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 MIC50 and MIC90 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 (fAUC24)/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
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 \( A. \) \textit{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**

\textit{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 \( A. \) \textit{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, \( A. \) \textit{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 \( A. \) \textit{baumannii} isolates are carbapenem-resistant, whereas few strains are resistant to colistin (colistin resistant \( A. \) \textit{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 \( A. \) \textit{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 (\( fAUC\)/MIC ratio ≥ 25) among patients with creatinine clearance ≥ 80 mL/min [7]. Conversely, the most \( A. \) \textit{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].
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 35ºC 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 fAUC/MIC ratio, and the target value was ≥25. Contrarily, the PK and PD properties of sulbactam and fosfomycin were represented as %fTime/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. fAUC/MIC for colistin and %fTime/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.
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 %/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 %/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).
### 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 | 0.25 | 0.5 | 1.06 | IND | 0.5 | SYN |
| 2 | 1 | 0.25 | 0.5 | 0.52 | ADD | 1.5 | IND |
| 3 | 1 | 0.25 | 0.5 | 0.75 | ADD | 1 | ADD |
| 4 | 1 | 0.25 | 0.5 | 0.5 | SYN | 1 | ADD |
| 5 | 1 | 0.25 | 0.5 | 0.5 | SYN | 1.5 | IND |
| 6 | 1 | 0.25 | 0.5 | 0.56 | ADD | 0.63 | ADD |
| 7 | 1 | 0.25 | 0.5 | 0.53 | ADD | 0.56 | ADD |
| 8 | 1 | 0.25 | 0.5 | 0.5 | SYN | 1.5 | IND |
| 9 | 1 | 0.25 | 0.5 | 0.63 | ADD | 0.3125 | SYN |
| 10 | 1 | 0.25 | 0.5 | 1.13 | IND | 1.5 | IND |
| 11 | 1 | 0.25 | 0.5 | 0.75 | ADD | 0.75 | ADD |
| 12 | 1 | 0.25 | 0.5 | 0.5 | SYN | 0.75 | ADD |
| 13 | 1 | 0.25 | 0.5 | 0.52 | ADD | 0.28 | SYN |
| 14 | 1 | 0.25 | 0.5 | 1 | ADD | 0.75 | ADD |
| 15 | 1 | 0.25 | 0.5 | 1 | ADD | 1 | ADD |
| 16 | 1 | 0.25 | 0.5 | 1 | ADD | 0.75 | ADD |
| 17 | 1 | 0.25 | 0.5 | 0.31 | SYN | 0.75 | ADD |
| 18 | 1 | 0.25 | 0.5 | 0.56 | ADD | 1 | ADD |
| 19 | 1 | 0.25 | 0.5 | 0.56 | ADD | 1 | ADD |
| 20 | 1 | 0.25 | 0.5 | 1 | ADD | 0.75 | ADD |
| 21 | 1 | 0.25 | 0.5 | 0.16 | SYN | 1.02 | IND |
| 22 | 1 | 0.25 | 0.5 | 0.75 | ADD | 0.75 | ADD |
| 23 | 1 | 0.25 | 0.5 | 1 | ADD | 1 | ADD |
| 24 | 1 | 0.25 | 0.5 | 0.27 | SYN | 0.27 | SYN |
| 25 | 1 | 0.25 | 0.5 | 1.06 | IND | 0.63 | ADD |
| 26 | 1 | 0.25 | 0.5 | 1 | 1.02 | IND | 0.56 | ADD |
| 27 | 1 | 0.25 | 0.5 | 0.63 | ADD | 1 | ADD |
| 28 | 1 | 0.25 | 0.5 | 1 | ADD | 0.75 | ADD |
| 29 | 1 | 0.25 | 0.5 | 0.63 | ADD | 1 | ADD |
| 30 | 1 | 0.25 | 0.5 | 0.5 | SYN | 0.5 | SYN |
| 31 | 1 | 0.25 | 0.5 | 0.75 | ADD | 1 | ADD |
| 32 | 1 | 0.25 | 0.5 | 1 | ADD | 1 | ADD |
| 33 | 1 | 0.25 | 0.5 | 1 | ADD | 0.75 | ADD |
| 34 | 1 | 0.25 | 0.5 | 0.63 | ADD | 0.5 | SYN |
| 35 | 1 | 0.25 | 0.5 | 0.56 | ADD | 0.63 | ADD |
| 36 | 1 | 0.25 | 0.5 | 1 | ADD | 0.75 | ADD |
| 37 | 1 | 0.25 | 0.5 | 1.33 | IND | 1 | ADD |
| 38 | 1 | 0.25 | 0.5 | 0.75 | ADD | 0.63 | ADD |
| 39 | 1 | 0.25 | 0.5 | 0.56 | ADD | 0.5 | SYN |
| 40 | 1 | 0.25 | 0.5 | 0.63 | ADD | 0.75 | ADD |
| 41 | 1 | 0.25 | 0.5 | 1.5 | IND | 0.75 | ADD |
| 42 | 1 | 0.25 | 0.5 | 0.07 | SYN | 0.63 | ADD |
| 43 | 1 | 0.25 | 0.5 | 0.38 | SYN | 0.25 | SYN |
| 44 | 1 | 0.25 | 0.5 | 0.38 | SYN | 0.38 | SYN |
| 45 | 1 | 0.25 | 0.5 | 1.06 | IND | 1 | ADD |
| 46 | 1 | 0.25 | 0.5 | 0.26 | SYN | 0.38 | SYN |
| 47 | 1 | 0.25 | 0.5 | 0.5 | SYN | 0.75 | ADD |
| 48 | 1 | 0.25 | 0.5 | 1 | ADD | 1.25 | IND |
| 49 | 1 | 0.25 | 0.5 | 0.5 | SYN | 0.5 | SYN |
| 50 | 1 | 0.25 | 0.5 | 1 | ADD | 1 | ADD |
| MIC50 | 1 | 0.25 | 0.5 | 0.5 | SYN | 15 (30%) | SYN |
| MIC90 | 1 | 0.25 | 0.5 | 0.5 | ADD | 28 (56%) | ADD |
| Min | 1 | 0.25 | 0.5 | 0.5 | SYN | 0.5 | SYN |
| Max | 1 | 0.25 | 0.5 | 0.5 | SYN | 0.5 | SYN |

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.
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 \( f_aUC24/MIC \geq 25 \) (for efficacy) and trough concentration \( \geq 3.3 \mu g/mL \) (risk of acute kidney injury).

| Creatinine clearance (mL/min) | Dosage regimens | PTA (%) | Trough concentration \( \geq 3.3 \mu g/mL \) (%) |
|-------------------------------|-----------------|---------|---------------------------------|
|                               | Loading dose    | Maintenance dose | Colistin MIC (µg/mL) against CRAB isolates |                               |
|                               | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 |
| 0 – 9                         | 300 mg | 100 mg q24h | 100 | 100 | 100 | 99 | 95 | 82 | 56 | 28 | 68 |
|                               | 100 mg q12h | 100 | 100 | 100 | 100 | 97 | 87 | 66 | 83 |
|                               | 150 mg q12h | 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 | 98 | 98 | 95 | 89 | 75 | 54 | 32 | 14 | 54 |
|                               | 150 mg q8h | 100 | 98 | 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 \( \geq 90\% \) PTA or \( \geq 90\% \) 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 \%\text{Time}/MIC = 100 and the CFR of sulbactam monotherapy and combinations with various dosing regimens.

| Daily dose | Infusion time (h) | SUL MIC (µg/mL) against CRAB isolates | PTA (%) | CFR (%) |
|------------|------------------|--------------------------------------|---------|---------|
|            | 4 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | 1,024 |
|            | SUL (mono) | SUL (with CST) |
| 1 g q8h    | 4 | 100 | 97 | 84 | 44 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 15 | 58 |
| 1 g q6h    | 4 | 100 | 99 | 92 | 64 | 18 | 1 | 0 | 0 | 0 | 0 | 25 | 79 |
| 1 g q4h    | 2 | 100 | 100 | 96 | 72 | 22 | 1 | 0 | 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 | 99 | 93 | 65 | 19 | 1 | 0 | 0 | 55 | 96 |
| 2 g q6h    | 4 | 100 | 100 | 99 | 94 | 71 | 24 | 1 | 0 | 0 | 61 | 95 |
| 2 g q4h    | 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 q6h    | 2 | 100 | 100 | 100 | 99 | 91 | 52 | 8 | 0 | 0 | 77 | 99 |
| 3 g q8h    | 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 \( \geq 90\% \) PTA or \( \geq 90\% \) 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; CST, colistin. Similarly, based on CFR \( \geq 90\% \), 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 (\( \geq 6 \) g/day) or fosfomycin (\( \geq 18 \) g/day) achieving \( \geq 90\% \) CFR (Table 5).
Table 4. PTA for the different fosfomycin dosing regimens in critically ill patients at steady state with a target of %/Time/MIC = 100 and the CFR of fosfomycin monotherapy and combinations with various dosing regimens

| Daily dose | Regimens | Infusion time (h) | PTA (%) | CFR (%) |
|------------|----------|-------------------|---------|---------|
| 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 |
| 16 g       | 4 g q6h  | 2                 | 100 100 100 100 98 89 59 10 0 | 43 82 |
|            | 4        | 100 100 100 100 98 92 70 26 0 | 52 86 |
| 18 g       | 6 g q8h  | 0.5               | 100 100 100 99 97 90 68 25 0 | 50 84 |
|            | 2        | 100 100 100 99 98 91 71 28 0 | 51 84 |
|            | 4        | 100 100 100 99 98 92 72 28 0 | 53 86 |
| 20 g       | 5 g q6h  | 2                 | 100 100 100 99 99 96 79 37 1 | 59 90 |
|            | 4        | 100 100 100 100 99 95 80 42 2 | 60 89 |
| 24 g       | 8 g q8h  | 0.5               | 100 100 100 99 98 94 80 46 4 | 61 89 |
|            | 2        | 100 100 100 100 99 98 94 81 48 4 | 61 89 |
|            | 4        | 100 100 100 100 99 95 83 51 5 | 63 90 |
| 18 g       | 6 g q6h  | 2                 | 100 100 100 100 96 99 86 54 8 | 65 92 |
|            | 4        | 100 100 100 100 98 99 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 regimen | CST (mono) | CST (with SUL) | CST (with FOF) |
|-------------------------------|----------------|------------|----------------|---------------|
| 0 – 9                         | 300 mg         | 91 100 100 100 69 | 100 100 100 100 83 | 100 100 100 100 83 |
| 10 – 25                       | 300 mg         | 97 100 100 100 70 | 100 100 100 100 70 | 100 100 100 100 70 |
| 26 – 50                       | 300 mg         | 89 99 99 99 76 | 99 99 99 99 76 | 99 99 99 99 76 |
| 51 – 90                       | 300 mg         | 90 99 99 99 76 | 99 99 99 99 76 | 99 99 99 99 76 |
| 91 – 130                      | 300 mg         | 60 89 89 89 15 | 96 96 96 96 54 | 96 96 96 96 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.
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 \( \text{fAUC}/\text{MIC} \) 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 \( \geq 90\% \) for \( \text{fAUC}24/\text{MIC} \geq 25 \) 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 \( \leq 0.5 \) 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 \( \geq 90\% \), no colistin monotherapy regimens had a \( \text{fAUC}24/\text{MIC} \) 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
the lowest risk of AKI ($C_{\text{trough}} \geq 3.3 \mu g/mL$). 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 $A. \text{baumannii}$ 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/
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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