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Research Article

Optimal dosing regimen of biapenem and fosfomycin sodium combination against multidrug resistant *Acinetobacter baumannii* infection in pediatric patients using Monte Carlo simulation

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ABSTRACT

The objective of this study was to determine the optimal dosage regimens of biapenem and fosfomycin combination achieving desirable pharmacodynamic effects against multidrug-resistant *Acinetobacter baumannii* (MDR-AB) infections in pediatric patients. A total of 120 clinical MDR-AB strains were collected from tertiary hospitals in Thailand. Minimum inhibition concentrations (MICs) of all the isolates were determined by broth microdilution method. Synergy studies were performed using the checkerboard method. The population pharmacokinetic (PK) parameters of biapenem were obtained from a previously published study. PK parameters of fosfomycin were analyzed by using published plasma concentrations of pediatric patients. Then, these PK parameters and MIC after synergy were used in Monte Carlo simulation to find the exposure time during which drug concentration remains above the MIC. MIC for 50% of the isolates (MIC_{50}) of biapenem before and after synergy with fosfomycin were 16 and 2 mcg/mL, respectively, and MIC_{50} of fosfomycin before and after synergy with biapenem were 256 and 32 mcg/mL, respectively, for MDR-AB. Biapenem 5 mg/kg q8 h 3-h infusion and fosfomycin 100 mg/kg q8 h 8-h infusion could be used for *A. baumannii* susceptible to biapenem and fosfomycin. For organisms that are resistant to biapenem and fosfomycin, only biapenem can be used. However, biapenem 5, 10 mg/kg q8 h 3-h infusion and fosfomycin 480-600 mg/kg/day with prolonged infusion provided >80% cumulative fraction of response (CFR). In conclusion, extended biapenem infusion combined with prolonged high-dose fosfomycin infusion would be an option for the treatment of MDR-AB infection in pediatric patients.

Keywords:
Biapenem, Fosfomycin, Monte Carlo simulation, *Acinetobacter baumnnii*, Pediatric patients

1. INTRODUCTION

Acinetobacter baumannii (A. baumannii) is a bacterium of the genus *Acinetobacter* spp. glucose-nonfermentative aerobic Gram-negative coccobacilli[1-2], causing serious infections such as blood stream infection, respiratory tract infection, urinary tract infection, skin and soft tissue infection, and meningitis. In pediatric patients, *A. baumannii* is one of the three common causes of ventilator associated pneumonia (VAP)[3] and the second most frequent cause of bloodstream infection[4], and is associated with high mortality rate, ranging from 17% to 52%[5]. In pediatric patients, carbapenem-resistant *A. baumannii* (CRAB) blood stream infection 2-week and 30-day case fatality rates were 39% and 42%, respectively. More importantly, the prevalence of multidrug-resistant *A. baumannii* (MDR-AB) is increasing in both adult and pediatric patients, making drugs of choice such as carbapenems, less effective.

In 2008, the World Health Organization (WHO) listed CRAB as a critical priority pathogen[6]. While waiting for new antibiotics to be developed, maximizing efficacy of

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the existing antibiotics is likely the measure to combat this resistant pathogen. Dosage regimen modification and combination of antibiotics to achieve desirable therapeutic target or synergistic effect based on pharmacokinetic modeling and pharmacokinetic-pharmacodynamic analysis can be useful.

Biapenem is a newest broad-spectrum parenteral carbapenem with activity against both gram-positive and gram-negative bacteria. It has been used for many infectious diseases, such as pneumonia, sepsis, urinary tract infections and intra-abdominal infections, in both adults and children[7]. It is mainly excreted by glomerular filtration[8]. There is a study showed biapenem had a $MIC_{50/90}$ against MDR-AB of 16/32, which was lower than imipenem and meropenem ($MIC_{50/90}$: 32/128 and 32/64, respectively)[9].

Fosfomycin is an older antibiotic agent, the injectable form was approved in Japan, many countries in Europe, and Thailand[10]. Fosfomycin is excreted unchanged in the urine about 93-99%[10]. Although *A. baumannii* is intrinsically resistant to fosfomycin, it has become an attractive antibiotic since many studies have shown synergistic activity between fosfomycin and other antibiotics against advanced resistant pathogens, such as colistin against OXA-23-producing *A. baumannii* and carbapenem against carbapenem-resistant *Pseudomonas aeruginosa*[10]. Moreover, the results of an *in vitro* study showed synergistic activity between biapenem and fosfomycin against MDR-AB[11]. However, clinical pharmacokinetic data to support appropriate dosage of this combination for pediatric patients are limited. This study therefore aimed to explore the optimal dosage regimen of biapenem and fosfomycin combination against *A. baumannii* infection in pediatric patients using Monte Carlo simulation.

2. MATERIALS AND METHODS

2.1. Biapenem and fosfomycin dosage regimens

Biapenem dosage regimens were used according to a previous study[12] as follows: 1-h infusion of 5 mg/kg q12 h, 10 mg/kg q12 h, 5 mg/kg q8 h and 10 mg/kg q8 h. These dosage regimens were also studied with extended infusion (3 hours infusion). Moreover, 1-h and 3-h infusion of 10 mg/kg q6 h and 15 mg/kg q8 h dosage regimens, along with the fosfomycin dosage regimens approved in Japan, Thailand (100-200 mg/kg/day in 2 to 4 divided doses for children), and United Kingdom (200-400 mg/kg/day in 3-4 divided doses for infants and children aged 1-12 years) were investigated. Dosage regimens greater than 400 mg/kg/day were also studied. Optimal dosage regimens according to creatinine clearance (CL_{cr}) were also investigated.

2.2. Microbiology data

A total of 120 clinical strains of MDR-AB were collected from tertiary hospitals in Thailand during 2016-2017. This study protocol was approved by The Ethics Committee of Faculty of Dentistry/Faculty of Pharmacy, Mahidol University (COA.No.MUDT/PY-IRB 2017/040. 2607).

According to Clinical Laboratory Standard Institute (CLSI) guidelines 2016[13], antimicrobial susceptibility testing was performed by broth microdilution in cation-adjusted Mueller-Hinton broth (CAMHB). Biapenem and fosfomycin sodium were tested against *A. baumannii* isolates. In two-fold dilutions, carbapenems (0.125-1024 μg/mL) and fosfomycin sodium (8-4096 μg/mL) concentration ranges were tested. Positive quality control isolates were performed by *E. coli* ATCC 25922 reference isolates. The CLSI guidelines 2016[13] were used as reference to interpret MICs and susceptibility rates. Fosfomycin sodium breakpoints are not provided by the CLSI guidelines[13]. Therefore, Fosfomycin sodium was used in accordance with the CLSI for Enterobacteriaceae (susceptibility, 64 μg/mL; resistance, >256 μg/mL[13].

Synergy studies were performed by using the checkerboard method[13-15], in triplicate in 96-well microtiter plates to identify synergistic effects. Combinations of biapenem and fosfomycin were tested. The checkerboard method used columns of wells that are filed by twofold serial dilution with biapenem and rows of wells that are filed by serial dilution with fosfomycin sodium. The bacterial inoculum was around 5×10^5 CFU/ml. The plates were incubated at 37°C overnight under aerobic conditions and turbidity was visually inspected to determine growth. For each combination, the fractional inhibitory concentration (FIC) of each antibiotic was calculated by dividing the MIC of the combination by the MIC of an individual antibiotic. The fractional inhibitory concentration index (FICI) is the sum of each individual FIC, as the following equation:

FICI = MIC (drug A in combination) / MIC (drug A alone) + MIC (drug B in combination) / MIC (drug B alone)

The FICI results for each combination against each test isolate were interpreted as follows: FICI <0.5, synergism; FICI of between 0.5 and <4, no interaction; FICI of >4, antagonism.

The standard powders of biapenem and fosfomycin were supported by Thai Meiji Pharmaceutical Co., Ltd.

2.3. Pharmacokinetic and pharmacodynamic data

For biapenem, the means of population pharmacokinetic parameters and standard deviation (SD) were obtained from a published study in pediatric patients[12].

Biapenem was fit to a two-compartment model; CL_{cr} and total body weight (TBW) presented significant effects on pharmacokinetic parameters (clearance and central volume of distribution). Then, to give an overview of pediatric patients, three TBW values, 15, 25, and 35 kg, and CL_{cr} values of 100, 50, 25 and 10 mL/min were utilized for determining proper dosage regimens. The steady-state concentration versus time profile was simulated, and percentage of the exposure time that the serum drug concentration remains above the MIC over the dosing period for each bacterium (%T>MIC) was analyzed by Monte Carlo simulation. Protein binding of biapenem is 3.4% and was used in these calculations[16]. Given the lack of the T>MIC target of biapenem against *A. baumannii*, we then applied the data from the study of biapenem against *Pseudomonas aeruginosa* (*P. aeruginosa*)[17]; and 30%T>MIC was used as a pharmacodynamic target of biapenem for bactericidal activity in this study.

The means of observed fosfomycin concentrations were obtained from a previously published pharmacokinetic study in children (15 pediatric patients age 3-15 years old, average age 7.12 years, average body weight 23.25 kg)[18]. Then, these data were analyzed to fit one-, two- or three-compartment pharmacokinetic models by Phoenix Winnonlin® commercial computer software. Visual inspection of the plots and Akaike's information criterion (AIC) values were compared to select the appropriate model. Pharmacokinetic parameters and their SD from the most fit model were used to simulate steady-state concentration versus time. Protein binding of fosfomycin is negligible and was disregarded in these calculations[19]. The pharmacodynamic target of fosfomycin for *A. baumannii* has not been clearly determined, were therefore decided to adopt the target for *P. aeruginosa.* Fosfomycin seems exhibiting a time dependent killing behavior against *P. aeruginosa*[10,20]. Given the T>MIC targets of all time-dependent antimicrobials range from 40 to 70%[21], we therefore selected 70%T>MIC as a pharmacodynamic target of fosfomycin in this study. Fosfomycin is mainly eliminated unchanged in the urine; however, relationship between CL_{cr} and clearance of fosfomycin has not been defined. Hence, Welling and Tozer's method[22] was utilized to simulate concentration of fosfomycin in pediatric patients with impaired renal function using the following equations:

$$Ke^{\text{renal impairment}} = Ke^{\text{normal}} \times Q$$

$$CL^{\text{renal impairment}} = CL^{\text{normal}} \times Q$$

$$Q \text{ (dosage adjustment factor)} = 1 - [f_e*(1-KF)]$$

f_e = fraction of drug eliminated renally unchanged in subjects with normal renal function

KF = ratio of patient's CL_{cr} to a presumed normal CL_{cr} of 120 mL × min^{-1} × 1.73 m^{-2}

2.4. Monte Carlo Simulation

Monte Carlo simulation (Oracle Crystal Ball 2016; Decisioneering Inc., Denver, CO USA) was used to analyze the probability of target attainment (PTA) and cumulative fraction of response (CFR). A 10,000 virtual subject cohort was generated for each dosage regimen of biapenem and fosfomycin. PTA was calculated as the percentage of the virtual subjects with the T>MIC of at least 30% of the dosing interval for biapenem and for at least 70% of the dosing interval for fosfomycin. The CFR was calculated as the percentage of PTA of each MIC according to the MIC distribution. Dosage regimens were considered optimal when their percentage of PTA or CFR were more than or equal to 80%[23].

3. RESULTS

3.1. Microbiology

The MIC for 50% of the isolates (MIC_{50}) and MIC for 90% of the isolates (MIC_{90}) of biapenem against *A. baumannii* were 16 and 32 mcg/mL, respectively (range 2-64 mcg/mL). The MIC_{50} and MIC_{90} of fosfomycin against *A. baumannii* were 256 and 512 mcg/mL, respectively (range 128-4,096 mcg/mL). Of 120 clinical strains of MDR-AB, 108 clinical strains showed synergism between biapenem and fosfomycin. There is no antimicrobial (concentration) combination that shows antagonism (Table 1). The best ratio of antimicrobial (concentration) combination were 16 (range 2-256). After combination, for *A. baumannii*, the MIC range of biapenem was 0.125-8 mcg/mL (n=108; MIC_{50}=2 mcg/mL; MIC_{90}=8 mcg/mL), and was 8-512 mcg/mL (n=108; MIC_{50}=32 mcg/mL; MIC_{90}=128 mcg/mL) for fosfomycin. MICs of biapenem were decreased by 4-32 times. MICs of fosfomycin were decreased by 2-32 times. Eighty percent of antimicrobial combinations were reduced by four to eight times.

3.2. Pharmacokinetic parameters of fosfomycin in pediatric patients

The best fit model of fosfomycin was one-compartment model, with parameter estimates shown in Table 2, and were used for fosfomycin concentrations simulation.

3.3. %PTA of biapenem against *A. Baumannii*

With creatinine clearance (CLcr) of 100 mL/min, the PTA values of 30%T>MIC target of the three total body weights (TBW) are shown in Table 3, and concentration-time profiles of biapenem according to TBW and CLcr are shown in Figure 1. Biapenem dosage regimens could achieve the target PTA (>80%) for non-life threatening infection, depending on TBW, the covariate of

Table 1. The percentage of synergistic effects of biapenem in combination with fosfomycin against multidrug resistant *Acinetobacter baumannii*.

Drug combination	Percentage (%)		
	Synergism	No interaction	Antagonism
Biapenem + fosfomycin	90	10	0

Table 2. Summary of the published demographic characteristics and pharmacokinetic data analyzed in the present study.

antibiotics	Demographics of pediatric patients (n=15) (mean±SD)	Pharmacokinetic parameters (mean ± SD)
fosfomycin	- age 7.12 ± 3.26 years	- CL (L/hr/kg) = 0.2473 ± 0.0647
	- body weight 23.25 ± 9.35 kg	- Vd (L/kg) = 0.3169 ± 0.0882
		- ke (hr^{-1}) = 0.8050 ± 0.2031

CL=clearance, hr=hour, ke=elimination rate constant, kg=kilogram, L=liter, SD=standard deviation, Vd=volume of distribution

Table 3. Probability of 30%T>MIC attainment (%) of biapenem at each TBW (15, 25 and 35 kg) in patients with CLcr 100 mL/min.

Biapenem regimen	%PTA at MIC 2 mcg/mL (MIC_{50}, EUCAST, CLSI)			%PTA at MIC 8 mcg/mL (MIC90)		
	TBW 15 kg	TBW 25 kg	TBW 35 kg	TBW 15 kg	TBW 25 kg	TBW 35 kg
5 mg/kg q12 h 1-h infusion*	10.19	40.39	64.73	0.01	0.44	3.74
5 mg/kg q12 h 3-h infusion	35.21	78.45	93.22	0.00	0.71	6.66
5 mg/kg q8 h 1-h infusion*	38.84	77.21	91.53	0.16	6.15	25.58
5 mg/kg q8 h 3-h infusion	98.59	99.99	100.00	0.79	15.18	44.20
10 mg/kg q12 h 1-h infusion*	31.77	66.95	84.90	0.95	11.64	32.72
10 mg/kg q12 h 3-h infusion	74.58	94.74	98.95	3.29	27.99	60.18
10 mg/kg q8 h 1-h infusion*	68.20	92.12	97.76	9.03	43.54	73.24
10 mg/kg q8 h 3-h infusion	99.99	100.00	100.00	44.66	89.48	98.17
10 mg/kg q6 h 1-h infusion	NP	NP	NP	23.79	NP	NP
10 mg/kg q6 h 3-h infusion	NP	NP	NP	65.10	NP	NP
15 mg/kg q8 h 1-h infusion	NP	NP	NP	25.11	NP	NP
15 mg/kg q8 h 3-h infusion	NP	NP	NP	88.89	NP	NP

*Ikawa et al. Regimen[12]; PTA=the percentage of target attainment; TBW=total body weight; NP=not performed in case of the lower dosage regimen already achieving the target PTA; bold fonts are the PTA of the lowest dosage regimen that achieves the target PTA

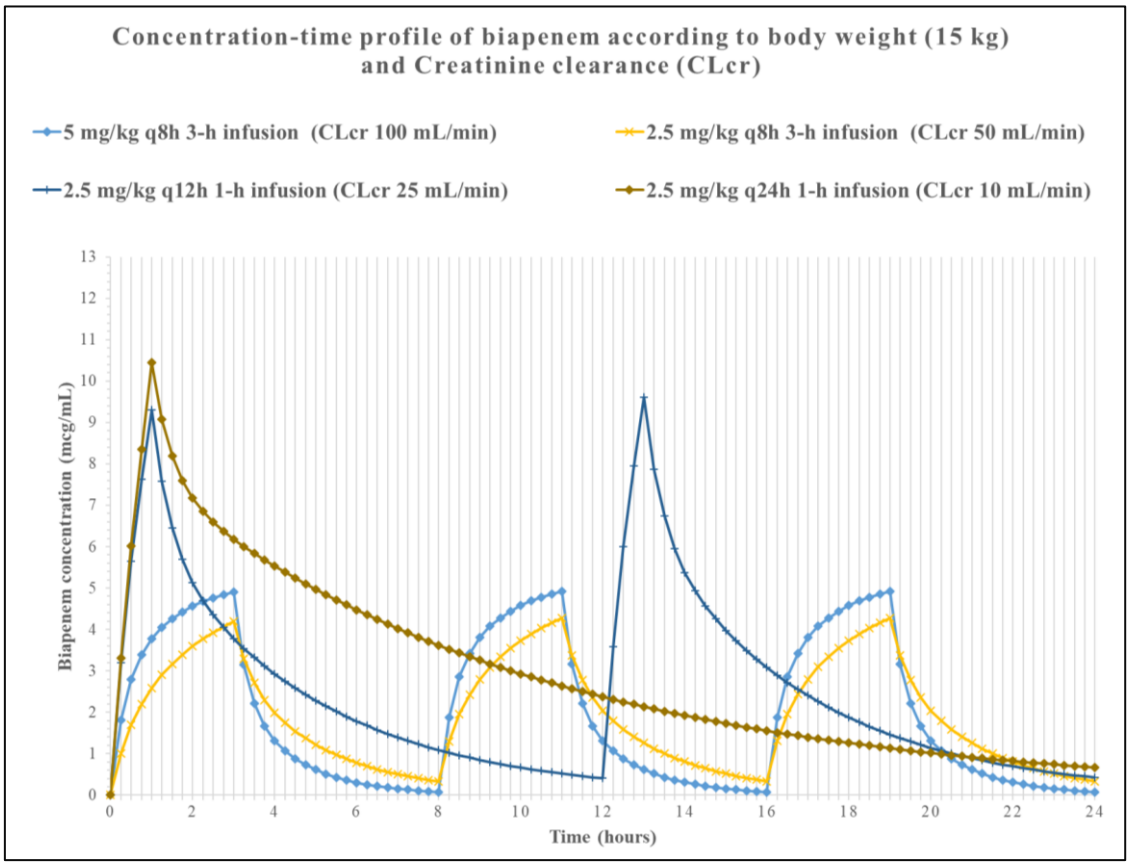

Figure 1. Describe concentration-time profile of biapenem according to body weight (15, 25, 35 kg) and creatinine clearance (CLcr).

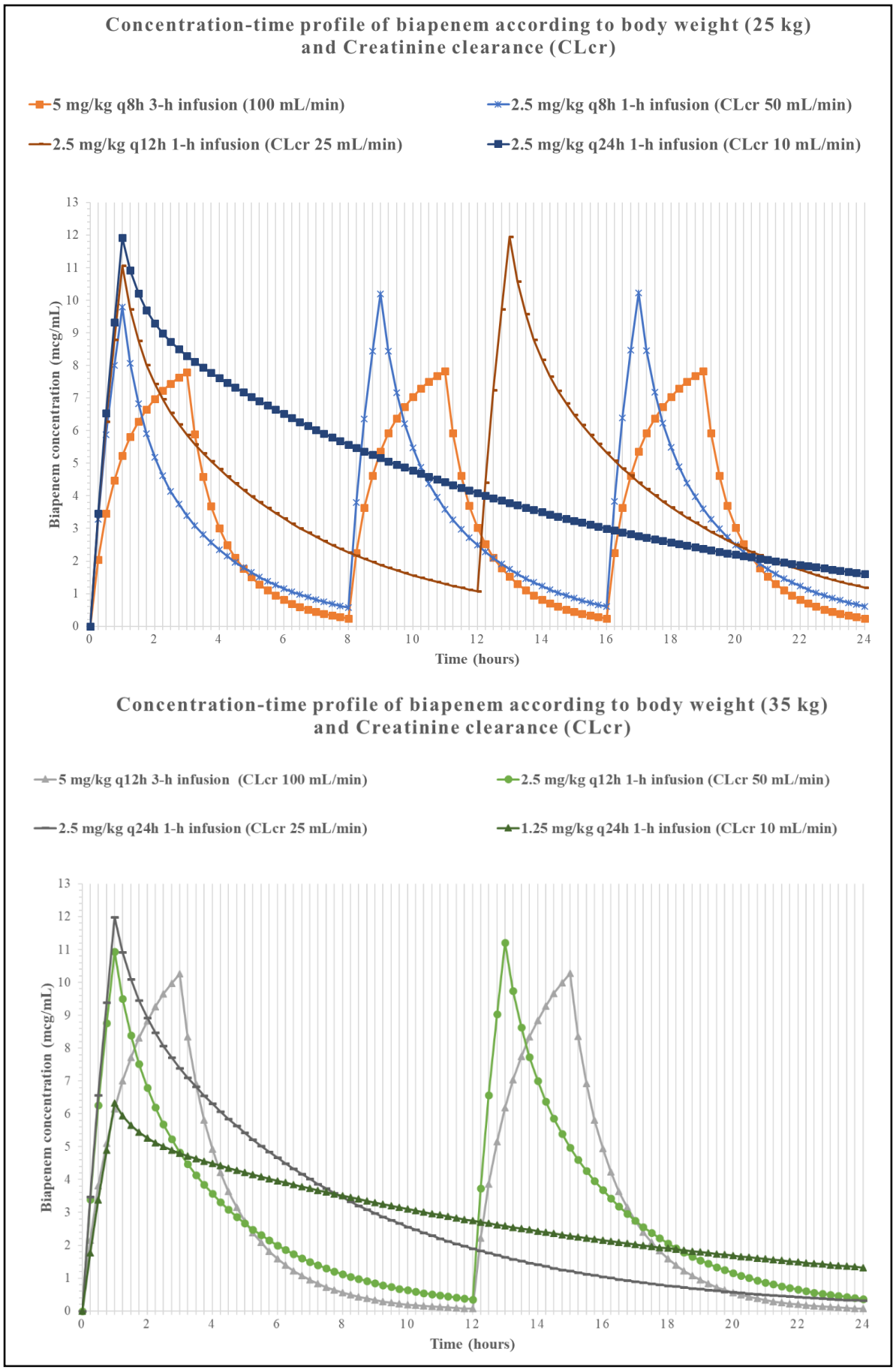

Figure 1. Describe concentration-time profile of biapenem according to body weight (15, 25, 35 kg) and creatinine clearance (CLcr).(cont.)

central volume of distribution (V_c).

At CLSI and EUCAST breakpoint (MIC 2 mcg/mL) of biapenem, PTA of the same dosage regimen increased with TBW. For TBW of 15 and 25 kg, biapenem 5 mg/kg q8 h 3-h infusion achieved more than 90% PTA (98.59, 99.99% PTA, respectively). For TBW of 35 kg, a lower dose of biapenem, 5 mg/kg q12 h 3-h infusion, was able to achieve target PTA (93.22%) as shown in Table 3. When CLcr was decreased, a lower dose could help achieve target PTA as shown in Table 4.

At MIC_{90} (MIC 8 mcg/mL) of biapenem, for TBW of 15 kg, biapenem 15 mg/kg q8 h 3-hour infusion achieved more than 80% PTA. For TBW of 25 and 35 kg, the extended infusion of a lower dose of biapenem, 10 mg/kg q8 h 3-h infusion, yielded more than 80% PTA, 89.48% PTA and 98.17% PTA, respectively as shown in Table 3.

3.4. %PTA of fosfomycin against *A. Baumannii*

The probability of 70% T>MIC attainment (%) and concentration profile of each fosfomycin dosage regimen is shown in Table 5 and Figure 2.

At the EUCAST breakpoint (MIC_{50} 32 mcg/mL), usual fosfomycin dosage regimens (100-200 mg/kg/day) in patients with normal renal function could not achieve target PTA, but fosfomycin regimens of 100 mg/kg q8 h 8-h infusion, 50 mg/kg q8 h 8-h infusion, 50 mg/kg q8 h 1-h infusion and 30 mg/kg q8 h 1-h infusion in patients with creatinine clearance of 51-100, 26-50, 11-25 and ≤10 mL/min, respectively (Table 6).

At the CLSI breakpoint (64 mcg/mL), for patients with CLcr 100 ml/min, the PTA values were lower than those at the EUCAST breakpoint; only a dosage regimen of more than 480 mg/kg/day and prolonged infusion were necessary to attain ≥80% PTA (120 mg/kg q6 h 6-h infusion). However, for patients with less CLcr, lower doses were required to achieve the target attainment, with CLcr values of 26-50, 11-25 and ≤10 mL/min and dose reduction of approximately 60%, 50% and 40% of the initial dose, respectively (Table 6). No dosage regimen achieved the target PTA for MIC_{90} (128 mcg/mL).

3.5. Cumulative fraction of response

The CFR was more than 80% with biapenem 5 mg/kg q8 h 3-h infusion in patients with TBW 25 and 35 kg, while patients with TBW 15 kg required a higher dose of biapenem (10 mg/kg q8 h 3-h infusion) to achieve the desired CFR.

The CFR was more than 80% with the following fosfomycin regimens: 120 mg/kg q6 h 6-h infusion, 80 mg/kg q4 hr 4-h infusion, 200 mg/kg q8 hr 6-h infusion and 150 mg/kg q6 hr 4-h infusion and 100 mg/kg q4 hr 4-h infusion.

3.6. Recommended dosage regimens of biapenem and Fosfomycin

Based on the PTA and CFR results, the recommended dosage regimens of biapenem and fosfomycin for each renal function category are listed in Table 7 and 8. The extended infusion of biapenem 15 mg/kg/day and

Table 4. Probability of 30%T>MIC attainment (%) of biapenem in renal insufficiency (MIC 2 mcg/mL).

CLcr	%PTA		
	TBW 15 kg	TBW 25 kg	TBW 35 kg
CLcr 50 mL/min			
-2.5 mg/kg q8 h 1-h infusion	63.41	93.05	
-2.5 mg/kg q8 h 3-h infusion	93.67	99.88	
-5 mg/kg q12 h 1-h infusion	63.50	90.91	
-5 mg/kg q12 h 3-h infusion	90.41	99.17	
-5 mg/kg q8 h 1-h infusion	90.55	NP	
-2.5 mg/kg q12 h 1-h infusion			88.48
-2.5 mg/kg q12 h 3-h infusion			97.47
-5 mg/kg q12 h 1-h infusion			97.38
CLcr 25 mL/min			
-2.5 mg/kg q12 h 1-h infusion	84.26	98.21	
-2.5 mg/kg q12 h 3-h infusion	94.79	99.73	
-5 mg/kg q12 h 1-h infusion	97.89	NP	
-2.5 mg/kg q24 h 1-h infusion			88.13
-2.5 mg/kg q24 h 3-h infusion			93.62
CLcr 10 mL/min			
-2.5 mg/kg q24 h 1-h infusion	95.25	99.71	
-2.5 mg/kg q24 h 3-h infusion	97.53	99.89	
-1.25 mg/kg q12 h 3-h infusion	98.02	NP	
-1.25 mg/kg q24 h 1-h infusion			98.84
-1.25 mg/kg q24 h 3-h infusion			99.30

PTA=the percentage of target attainment; TBW=total body weight; NP=not performed in case of the lower dosage regimen already achieving the target PTA; bold fonts=the PTA of the lowest dosage regimen that achieves the target PTA; shadow blocks=no simulation was performed.

Table 5. Probability of 70% T>MIC attainment (%) of fosfomycin in patients with normal renal function.

Fosfomycin regimen	%PTA at MIC 32 mcg/mL (MIC_{50}, EUCAST breakpoint)	%PTA at MIC 64 mcg/mL (CLSI breakpoint)	%PTA at MIC 128 mcg/mL (MIC_{90})
100-200 mg/kg/day			
50 mg/kg q12 h 1-h infusion*	0.00	0.00	0.00
50 mg/kg q12 h 12-h infusion	0.95	0.00	0.00
50 mg/kg q8 h 1-h infusion*	0.43	0.00	0.00
50 mg/kg q8 h 8-h infusion	21.29	0.02	0.00
100 mg/kg q12 h 1-h infusion*	0.06	0.01	0.00
100 mg/kg q12 h 12-h infusion	62.55	0.80	0.00
300-400 mg/kg/day			
100 mg/kg q8 h 1-h infusion**	7.44	0.55	0.01
100 mg/kg q8 h 8-h infusion	96.81	21.65	0.02
200 mg/kg q12 h 1-h infusion**	1.05	0.07	0.00
200 mg/kg q12 h 12-h infusion	99.83	62.25	0.87
100 mg/kg q6 h 1-h infusion**	49.00	11.70	0.36
100 mg/kg q6 h 3-h infusion	81.46	10.04	0.03
100 mg/kg q6 h 6-h infusion	99.91	62.82	0.79
>400 mg/kg/day			
80 mg/kg q4 hr 1-h infusion	92.07	52.29	4.69
80 mg/kg q4 hr 4-h infusion	99.99	85.62	5.14
120 mg/kg q6 h 1-h infusion	60.82	20.22	1.04
120 mg/kg q6 h 6-h infusion	99.98	85.59	5.10
200 mg/kg q8 h 1-h infusion	29.76	7.45	0.53
200 mg/kg q8 h 6-h infusion	100.00	89.41	7.53
200 mg/kg q8 h 8-h infusion	100.00	97.15	21.61
150 mg/kg q6 h 1-h infusion	71.30	31.45	3.92
150 mg/kg q6 h 4-h infusion	99.98	84.51	5.18
150 mg/kg q6 h 6-h infusion	100.00	97.12	20.86

PTA=the percentage of target attainment;
*Thailand and Japan approved doses; **UK approved doses; bold fonts are the PTA of the lowest dosage regimen that achieves the target PTA

Table 6. Probability of 70%T>MIC attainment (%) of fosfomycin in renal insufficiency.

CLcr (mL/min)	%PTA	
	MIC 32 mcg/mL (EUCAST breakpoint)	MIC 64 mcg/mL (CLSI breakpoint)
100 mL/min		
-100 mg/kg q8 h 8-h infusion (300 mg/kg/day)	96.81	21.65
-120 mg/kg q6 h 6-h infusion (480 mg/kg/day)		85.59
50 mL/min		
-50 mg/kg q8 h 8-h infusion (150 mg/kg/day)	86.82	
-100 mg/kg q12 h 12-h infusion (200 mg/kg/day)	98.30	
-100 mg/kg q8 h 1-h infusion (300 mg/kg/day)	84.66	
-60 mg/kg q6 h 6-h infusion (240 mg/kg/day)		63.36
-70 mg/kg q6 h 6-h infusion (280 mg/kg/day)		81.34
25 mL/min		
-50 mg/kg q12 h 12-h infusion (100 mg/kg/day)	71.42	
-40 mg/kg q8 h 8-h infusion (120 mg/kg/day)	86.65	
-50 mg/kg q8 h 1-h infusion (150 mg/kg/day)	86.53	
-50 mg/kg q6 h 6-h infusion (200 mg/kg/day)		73.66
-60 mg/kg q6 h 6-h infusion (240 mg/kg/day)		88.19
10 mL/min		
-25 mg/kg q8 h 1-h infusion (75 mg/kg/day)	77.87	
-25 mg/kg q8 h 3-h infusion (75 mg/kg/day)	56.17	
-30 mg/kg q8 h 1-h infusion (90 mg/kg/day)	83.77	
-30 mg/kg q8 h 8-h infusion (90 mg/kg/day)	77.81	
-50 mg/kg q6 h 3-h infusion (200 mg/kg/day)		82.28
-50 mg/kg q6 h 6-h infusion (200 mg/kg/day)		86.27

PTA=the percentage of target attainment; bold fonts are the PTA of the lowest dosage regimen that achieves the target PTA; shadow blocks=no simulation was performed.

Table 7. The recommended dosage regimens of biapenem in renal insufficiency required to achieve more than 80%PTA (30%T>MIC of biapenem) at an MIC of 2 mcg/mL.

CL_{cr} (mL/min)	Total body weight (TBW)		
	15 kg	**25 kg**	**35 kg**
51-100 mL/min	5 mg/kg q8 h 3-h infusion	5 mg/kg q8 h 3-h infusion	5 mg/kg q12 h 3-h infusion
26–50 mL/min	2.5 mg/kg q8 h 3-h infusion	2.5 mg/kg q8 h 1-h infusion	2.5 mg/kg q12 h 1-h infusion
11–25 mL/min	2.5 mg/kg q12 h 1-h infusion	2.5 mg/kg q12 h 1-h infusion	2.5 mg/kg q24 h 1- h infusion
≤10 mL/min	2.5 mg/kg q24 h 1-h infusion	2.5 mg/kg q24 h 1- h infusion	1.25 mg/kg q24 h 1-h infusion

Table 8. The recommended dosage regimens of fosfomycin in patients with renal insufficiency.

CL_{cr} (mL/min)	MIC 32 mcg/mL (EUCAST breakpoint)	MIC 64 mcg/mL (CLSI breakpoint)
51-100 mL/min	100 mg/kg q8 h 8-h infusion (300 mg/kg/day)	120 mg/kg q6 h 6-h infusion (480 mg/kg/day)
26-50 mL/min	50 mg/kg q8 h 8-h infusion (150 mg/kg/day)	70 mg/kg q6 h 6-h infusion (280 mg/kg/day)
11-25 mL/min	50 mg/kg q8 h 1-h infusion (150 mg/kg/day)	60 mg/kg q6 h 6-h infusion (240 mg/kg/day)
≤10 mL/min	30 mg/kg q8 h 1-h infusion (90 mg/kg/day)	50 mg/kg q6 h 3-h infusion (200 mg/kg/day)

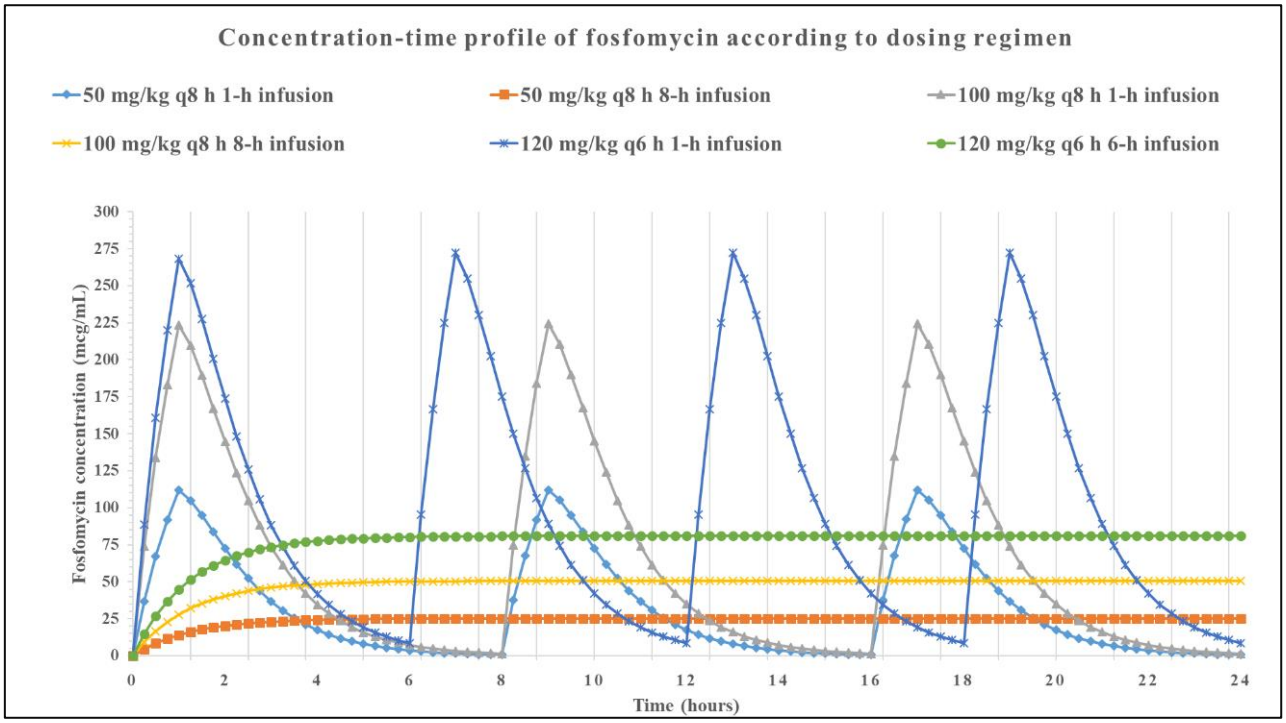

Figure 2. Describe concentration-time profile of fosfomycin according to dosing regimen.

prolonged infusion of fosfomycin 300 mg/kg/day would be effective for MDR-AB treatment in pediatric patients.

4. DISCUSSION

The MICs of *A. baumannii* used in our study were collected from tertiary hospitals in Thailand during 2016-2017 in which the MIC_{50} and MIC_{90} of biapenem were 16 and 32 mcg/mL, respectively. The MIC_{50} and MIC_{90} of fosfomycin were 256 and 512 mcg/mL, respectively. However, combining biapenem and fosfomycin decreased the MICs of *A. baumannii* for both drugs, making the MIC_{50} and MIC_{90} of biapenem 2 and 8 mcg/mL, respectively, and 32 and 128 mcg/mL, respectively, for fosfomycin. These findings were in line with an *in vitro* synergistic study discovered that carbapenem and fosfomycin were the most effective combination against carbapenem-resistant *A. baumannii* compared to carbapenem

and amikacin and carbapenem and colistin, synergism percentages were 65.2%, 30.8-46.2% and 17.4%, respectively[24]. In Thailand, a study conducted at Siriraj Hospital during 2006-2009 showed that *A. baumannii* had an MIC_{50} of 32 and an MIC_{90} of 64 mcg/mL for biapenem[25], which was higher than the results found in this study, possibly because Siriraj Hospital is a teaching hospital with higher prevalence of MDR-AB than several other tertiary hospitals. Another study in Thailand also showed higher MIC_{50} (32 mcg/mL) and MIC_{90} (128 mcg/mL) of MDR-AB for biapenem and MIC_{50} (512 mcg/mL) and MIC_{90} (2,048 mcg/mL) of MDR-AB for fosfomycin[26]. This could be because these studies included not only tertiary hospitals but also teaching hospitals. However, the results of these studies showed that biapenem combined with fosfomycin yielded higher percentage of synergism than the other carbapenems (biapenem 34.18%, imipenem 29.11%, meropenem 27.43% and doripenem 23.63%). The higher MIC_{50} and MIC_{90} of *A. baumannii* for biapenem and fosfomycin in teaching hospitals were consistent with studies in China[27-28].

There is no study about the population pharmacokinetic parameter of fosfomycin in pediatric patients. Therefore, we used data from a previous pharmacokinetic study of fosfomycin in pediatric patients[18]. However, this previous study divided patients into 4 groups based on dosage given (25, 50 mg/kg) and administration methods (short intravenous infusion for 1 hr), and then pharmacokinetic parameters of each group were analyzed and reported separately. Moreover, this study did not report clearly about how to administer "one shot intravenous injections". To enhance reliability of the data, more subjects are needed. Then, the serum concentrations of all patients (n=15) from this study were analyzed by Phoenix Winnolin® to find the best appropriate PK data. As a result, the best fit model was the one-compartment model and was the same as in a previous study. The pharmacokinetic parameters were also comparable to those in a previous study[18]. However, these pharmacokinetic parameters were different from another pharmacokinetic study[29]. This may be because they studied parameters only in children aged 5-6 years old, whereas our pharmacokinetic parameters were obtained from children aged 3-15 years old.

For carbapenems, the PK/PD index is calculated using the T>MIC, stasis and near-maximal cell killing occur at 20% and 40% of the dosing interval, respectively[30]. Biapenem was found to have T>MIC targets of 17% and 30%, respectively, for bacteriostatic and bactericidal (3-log killing) against *P. aeruginosa* infection[17]. Since there is no PK/PD target for biapenem and fosfomycin against *A. baumannii*, the PK/PD targets used in this study were adopted for *P. aeruginosa*, which has similar characteristics with *A. baumannii*, such as non-fermenting gram-negative organisms[10] and values of MIC breakpoints[13]. There is no study about the PK/PD target for biapenem combined with fosfomycin against *A. baumannii*. Therefore, when we simulated the dosage regimens combined between biapenem and fosfomycin, the PK/PD targets were used as their targets. This approach used in our study has been described previously in PK/PD combination model studies[31].

To our knowledge, this is the first study demonstrating an optimal dosing regimen of biapenem and fosfomycin combination against *A. baumannii* infection in pediatric patients using Monte Carlo simulation. Regarding biapenem, since we used pharmacokinetic data from Ikawa et al.[12], our results were similar to their findings. At the same dosage regimen of biapenem, the increase in TBW resulted in the greater %PTA. Since TBW is a significant covariate of central volume of distribution, increasing TBW will increase the central volume of distribution; as a result, the serum drug concentration was maintained and then spent more time above the MIC. Moreover, our study is the first to evaluate extended infusion (3-h infusion) regimens of biapenem in pediatric patients, supporting its better potential to achieve more %PTA than one-hour infusion regimens. This finding is consistent with another study by Hang et al[32] that evaluated various biapenem dosage regimens in adult intensive care unit patients. Unsurprisingly, since biapenem is a time-dependent antibiotic, extended infusion would provide more time above the MIC and greater %PTA.

Our study also indicated that the approved fosfomycin dose in Thailand and Japan (100-200 mg/kg/day) was not enough to achieve the target PTA for *A. baumannii*. This result is similar to that of Traunmuller et al[33] revealing that the PTA of dosage regimens approved in Thailand and Japan produced approximately 20-40%PTA at MIC of 32 mcg/mL (EUCAST breakpoint). However, the dosage regimen of 100 mg/kg q8 h 8-h infusion, designed based on the approved dose in the United Kingdom (200-400 mg/kg/day), was able to achieve the target PTA at the EUCAST breakpoint, but not at the CLSI breakpoint. The reason that the approved regimens in Thailand and Japan were not able to achieve the target PTA both for adults and children could be that the approved fosfomycin regimens were designed based on the MIC of *A. baumannii* in the past that was not as high as in the present.

As our results, the MIC_{50} of biapenem and fosfomycin combination were equal to the MIC breakpoints of each antimicrobial agent. Therefore, the dosage regimens that achieve the target PTA at MIC breakpoints is only appropriate for documented treatment of biapenem- or fosfomycin- susceptible strain as shown in Table 7 and 8.

Pertaining to our recommended dosage regimens, proper dose of biapenem for MDR-AB would be 225, 375 and 350 mg per day in children weighing 15, 25 and 35 kg, respectively, still lower than the maximum daily dose in adult patients. However, the common adverse

drug reactions should still be monitored such as skin eruptions/rashes, nausea, vomiting and diarrhea[7]. Our recommended fosfomycin dosage regiments are 12-19.2 grams per day in children weighing 40 kg; clinicians should be vigilant, especially when fosfomycin is in the form of a sodium salt, as fosfomycin 1 gram contains sodium 0.33 grams or 14.4 milliequivalents[34]. Fosfomycin 12-19.2 grams/day would provide 4.35-6.96 milliequivalents of sodium in children weighing 40 kg. Hypokalemia was also reported as a common adverse effect of fosfomycin[35]. Therefore, when using our recommended high dose of fosfomycin, benefits and risks should be considered, and serum sodium and potassium should be monitored during therapy.

There are several limitations in this study. First, the pharmacokinetic parameters of fosfomycin used in this study were not population pharmacokinetic parameters; thus, they might not represent the pediatric population. Second, the MICs used in this study were from tertiary hospitals in Thailand, which might not be applicable to other types of hospital or region with different magnitude of *A. baumannii* resistance; therefore, our recommended dosage regimens would be appropriate for hospitals with *A. baumannii* with MIC distributions similar to ours. Third, the PK/PD targets in this study were determined using insufficient data, and clinicians should keep these in mind when ordering the recommended dosage regimen in this study.

5. CONCLUSION

Combination of biapenem with fosfomycin helped decrease MIC of MDR-AB. Higher doses and longer infusion time of each individual antibiotic are also required to maximize treatment efficacy.

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