainment (PTA) and the cumulative fraction of response (CFR). Nephrotoxicity based on RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria was indicated by colistin trough concentration exceeding ≥3.3 μg/mL.
Results: A total of 50 CRAB isolates were included. The MIC_{50} and MIC_{90} were 64 and 128 μg/mL, respectively, for sulbactam, 256 and 2,048 μg/mL, respectively, for fosfomycin, and 1 and 4 μg/mL, respectively, for colistin. In patients with creatinine clearance of 91 – 130 m/min, the dosing regimens of 180 mg every 12 h and 150 mg every 8 h achieved ≥ 90% of target of the area under the free drug plasma concentration–time curve from 0 to 24 hr (*f*AUC24)/MIC ≥25 against isolates MICs of ≤0.25 and ≤0.5 μg/mL, respectively, and their rates of colistin trough concentration more than ≥3.3 μg/mL were 35 and 54%, respectively. Colistin combined with sulbactam or fosfomycin decreased the colistin MIC of CRAB isolates from 1 – 16 μg/mL to 0.0625 – 1 and 0.0625 – 2 μg/mL, respectively. Based on CFR ≥ 90%, no colistin monotherapy regimens in patients with creatinine clearance of 91 – 130 mL/min were effective against all of the studied CRAB isolates. For improving efficacy and

Conflict of Interest
No conflicts of interest.

Author Contributions
Conceptualization: DC, ST, WiS. Data curation: WeS, WiS, PN. Formal analysis: WeS, WiS, PN. Funding acquisition: WiS. Investigation: DC, ST, WiS. Methodology: DC, ST, WiS. Project administration: WiS. Resources: DC, ST, PJ. Software: WiS. Supervision: DC, ST, PJ, WiS. Validation: WeS, WiS, PN. Visualization: DC, ST, WiS. Writing - original draft: WiS. Writing - review & editing: WeS, DC, ST, PJ, PN.

reducing the risk of nephrotoxicity, colistin 150 mg given every 12 h together with sulbactam (≥6 g/day) or fosfomycin (≥18 g/day) was effective in patients with creatinine clearance of 91 – 130 mL/min. Additionally, both colistin combination regimens were effective against five colistin-resistant *A. baumannii* isolates.
Conclusion: Colistin monotherapy at the maximum recommended dose might not cover some CRAB isolates. Colistin combination therapy appears appropriate for achieving the pharmacokinetic/pharmacodynamic targets of CRAB treatment.

Keywords: Colistin resistance; Colistimethate; Combination; Synergism

INTRODUCTION

Acinetobacter baumannii has been recognized as a cause of nosocomial infection because of its resistance to multiple classes of antibiotics, especially carbapenems, and the microbe exhibits long-term survival in healthcare settings [1]. To date, polymyxins, the last-resort therapeutic agents for carbapenem-resistant *A. baumannii* (CRAB), have been sporadically used [2, 3]. Thus, the small number of effective antibiotic options against CRAB represents a challenge to human health.

In data from the National Antimicrobial Resistance Surveillance Thailand Center, *A. baumannii* was the third-most common gram-negative bacterium and fifth-most common bacterium overall isolated from blood specimens in 2019. Unfortunately, more than half of *A. baumannii* isolates are carbapenem-resistant, whereas few strains are resistant to colistin (colistin resistant *A. baumannii*; CoRAB) [4].

Currently, polymyxins including polymyxin B and colistin (polymyxin E) are important treatments for CRAB, which displayed extensive resistance to other antimicrobials. However, the emergence of strains with elevated colistin minimum inhibitory concentrations (MICs) and polymyxin resistance has been documented, and polymyxin monotherapy has failed to meet pharmacokinetic/pharmacodynamic (PK/PD) targets [2, 3]. Polymyxins in combination with other agents are often used in the empirical treatment of CRAB infection, and novel treatment options are needed to increase antimicrobial activity and reduce the development of resistance in extensively drug-resistant *A. baumannii* isolates [3, 5, 6].

Jitaree et al. determined the optimal colistin monotherapy regimen using Monte Carlo simulations. They found that at an MIC of 1 μg/mL, only a daily dose of at least 450 mg could achieve 90% probability of target attainment (PTA) of the area under the unbound colistin plasma concentration–time curve (*f*AUC)/MIC ratio ≥25 among patients with creatinine clearance ≥80 mL/min [7]. Conversely, the most *A. baumannii* isolates had MICs of 1 - 2 μg/mL [6]. Thus, combination regimens with synergistic effects might result in better efficacy and prevent the need for high colistin doses, which increase the risk of nephrotoxicity. Together, the previous data indicated that the trough concentrations of colistin more than 3.3 μg/mL were a predictor for occurrence of acute kidney injury (AKI) [8].

Sulbactam, a beta-lactamase inhibitor, has exhibited activity against CRAB. However, high doses were recommended because of its higher MICs in CRAB isolates. According to Saelim et al., only the maximum daily recommended dose of sulbactam (12 g) delivered using a 2 - 4h infusion or continuous infusion was effective against all isolates with sulbactam MICs of 96 μg/

mL based on meeting the PTA or cumulative fraction of response (CFR) target of the percentage of free drug time exceeding the MIC (*f*Time/MIC). Conversely, 118 CRAB isolates in the study had minimum inhibitory concentration required to inhibit the growth of 50% of organisms (MIC_{50}) and MIC_{90} values of 64 and 192 μg/mL, respectively, for sulbactam [9]. Therefore, monotherapies such as colistin and sulbactam failed to achieve the PK/PD targets.

To date, colistin combinations have been recommended to treat CRAB because most strains remain sensitive to polymyxins [10]. Vardakas et al. evaluated the benefit of colistin in combination with other antibiotics to reduce mortality compared with the effects of colistin monotherapy. A significantly lower death rate was observed for the colistin combination regimen in patients with bloodstream infections and in patients with *Acinetobacter* infections [11].

Certain studies focused on determining the synergistic effects of colistin plus sulbactam or fosfomycin against *A. baumannii* [5, 6]. Our previous study revealed colistin plus sulbactam and colistin plus fosfomycin regimens had synergistic or additive effects against 53.3 and 73.3% of isolates, respectively. No antagonistic effect was observed for any colistin-based combination [6]. Thus, our study illustrated that colistin plus sulbactam might represent a treatment option for CRAB with better PK profiles and low-to-moderate protein binding [12]. Moreover, colistin combined with fosfomycin exerted synergistic or additive effects against CRAB strains and extensively drug-resistant *A. baumannii*. Sulbactam and fosfomycin are currently used at their maximum doses to cover some drug-resistant strains [13, 14].

Thus, the present study aimed to determine the pharmacodynamics of colistin alone or in combination with sulbactam or fosfomycin and develop a potentially appropriate dosage regimen based on Monte Carlo simulation to achieve PK/PD targets for efficacy or nephrotoxicity in critically ill patients with CRAB infection.

MATERIALS AND METHODS

1. Study design and study samples

Fifty CRAB strains were isolated from inpatients admitted to Phramongkutklao Hospital, a 1,200-bed medical school hospital in Bangkok, Thailand, from January 2014 to December 2015. CRAB was defined by resistance to either imipenem or meropenem according to the Clinical and Laboratory Standards Institute (CLSI) interpretation [15]. Based on our inclusion criteria, all clinical isolates were first obtained from blood specimens. Duplicate isolates identified in the same patient or specimens from other sources were excluded. All CRAB strains were stored at −70°C until analysis. The institutional review board approved the research protocol with a waiver for informed consent [No. Q014h/59].

Determination of the colistin MIC was performed using the broth microdilution method. The concentration of colistin was between 0.125 - 16 μg/mL. The MICs of sulbactam and fosfomycin were determined using the agar dilution method with Mueller–Hinton agar plates (Difco, Detroit, MI, USA). Specifically, agar plates contained serial dilutions of fosfomycin plus 25 μg/mL glucose-6-phosphate (G-6-P). The concentration of sulbactam was between 2 - 4,096 μg/mL and fosfomycin was between 2 - 4,096 μg/mL. *Escherichia coli* ATCC 25922 (Department of Medical Sciences Type culture collection, Bangkok, Thailand) was used as a quality control to quantify the accuracy of MIC determination based on CLSI standards [15].

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The MICs of colistin and sulbactam were interpreted using the CLSI susceptibility breakpoints of ≤2 and ≤4 μg/mL, respectively (15). Because of the lack of standard MIC breakpoints fosfomycin against *A. baumannii* in the CLSI criteria, a breakpoint of ≤32 μg/mL was established for fosfomycin according to the European Committee on Antimicrobial Susceptibility Testing [16].

2. Assessments of synergy

The synergy of colistin combined with sulbactam or fosfomycin was assessed using the checkerboard technique. The concentrations of colistin, sulbactam, and fosfomycin were between 0.0625 - 8 μg/mL, 2 - 4,096 μg/mL, and 2 - 4,096 μg/mL, respectively. This technique was performed using cation-adjusted Mueller–Hinton broth (Difco, USA), which was specifically supplemented with 25 g/mL G-6-P for fosfomycin-containing combinations. All samples were incubated at 35°C for 20 h.

The fractional inhibitory concentration index (FICI) is the summation of the individual fractional inhibitory concentrations (FICs) of drugs used in combination. FIC represents the MIC of a drug in combination divided by the MIC of the drug as monotherapy. The FICI was calculated for each combination regimen and interpreted as follows: synergy, ≤0.5; additivity, 0.5 - ≤1; no interaction, >1 - 4; and ≥4, antagonism.

3. Monte Carlo simulation

All PK parameters obtained from published studies of colistin [17], sulbactam [18], and fosfomycin [19] in critically ill patients were collected. The concentration versus time curve was generated using a two-compartment model for sulbactam and fosfomycin and a one-compartment model for colistin. The PK and PD properties of colistin were represented as *f*AUC/MIC ratio, and the target value was ≥25. Contrarily, the PK and PD properties of sulbactam and fosfomycin were represented as %*f*Time/MIC ratio, and the target value was 100%. Nephrotoxicity based on RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria was indicated by colistin trough concentration on day 7 of treatment exceeding 3.3 μg/mL [8].

The optimized dosing regimens of colistin, sulbactam, and fosfomycin were identified using Monte Carlo simulations (Oracle Crystal Ball Classroom Faculty Edition-Oracle 1-Click Crystal Ball 201, Thailand). The Monte Carlo simulation produced 10,000 subjects based on the PK parameters of the studied antibiotics to generate the drug concentration over 24 h. *f*AUC/MIC for colistin and %*f*Time/MIC for sulbactam and fosfomycin were analyzed to indicate the efficacy of each regimen.

The simulation was conducted for various colistin, sulbactam, and fosfomycin dosing regimens using various daily dosages and dosage intervals. The PTA was estimated at each MIC, and the CFR was calculated as the sum of each %PTA against the antibiotic MIC distributions for CRAB. Dosing regimen that reached above 90% of PTA and CFR was highly recommended for documented therapy and empirical therapy against CRAB, respectively. Whereas dosing regimen that reached between 80 - 89% of PTA and CFR was considered as moderately recommended doses for documented therapy and empirical therapy, respectively.

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RESULTS

1. Characteristics, MICs, and antibiotic sensitivities of the study isolates

Fifty unique CRAB strains were collected from blood samples during the study period. Using the disk diffusion method, all CRAB isolates were found to be resistant to ceftazidime, cefepime, piperacillin/tazobactam, imipenem, meropenem, gentamicin, amikacin, and ciprofloxacin, leading to a classification of extensively drug-resistant *A. baumannii*.

MIC_{50}, MIC_{90}, and the MIC range for the studied monotherapies against the CRAB isolates were as follows: 1, 4, and 1 - 16 μg/mL, respectively, for colistin; 64, 128, and 16 - 2,048 μg/mL, respectively, for sulbactam; and 256, 2,048, and 128 – 2,048 μg/mL, respectively, for fosfomycin (**Table 1**).

The combination of colistin and sulbactam exhibited synergistic and additive effects against 15 (30%) and 28 isolates (56%), respectively. Conversely, colistin plus fosfomycin had synergistic and additive effects against 11 (22%) and 33 isolates (66%), respectively. No combination displayed antagonistic effects against any of the strains (**Table 1**).

The use of sulbactam or fosfomycin in combination with colistin resulted in reduced MICs for the latter drug in most of the CRAB isolates (**Table 1**). For the colistin and sulbactam combination, the colistin MIC range decreased from 1 - 16 to 0.0625 – 1 μg/mL. Similarly, the colistin MIC range was reduced to 0.0625 – 2 μg/mL for the colistin and fosfomycin combination. Additionally, both colistin combination regimens were revealed to revert five CoRAB isolates to a colistin-susceptible status.

2. PTA

Regarding PTA for various colistin regimens in critically ill patients, for pathogens with an MIC of 2 μg/mL (the current susceptibility breakpoint for colistin), the ≥90% PTA was only achieved in patients with creatinine clearance <50 mL/min. However, the recommended colistin doses for patients with creatinine clearance of 91 – 130 mL/min, namely 180 mg every 12 h and 150 mg every 8 h, were effective against isolates with colistin MICs of ≤0.25 and ≤0.5 μg/mL, respectively, and the rates of nephrotoxicity were 35 and 54%, respectively (**Table 2**).

For sulbactam dosage regimens that met the PTA target of %*f*Time/MIC = 100%, sulbactam doses as high as 6 g/day for continuous infusion and 8 - 12 g/day for 2 - 24h infusions covered isolates with sulbactam MICs of ≤32 μg/mL (**Table 3**). Meanwhile, only fosfomycin doses of 16 - 24 g/day using 2-, 4-, or 24-h infusions met the PTA target of %*f*Time/MIC = 100% for isolates with fosfomycin MICs of ≤128 μg/mL (**Table 4**).

3. CFR

Based on a CFR of ≥90%, colistin monotherapy regimens were effective against all studied CRAB isolates in patients with creatinine clearance <50 mL/min (**Table 5**).

None of the studied sulbactam or fosfomycin monotherapy regimens gave CFR ≥90% in critically ill patients with CRAB infection. When colistin combinations were used, 6 g/day sulbactam administered via a 4-h or continuous infusion and 8 - 12 g/day administered via 2 - 24h infusion were considered appropriate dosage regimens to archive the CFR target of ≥90% (**Table 3**). For colistin plus fosfomycin combinations, doses of 18 - 24 g administered via continuous infusion, 8 g infused for 4 h every 8 h, and 6 g infused for 2 - 4 h every 6 h were considered appropriate for achieving the CFR target of ≥90% (**Table 4**).

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Table 1. MICs of colistin, sulbactam, and fosfomycin as monotherapy and combination regimens and the FICI-against carbapenem-resistant *Acinetobacter baumannii* isolates (n = 50)

Isolate	MIC (μg/mL)					Synergy study			
	CST	SUL	FOF	CST (+ SUL)	CST (+ FOF)	FICI (CST + SUL)	Result	FICI (CST + FOF)	Result
1	1	32	2,048	1	0.25	1.06	IND	0.5	SYN
2	1	64	128	0.5	0.5	0.52	ADD	1.5	IND
3	1	64	256	0.25	0.5	0.75	ADD	1	ADD
4	1	64	256	0.25	0.5	0.5	SYN	1	ADD
5	1	64	128	0.25	0.5	0.5	SYN	1.5	IND
6	1	128	2,048	0.0625	0.5	0.56	ADD	0.63	ADD
7	1	256	2,048	0.5	0.5	0.53	ADD	0.56	ADD
8	1	64	128	0.25	0.5	0.5	SYN	1.5	IND
9	1	128	1,024	0.5	0.25	0.63	ADD	0.3125	SYN
10	1	16	128	1	0.5	1.13	IND	1.5	IND
11	1	64	256	0.5	0.5	0.75	ADD	0.75	ADD
12	2	64	512	0.5	0.5	0.5	SYN	0.75	ADD
13	16	64	512	0.25	0.5	0.52	ADD	0.28	SYN
14	1	32	512	0.5	0.5	1	ADD	0.75	ADD
15	1	64	256	0.5	0.5	1	ADD	1	ADD
16	1	64	256	0.5	0.25	1	ADD	0.75	ADD
17	1	32	256	0.0625	0.25	0.31	SYN	0.75	ADD
18	1	32	2,048	0.5	0.0625	1	ADD	0.56	ADD
19	1	64	2,048	0.25	0.0625	0.5	SYN	0.56	ADD
20	1	64	512	0.5	0.25	1	ADD	0.75	ADD
21	16	64	256	0.5	0.25	0.16	SYN	1.02	IND
22	1	128	256	0.5	0.25	0.75	ADD	0.75	ADD
23	1	64	256	0.5	0.5	1	ADD	1	ADD
24	16	64	512	0.25	0.25	0.27	SYN	0.27	SYN
25	16	32	256	1	2	1.06	IND	0.63	ADD
26	16	32	256	0.25	1	1.02	IND	0.56	ADD
27	1	128	256	0.5	0.5	0.63	ADD	1	ADD
28	1	16	256	0.5	0.5	1	ADD	0.75	ADD
29	1	64	256	0.5	0.5	0.63	ADD	1	ADD
30	2	128	256	0.5	0.5	0.5	SYN	0.5	SYN
31	1	128	256	0.5	0.5	0.75	ADD	1	ADD
32	1	64	128	0.5	0.5	1	ADD	1	ADD
33	1	32	256	0.5	0.5	1	ADD	0.75	ADD
34	1	128	256	0.5	0.25	0.63	ADD	0.5	SYN
35	1	64	256	0.5	0.125	0.56	ADD	0.63	ADD
36	1	64	256	0.5	0.25	1	ADD	0.75	ADD
37	1	64	128	0.125	0.5	1.13	IND	1	ADD
38	1	64	1,024	0.5	0.5	0.75	ADD	0.63	ADD
39	1	128	512	0.5	0.25	0.56	ADD	0.5	SYN
40	1	128	256	0.5	0.25	0.63	ADD	0.75	ADD
41	1	32	256	0.5	0.25	1.5	IND	0.75	ADD
42	2	2,048	256	0.125	0.25	0.07	SYN	0.63	ADD
43	2	256	1,024	0.5	0.25	0.38	SYN	0.25	SYN
44	2	256	2,048	0.25	0.5	0.38	SYN	0.38	SYN
45	1	64	256	0.0625	0.5	1.06	IND	1	ADD
46	2	2,048	1,024	0.5	0.5	0.26	SYN	0.38	SYN
47	1	64	512	0.25	0.5	0.5	SYN	0.75	ADD
48	1	16	256	0.5	1	1	ADD	1.25	IND
49	2	64	512	0.5	0.5	0.5	SYN	0.5	SYN
50	1	64	256	0.5	0.5	1	ADD	1	ADD
MIC50	1	64	256	0.5	0.5	SYN	15 (30%)	SYN	11 (22%)
MIC90	4	128	2,048	0.5	0.5	ADD	28 (56%)	ADD	33 (66%)
Min	1	16	128	0.0625	0.0625	IND	7 (14%)	IND	6 (12%)
Max	16	2,048	2,048	1	2	Total	50	Total	50

MIC, minimum inhibitory concentration; FICI, fractional inhibitory concentration index; CST, colistin; SUL, sulbactam; FOF, fosfomycin; IND, indifference (FICI = 1 - 4); SYN, synergistic effect (FICI ≤0.5); ADD, additive effect (FICI 0.5 - ≤1); Max, maximum; Min, minimum; MIC50, 50% minimum inhibitory concentration; MIC90, 90% minimum inhibitory concentration.

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Table 2. The PTA for the different colistin regimens in critically ill patients according to kidney function (creatinine clearance) at steady state with targets of *f*AUC24/MIC ≥25 (for efficacy) and trough concentration ≥3.3 μg/mL (risk of acute kidney injury)

Creatinine clearance (mL/min)	Dosage regimens		PTA (%)								Trough concentration ≥3.3 μg/mL (%)
			Colistin MIC (μg/mL) against CRAB isolates								
	Loading dose	Maintenance dose	0.125	0.25	0.5	1	2	4	8	16	
0 – 9	300 mg	100 mg q24h	100	100	100	99	95	82	56	28	69
		100 mg q12h	100	100	100	100	100	97	87	66	83
		150 mg q12h	100	100	100	100	100	97	86	66	83
		150 mg q24h	100	100	100	99	96	81	55	28	70
		180 mg q24h	100	100	100	99	96	81	56	28	70
10 – 25	300 mg	100 mg q12h	100	100	100	100	98	92	75	49	90
		150 mg q12h	100	100	100	100	98	90	73	49	89
		150 mg q24h	100	100	100	97	88	66	37	14	53
		180 mg q24h	100	100	100	97	88	65	36	14	52
26 – 50	300 mg	100 mg q12h	100	100	99	97	91	77	54	29	76
		150 mg q12h	100	100	99	98	92	77	54	29	76
		150 mg q24h	100	99	97	89	70	43	19	6	32
		180 mg q24h	100	99	97	89	71	43	20	6	32
51 – 90	300 mg	150 mg q24h	98	95	87	71	46	22	7	2	15
		150 mg q12h	99	98	95	89	75	54	32	14	54
		150 mg q8h	100	99	98	94	86	71	51	30	73
		180 mg q12h	100	99	96	89	75	54	31	14	55
		180 mg q8h	100	99	98	94	86	72	51	30	74
91 – 130	300 mg	150 mg q12h	98	95	88	75	56	34	16	6	34
		150 mg q8h	99	97	93	84	71	52	32	16	54
		180 mg q12h	98	95	87	75	55	33	16	6	35
		180 mg q8h	99	97	93	85	71	51	31	14	54

Color codes Strongly recommended dose based on ■ ≥90% PTA or □ ≥90% CFR.
Moderately recommended dose based on 80 - 89% PTA or 80 - 89% CFR.
PTA, probability of target attainment; AUC, area under the curve; MIC, minimum inhibitory concentration; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CFR, cumulative fraction of response.

Table 3. PTA for different sulbactam doses in critically ill patients at steady state with a target of %*f*Time/MIC = 100 and the CFR of sulbactam monotherapy and combinations with various dosing regimens

Daily dose	Infusion time (h)	PTA (%)									CFR (%)	
		SUL MIC (μg/mL) against CRAB isolates									SUL (mono)	SUL (with CST)
		4	8	16	32	64	128	256	512	1,024		
1 g q8h	4	100	97	84	44	5	0	0	0	0	15	68
1 g q6h	4	100	99	92	64	18	1	0	0	0	25	79
1 g q6h	2	100	100	96	72	22	1	0	0	0	28	83
2 g q8h	4	100	100	97	85	45	6	0	0	0	43	90
6 g	24	100	100	100	97	64	10	0	0	0	55	96
2 g q6h	4	100	100	99	93	65	19	1	0	0	57	95
2 g q6h	2	100	100	100	96	73	23	1	0	0	62	97
3 g q8h	4	100	100	99	94	71	24	1	0	0	61	95
9 g	24	100	100	100	100	89	39	2	0	0	74	99
4 g q8h	4	100	100	100	97	85	45	6	0	0	72	98
4 g q8h	2	100	100	100	99	91	52	8	0	0	77	99
3 g q6h	4	100	100	99	96	79	39	5	0	0	68	97
3 g q6h	2	100	100	100	97	85	44	6	0	0	72	98
12 g	24	100	100	100	100	97	65	11	0	0	83	100

Color codes Strongly recommended dose based on ■ ≥90% PTA or □ ≥90% CFR.
Moderately recommended dose based on 80% - 89% PTA or 80% - 89% CFR.
PTA, probability of target attainment; MIC, minimum inhibitory concentration; CFR, cumulative fraction of response; SUL; sulbactam; CRAB, carbapenem-resistant *Acinetobacter baumannii*; mono, monotherapy; CST, colistin.

Similarly, based on CFR ≥90%, no colistin monotherapy regimens covered all studied CRAB isolates for patients with creatinine clearance of 91 – 130 mL/min. Interestingly, the appropriate colistin dose for patients with creatinine clearance of 91 – 130 mL/min was 150 mg given every 12 h in combination with sulbactam (≥6 g/day) or fosfomycin (≥18 g/day) achieving ≥90% CFR (**Table 5**).

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Table 4. PTA for the different fosfomycin dosing regimens in critically ill patients at steady state with a target of %*f*Time/MIC = 100 and the CFR of fosfomycin monotherapy and combinations with various dosing regimens

Daily dose	Regimens	Infusion time (h)	PTA (%)									CFR (%)	
			FOF MIC (μg/mL) against CRAB isolates									FOF (mono)	FOF (with CST)
			4	8	16	32	64	128	256	512	1,024		
12 g	4 g q8h	0.5	100	100	100	98	93	80	47	5	0	35	74
		2	100	100	100	98	94	81	49	5	0	36	75
		4	100	100	100	99	95	84	51	5	0	37	78
	3 g q6h	2	100	100	100	99	95	83	53	8	0	39	77
		4	100	100	100	99	96	85	55	8	0	40	79
	12 g	24	100	100	100	100	98	89	59	10	0	43	82
16 g	4 g q6h	2	100	100	100	99	97	90	68	25	0	50	84
		4	100	100	100	100	98	92	70	26	0	52	86
	16 g	24	100	100	100	100	99	94	74	29	0	54	88
18 g	6 g q8h	0.5	100	100	100	99	97	90	69	26	0	51	84
		2	100	100	100	99	98	91	71	28	0	52	85
		4	100	100	100	100	98	92	72	28	0	53	86
	18 g	24	100	100	100	100	100	96	79	37	1	59	90
20 g	5 g q6h	2	100	100	100	100	99	93	77	41	2	58	88
		4	100	100	100	100	99	95	80	42	2	60	89
	20 g	24	100	100	100	100	100	97	83	46	3	62	91
24 g	8 g q8h	0.5	100	100	100	99	98	94	80	46	4	61	89
		2	100	100	100	100	98	94	81	48	4	61	89
		4	100	100	100	100	99	95	83	51	5	63	90
	6 g q6h	2	100	100	100	100	99	96	83	53	7	64	91
		4	100	100	100	100	99	97	85	54	8	65	92
	24 g	24	100	100	100	100	100	98	89	59	10	68	93

Color codes Strongly recommended dose based on ■ ≥90% PTA or □ ≥90% CFR.
Moderately recommended dose based on 80% - 89% PTA or 80% - 89% CFR.
PTA, probability of target attainment; MIC, minimum inhibitory concentration; CFR, cumulative fraction of response; FOF, fosfomycin; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CST, colistin.

Table 5. CFR of colistin monotherapy and colistin plus sulbactam or fosfomycin combinations with various dosing regimens

Creatinine clearance (mL/min)	Dosage regimens		CFR (%)			Trough concentration ≥3.3 μg/mL (%)
	Loading dose	Maintenance dose	CST (mono)	CST (with SUL)	CST (with FOF)	
0 – 9	300 mg	100 mg q24h	91	100	100	69
		100 mg q12h	97	100	100	83
		150 mg q12h	97	100	100	83
		150 mg q24h	91	100	100	70
		180 mg q24h	91	100	100	70
10 – 25	300 mg	100 mg q12h	95	100	100	90
		150 mg q12h	95	100	100	89
		150 mg q24h	87	100	100	53
		180 mg q24h	87	100	100	52
26 – 50	300 mg	100 mg q12h	89	99	99	76
		150 mg q12h	90	99	99	76
		150 mg q24h	78	97	97	32
		180 mg q24h	78	97	97	32
51 – 90	300 mg	150 mg q24h	60	89	89	15
		150 mg q12h	80	96	96	54
		150 mg q8h	86	98	98	73
		180 mg q12h	80	97	96	55
		180 mg q8h	86	98	98	74
91 – 130	300 mg	150 mg q12h	65	90	90	34
		150 mg q8h	75	94	94	54
		180 mg q12h	65	90	90	35
		180 mg q8h	76	94	94	54

Color codes Strongly recommended dose based on ■ ≥90% PTA or □ ≥90% CFR.
Moderately recommended dose based on 80 - 89% PTA or 80 - 89% CFR.
CFR, cumulative fraction of response; CST, colistin; mono, monotherapy; SUL; sulbactam; FOF, fosfomycin; PTA, probability of target attainment.

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DISCUSSION

At present, *A. baumannii* represents a major cause of nosocomial infections, and few effective agents are available for CRAB isolates. Thus, optimization of the available drug regimens is critical for treating infections caused by this pathogen. The application of PK/PD principles based on Monte Carlo simulation is a method for identifying optimal antibiotic regimens for empirical or documented therapy, especially considering increases in drug MICs in the drug resistance era [20].

The only PK/PD index predicting colistin efficacy against *A. baumannii* was described in an *in vivo* study of neutropenic murine thigh and lung infection models. The *f*AUC/MIC targets required to achieve 1 log reduction (bacteriostatic effect) and 2 log reduction (bactericidal effect) against the multidrug-resistant (MDR)-AB strain were 13.6 and 24.7, respectively, in the thigh infection model. Meanwhile, the corresponding indices in the lung infection model were 12.9 and 22.5, respectively [21]. Similarly, recommendations from the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP) suggested AUCss,24 h of approximately 50 mg·h/L for the total drug content (25 mg·h/L for the free drug), equating to an average steady state plasma concentration of approximately 2 mg/L for MDR Gram-negative bacteria [10].

Unfortunately, our data illustrated that no colistin monotherapy regimen achieved PTA of ≥90% for $fAUC_{24\,h}$/MIC ≥25 against *A. baumannii* isolates with MIC of 2 μg/mL in patients with creatinine clearance >50 mL/min. Because of the elevated colistin MICs observed in this study, the current recommended dose of colistin (150 - 180 mg every 12 h) was not sufficient for *A. baumannii* treatment, especially among patients with normal renal function (creatinine clearance >90 mL/min) [10]. In addition, a high colistin dose of 180 mg every 8 h was effective only against isolates with MIC ≤0.5 μg/mL.

Additionally, nephrotoxicity is a key side effect of colistin. Sorli et al. found that plasma colistin concentrations exceeding 3.3 μg/mL on day 7 of therapy were significantly associated with AKI [8]. Using this threshold, our results confirmed the difficulty of balancing efficacy and nephrotoxicity risk for colistin monotherapy.

The findings regarding the synergy and additivity of the colistin-containing combination regimens were similar to our previous results. Specifically, our prior research identified synergistic/additive effects of colistin plus sulbactam and colistin plus fosfomycin against 13.3/40 and 26.7%/46.7% of CRAB isolates, respectively. Similarly, our prior analysis also identified no evidence of antagonism [6]. The observed synergy and additivity resulted in reduced MIC ranges for most studied isolates, and the regimens also converted a group of five CoRAB isolates to a colistin-susceptible status. Thus, the synergistic and additive effects of colistin-based combination increased the probability of achieving the colistin PK/PD index.

From our findings, for CFR ≥90%, no colistin monotherapy regimens had a *f*AUC24/MIC ratio of at least 25 in patients with creatinine clearance >50 mL/min. Interestingly, several combination regimens containing sulbactam or fosfomycin were effective. Moreover, these regimens also reduced the risk of colistin-associated nephrotoxicity. Among these regimens, we recommended the colistin dose giving the CFR more than 90% but such regimen showed

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the lowest risk of AKI (C_{trough} ≥3.3 μg/mL). Thus, antibiotic combination therapy can balance efficacy and safety of colistin therapy.

In line with our findings regarding the effective doses, high sulbactam doses were applied in several previous clinical studies [13, 22, 23]. Meanwhile, although the use of high fosfomycin doses has been reported [24], the associated risks of hypernatremia and hypokalemia are concerning [25].

According to a clinical study of colistin combination regimens, the risk of mortality was significantly lower for colistin-based combinations than for colistin monotherapy, including the combination of colistin and carbapenems (odds ratio [OR] = 1.58, 95% confidence interval [CI] = 1.03 - 2.42) and colistin in combination with tigecycline, aminoglycosides, or fosfomycin (OR = 1.57, 95% CI = 1.06 - 2.32) [26]. Kengkla et al. also found that colistin in combination with sulbactam was associated with a significantly higher microbiological cure rate than colistin monotherapy (relative risk = 1.21, 95% CI = 1.06 - 1.38) [27]. Additionally, Sirijatuphat and Thamlikitkul performed a randomized controlled trial to compare colistin monotherapy and colistin plus fosfomycin for the treatment of CRAB infections. They found that patients who received the combination regimen had a significantly more favorable microbiological response than those who received colistin monotherapy, in addition to numerically better rates of good clinical outcomes and mortality [28]. Thus, the use of colistin in combination with sulbactam or fosfomycin represents an alternative strategy for combating CRAB.

Colistin combination therapy represents an interesting treatment option for *A. baumannii* infections. However, the ACCP, ESCMID, IDSA, ISAP, SCCM, and SIDP recommendations suggested that if a second active agent is unavailable, colistin should be used as monotherapy. However, this recommendation was not strongly supported (the panel voted 8 - 7 in favor of monotherapy), and it was based on moderate quality evidence [10]. According to the controversial data, further research is needed to determine the role of colistin-based combinations in the management of infections caused by CRAB. Finally, newer antibiotics have been launched for CRAB treatment, including everacycline, cefiderocol, and plazomicin, and they might represent interesting therapeutic options for CRAB infections [29].

From our findings, the susceptibility data as MIC values is used for optimization of colistin monotherapy regimens against CRAB infection with less nephrotoxicity. If the synergy testing is feasible to perform in the clinical setting. The synergy testing might require for patient whose CRAB has high MIC of colistin in order to reduce colistin dosage, and to prevent the nephrotoxicity.

For limitation in our study, we used the PK parameters of colistin and sulbactam from Asian population as a first priority but the population PK in critically ill patients for fosfomycin in Asian population was not available. Moreover, there is limited data published with regards to comparing PK parameters for colistin, sulbactam, and fosfomycin across ethic populations. Thus, the impact of different PK and the application of our findings to other populations had to be concerned. Even the appropriate sulbactam and fosfomycin doses in combination with colistin for patients with creatinine clearance of 91–130 mL/min were as ≥6 g/day and fosfomycin ≥18 g/day, respectively. The doses of sulbactam and fosfomycin for patients with creatinine clearance less than 90 mL/min have to be adjusted for their renal function. Lastly, our study only recommended the possible dose of studied antibiotics to meet the PK/

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PD target in each drug. The clinical studies of our recommended dosing have to confirm the benefits of colistin combination with sulbactam or tigecycline against CRAB infections.

In conclusion, colistin monotherapy was ineffective against CRAB isolates, especially in patients with creatinine clearance >90 mL/min. Additionally, the current dosing of 360 mg/day based on ACCP, ESCMID, IDSA, ISAP, SCCM, and SIDP recommendations might not be optimal for infection by CRAB isolates with MIC 1 - 2 μg/mL. The use of colistin combined with sulbactam at 6 g/day or fosfomycin at 18g/day might increase a probability for achievement colistin PK/PD targets and decrease the risk of nephrotoxicity.

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REFERENCES

1. Ramirez MS, Bonomo RA, Tolmasky ME. Carbapenemases: Transforming *Acinetobacter baumannii* into a yet more dangerous menace. Biomolecules 2020;10:720.
PUBMED | CROSSREF
2. Santimaleeworagun W, Thunyaharn S, Juntanawiwat P, Thongnoy N, Harindhanavudhi S, Nakeesathit S, Teschumroon S. The prevalence of colistin-resistant Gram-negative bacteria isolated from hospitalized patients with bacteremia. J Appl Pharm Sci 2020;10:056-9.
CROSSREF
3. Lertsrisatit Y, Santimaleeworagun W, Thunyaharn S, Traipattanakul J. In vitro activity of colistin mono- and combination therapy against colistin-resistant *Acinetobacter baumannii*, mechanism of resistance, and clinical outcomes of patients infected with colistin-resistant *A. baumannii* at a Thai university hospital. Infect Drug Resist 2017;10:437-43.
PUBMED | CROSSREF
4. National Antimicrobial Resistant Surveillance Center. Thailand (NARST). Antibiogram 2019. Available at: http://narst.dmsc.moph.go.th/. Accessed 15 November 2020.
5. Santimaleeworagun W, Wongpoowarak P, Chayakul P, Pattharachayakul S, Tansakul P, Garey KW. In vitro activity of colistin or sulbactam in combination with fosfomycin or imipenem against clinical isolates of carbapenem-resistant *Acinetobacter baumannii* producing OXA-23 carbapenemases. Southeast Asian J Trop Med Public Health 2011;42:890-900.
PUBMED
6. Leelasupasri S, Santimaleeworagun W, Jitwasinkul T. Antimicrobial susceptibility among colistin, sulbactam, and fosfomycin and a synergism study of colistin in combination with sulbactam or fosfomycin against Clinical isolates of carbapenem-resistant *Acinetobacter baumannii*. J Pathogens 2018;2018:3893492.
PUBMED | CROSSREF
7. Jitaree K, Sathirakul K, Houngsaitong J, Asuphon O, Saelim W, Thamlikitkul V, Montakantikul P. Pharmacokinetic/pharmacodynamic (PK/PD) simulation for dosage optimization of colistin against carbapenem-resistant *Klebsiella pneumoniae* and carbapenem-resistant *Escherichia coli*. Antibiotics (Basel) 2019;8:125.
PUBMED | CROSSREF
8. Sorli L, Luque S, Grau S, Berenguer N, Segura C, Montero MM, et al. Trough colistin plasma level is an independent risk factor for nephrotoxicity: a prospective observational cohort study. BMC Infect Dis 2013;13:380.
PUBMED | CROSSREF
9. Saelim W, Santimaleeworagun W, Thunyaharn S, Changpradub D, Juntanawiwat P. Pharmacodynamic profiling of optimal sulbactam regimens against carbapenem-resistant *Acinetobacter baumannii* for critically ill patients. Asian Pac J Trop Biomed 2018;8:14-8.
CROSSREF

10. Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, Giacobbe DR, Viscoli C, Giamarellou H, Karaiskos I, Kaye D, Mouton JW, Tam VH, Thamlikitkul V, Wunderink RG, Li J, Nation RL, Kaye KS. International consensus guidelines for the optimal use of the polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy 2019;39:10-39.
PUBMED | CROSSREF

11. Vardakas KZ, Mavroudis AD, Georgiou M, Falagas ME. Intravenous colistin combination antimicrobial treatment vs. monotherapy: a systematic review and meta-analysis. Int J Antimicrob Agents 2018;51:535-47.
PUBMED | CROSSREF

12. Vila J, Pachón J. Therapeutic options for *Acinetobacter baumannii* infections: an update. Expert Opin Pharmacother 2012;13:2319-36.
PUBMED | CROSSREF

13. Betrosian AP, Frantzeskaki F, Xanthaki A, Georgiadis G. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant *Acinetobacter baumannii*. Scand J Infect Dis 2007;39:38-43.
PUBMED | CROSSREF

14. Shorr AF, Pogue JM, Mohr JF. Intravenous fosfomycin for the treatment of hospitalized patients with serious infections. Expert Rev Anti Infect Ther 2017;15:935-45.
PUBMED | CROSSREF

15. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing: Twenty-ninth informational supplement. Wayne, PA: CLSI; 2019.

16. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Clinical breakpoint tables for interpretation of MICs and zone diameters Version 10, 2019. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed 15 May 2020.

17. Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, Silveira FP, Forrest A, Nation RL. 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;55:3284-94.
PUBMED | CROSSREF

18. Jaruratanasirikul S, Wongpoowarak W, Wattanavijitkul T, Sukarnjanaset W, Samaeng M, Nawakitrangsan M, Ingviya N. Population pharmacokinetics and pharmacodynamics modeling to optimize dosage regimens of sulbactam in critically ill patients with severe sepsis caused by *Acinetobacter baumannii*. Antimicrob Agents Chemother 2016;60:7236-44.
PUBMED | CROSSREF

19. Parker SL, Frantzeskaki F, Wallis SC, Diakaki C, Giamarellou H, Koulenti D, Karaiskos I, Lipman J, Dimopoulos G, Roberts JA. Population pharmacokinetics of fosfomycin in critically ill patients. Antimicrob Agents Chemother 2015;59:6471-6.
PUBMED | CROSSREF

20. Asín-Prieto E, Rodríguez-Gascón A, Isla A. Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents. J Infect Chemother 2015;21:319-29.
PUBMED | CROSSREF

21. Dudhani RV, Turnidge JD, Nation RL, Li J. fAUC/MIC is the most predictive pharmacokinetic/pharmacodynamic index of colistin against *Acinetobacter baumannii* in murine thigh and lung infection models. J Antimicrob Chemother 2010;65:1984-90.
PUBMED | CROSSREF

22. Jaruratanasirikul S, Nitchot W, Wongpoowarak W, Samaeng M, Nawakitrangsan M. Population pharmacokinetics and Monte Carlo simulations of sulbactam to optimize dosage regimens in patients with ventilator-associated pneumonia caused by *Acinetobacter baumannii*. Eur J Pharm Sci 2019;136:104940.
PUBMED | CROSSREF

23. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. J Infect 2008;56:432-6.
PUBMED | CROSSREF

24. Tsegka KG, Voulgaris GL, Kyriakidou M, Falagas ME. Intravenous fosfomycin for the treatment of patients with central nervous system infections: evaluation of the published evidence. Expert Rev Anti Infect Ther 2020;18:657-68.
PUBMED | CROSSREF

25. Kanchanasurakit S, Santimaleeworagun W, McPherson CE, Piriyachananusorn N, Boonsong B, Katwilat P, Saokaew S. Fosfomycin dosing regimens based on monte carlo simulation for treated carbapenem-resistant *Enterobacteriaceae* Infection. Infect Chemother 2020;52:516-29.
PUBMED | CROSSREF

26. Zusman O, Altunin S, Koppel F, Dishon Benattar Y, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. J Antimicrob Chemother 2017;72:29-39.
PUBMED | CROSSREF

27. Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: a systematic review and network meta-analysis. J Antimicrob Chemother 2018;73:22-32.
PUBMED | CROSSREF

28. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections. Antimicrob Agents Chemother 2014;58:5598-601.
PUBMED | CROSSREF

29. Santimaleeworagun W, Changpradub D, Thunyaharn S, Hemapanpairoa J. Optimizing the Dosing Regimens of Daptomycin Based on the Susceptible Dose-Dependent Breakpoint against Vancomycin-Resistant Enterococci Infection. Antibiotics (Basel) 2019;8:245.
PUBMED | CROSSREF