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Fosfomycin Dosing Regimens based on Monte Carlo Simulation for Treated Carbapenem-Resistant *Enterobacteriaceae* Infection

Sukrit Kanchanasurakit [1,2,3,4], Wichai Santimaleeworagun [5,6], Charles E. McPherson, III [7], Napacha Piriyachananusorn [2], Benjawan Boonsong [2], Papanin Katwilat [8], and Surasak Saokaew [1,3,4,9,10,11]

[1]Division of Pharmacy Practice, Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand
[2]Division of Pharmaceutical care, Department of Pharmacy, Phrae Hospital, Phrae, Thailand
[3]Center of Health Outcomes Research and Therapeutic Safety (Cohorts), School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand
[4]Unit of Excellence on Clinical Outcomes Research and IntegratioN (UNICORN), School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand
[5]Pharmaceutical Initiative for Resistant Bacteria and Infectious Diseases Working Group (PIRBIG), Nakorn Pathom, Thailand
[6]Department of Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakorn Pathom, Thailand
[7]College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, USA
[8]Division of Infectious Disease, Department of Medicine, Phrae Hospital, Phrae, Thailand
[9]Unit of Excellence on Herbal Medicine, School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand
[10]Biofunctional Molecule Exploratory Research Group, Biomedicine Research Advancement Centre, School of Pharmacy, Monash University Malaysia, Bandar Sunway, Selangor Darul Ehsan, Malaysia
[11]Novel Bacteria and Drug Discovery Research Group, Microbiome and Bioresource Research Strength, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway, Selangor Darul Ehsan, Malaysia

ORCID iDs
Sukrit Kanchanasurakit
https://orcid.org/0000-0002-1268-2665
Wichai Santimaleeworagun
https://orcid.org/0000-0001-9974-957X
Charles E. McPherson, III
https://orcid.org/0000-0002-5062-9320
Napacha Piriyachananusorn
https://orcid.org/0000-0001-5125-309X
Benjawan Boonsong
https://orcid.org/0000-0002-7697-013X
Papanin Katwilat
https://orcid.org/0000-0001-7938-8666

ABSTRACT

Background: Infections by Carbapenem-Resistant *Enterobacteriaceae* (CRE) remain a leading cause of death in critically ill patients. Fosfomycin has been regarded as an alternative therapy for treatment of infections caused by CRE organisms. The purpose of this study is to evaluate clinical outcomes amongst patients with CRE infection who are receiving a fosfomycin dosing regimen using a Monte Carlo simulation and fosfomycin minimum inhibitory concentration (MIC).

Materials and Methods: Fosfomycin MIC was defined by the E-test method. We used Fosfomycin pharmacokinetic parameters from a previously published study. The percent of the time period in which the drug concentration exceeded the MIC, or %T>MIC, used in this study were determined to be 70% of T>MIC and 100% of T>MIC, respectively. All dosing regimens were estimated for the probability of target attainment using a Monte Carlo simulation.

Results: In this study, we found the MIC's of fosfomycin against CRE isolates ranged from 8 mg/L to 96 mg/L. The total daily dose of fosfomycin ranged from 16 - 24 g and was administered utilizing various fosfomycin dosing regimens to achieve the pharmacokinetic/pharmacodynamic (PK/PD) target in pathogens with a MIC of 32 mg/L for 70%T>MIC and a MIC of 12 mg/L for 100%T>MIC, respectively. For the twelve patients who received the recommended fosfomycin dosing regimen, eleven achieved bacterial eradication
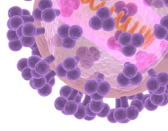
Surasak Saokaew
https://orcid.org/0000-0002-1382-0660

Conflict of Interest
No conflicts of interest.

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for a microbiological cure rate of 91%; and of those patients achieving eradication, two died despite having negative cultures for CRE; the one remaining patient had bacterial persistence. The most commonly observed adverse drug reactions were hypernatremia (3 cases) and hypokalemia (3 cases) and acute kidney injury (3 cases).

Conclusion: Our findings suggest fosfomycin has tended to good efficacy when using dosing regimens that achieve the PK/PD target. Nonetheless, further validation of these regimens in larger populations is needed.

Keywords: Fosfomycin; Monte Carlo; Carbapenem-Resistant *Enterobacteriaceae*; Microbial sensitivity tests

INTRODUCTION

Infections caused by Carbapenem-Resistant *Enterobacteriaceae* (CRE) organisms are an important challenge in health-care settings and are increasingly becoming a concern worldwide. The first case of CRE infection occurred in Japan in 1980. Subsequently, cases were discovered in London in 1982, in California in 1984, and in France in 1990. Currently, CRE are widespread and can be found in several parts of the globe, particularly in Europe, South America, and Asia [1]. The surveillance of CRE among clinical isolates of *Enterobacteriaceae* from the hospital in Thailand during January to June, 2019, the prevalence of CRE in each region were 9.2% in the central part, 8.9% in the northern part, 10.3% in the eastern part, 7.2% in the northeastern part, 5.2% in the southern part, and 7.9% in Bangkok [2]. Infections caused by CRE are correlated with significant morbidity and mortality [1]. These pathogens cause a variety of severe infections including urinary tract infections (UTIs), bacteremias, ventilator-associated pneumonias (VAPs), surgical site infections (SSIs), and intra-abdominal infections (IAIs).

Increasing antimicrobial resistance by CRE organisms has a significant impact on patient outcomes with major economic implications for hospitals and health care systems alike [3]. There are two common mechanisms by which pathogens develop resistance to carbapenems-structural mutation and carbapenemase production. Three major classes of carbapenemase have been reported, including 1) Ambler Class A *Klebsiella pneumoniae* carbapenemase (KPC); 2) Class B Metallo-β-lactamase (MBLs) such as imipenemase (IMP), New Delhi MBL (NDM), and Verona integrin-encoded MBL (VIM); and 3) Class D oxacillinases (OXA)-type enzymes such as OXA-48 [4]. Currently, the previous review articles recommend colistin base regimens as a drug of choice for treatment in patients with CRE infection [1, 5]. However, some studies had reported colistin-resistant Gram-negative bacteria, particularly *Enterobacteriaceae* organisms [6, 7]. Therefore, the alternative therapy of CRE infection might be useful for treatment at present.

Fosfomycin is a broad-spectrum antibiotic which inhibits an enzyme-catalyzed reaction during the first step of the cell wall synthesis of both Gram-negative and Gram-positive bacteria [8]. Pharmacokinetically, this drug exhibits good distribution into tissues and reaches sufficient concentrations at the site of infection [8, 9]. Consequently, it has been used as an alternative therapy in the treatment of infections caused by CRE organisms. Fosfomycin combined with other antibiotics were attractive options for CRE treatment [5, 7, 10]. Additionally, the effectiveness of parenteral fosfomycin in combination with other antibiotics for treatment of CRE infection has also been evaluated in several studies [11,

12]. In those studies, however, optimal dosing is varied and has not been well established for clinical use [5]. The achievement of pharmacokinetic/pharmacodynamic (PK/PD) target is an important issue for CRE treatment. It is a fact that the inappropriate antibiotic dosing leads to the emergence of drug resistance and consequently, worsening treatment outcomes. Hence, the achievement of PK/PD target based on Monte Carlo simulation allows optimizing antibiotic dosing regimens in order to conserve their activities against pathogens [13].

We conducted this prospective, pilot study to evaluate treatment outcomes by using fosfomycin minimum inhibitory concentration (MIC) determination and dosing regimen optimization of PK/PD targets to guide therapy for patients with CRE infection.

MATERIALS AND METHODS

1. Microbiology and minimum inhibitory concentration

All CRE isolates were obtained from infected patients who were admitted to Phrae Hospital, Phrae, Thailand between July 1st, 2019 and February 29th, 2020. According to the 2020 European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, CRE strains are defined as having resistance to at least one agent in the class of carbapenems (*i.e.*, meropenem, imipenem, doripenem, and ertapenem) [14]. The isolates of CRE were collected from various clinical specimens, including urine, sputum, pus, blood, pleural fluid, and ascites fluid.

MIC values for fosfomycin were defined using the E-test method. E-test strips reinforced with glucose-6-phosphate (Liofilchem, Teramo, Italy) were stamped onto the surface of Mueller-Hinton agar plates (Difco, Sparks, Maryland, USA). MIC values were read from the scale in terms of mg/L with complete inhibition seen where the pointed end of the ellipse edge intersects with the strip [14]. Fosfomycin was manufactured and repacked by the Meiji Seika Pharma Co., Ltd. (Tokyo, Japan) and the Thai Meiji Pharmaceutical Co., Ltd. (Bangkok, Thailand), respectively.

2. Pharmacokinetic and pharmacodynamics model

Pharmacokinetic parameters for fosfomycin were obtained from a previous study of intravenous fosfomycin in nine patients with sepsis and required mechanical ventilation. The mean age and Acute physiology and chronic health evaluation II (APACHE II) score of the patients were 67 years and 23 points, respectively. In that study, the one-compartment model was found to be the best base model for critically ill patients [9]. A set of parameters was randomly generated according to the mean and standard deviation of the parameters. For each patient, steady-state concentration versus time was simulated using the one-compartment model. The mean ± standard deviation (SD) of the volume of distribution (V_d), clearance (Cl), and half-life ($T_{1/2}$) were 31.50 ± 4.50 L, 7.20 ± 1.30 L/h, and 3.90 ± 0.90 h, respectively [9].

The pharmacodynamic properties of fosfomycin were described by the percentage of time above the MIC (%T>MIC), and previous studies have shown microbiological success of using fosfomycin against CRE requires at least 70% of T>MIC [13, 15, 16]. Therefore, the PK/PD target of fosfomycin against CRE infections was set at 70% T>MIC for non-severe infections, such as skin and soft tissue infections and UTI. However, we used the target of 100% T>MIC for more severe infection, such as bacteremia, pneumonia, and febrile neutropenia [17, 18].

3. Simulated dosing scenarios for fosfomycin

In order to obtain the optimal dose for intravenous fosfomycin, both prolonged and continuous infusion dosing regimens were assessed in this simulation model. Previous work in this area suggests high serum concentrations of fosfomycin may be sustained when these dosing strategies are used, compared to that achieved with intermittent dosing regimens [5, 11, 19, 20]. Prolonged infusion scenarios for fosfomycin consisted of a loading dose of the drug, followed by a maintenance infusion regimen. Fosfomycin loading doses (LD) were infused for 30 minutes and the maintenance doses (MD) were begun immediately after the loading dose. For each loading dose, many different maintenance doses were evaluated.

For those simulations in which a 2 g loading dose was administered, two different maintenance doses were evaluated:

(1) 2 g LD, followed by MD of 2 g infused over 4 hours at 12-hour intervals, and (2) 2 g LD, followed by MD of 2 g infused over 4 hours at 8-hour intervals.

For those simulations in which a 4 g loading dose of fosfomycin was administered, four different maintenance doses were evaluated:

(1) 4 g LD, followed by MD of 2 g infused over 4 hours at 6-hour intervals,
(2) 4 g LD, followed by MD of 4 g infused over 4 hours at 8-hour intervals,
(3) 4 g LD, followed by MD of 4 g infused over 6 hours at 8-hour intervals, and (4) 4 g LD, followed by MD of 4 g infused over 4 hours at 6-hour intervals.

For those simulations in which a 8 g loading dose of fosfomycin was administered, three different maintenance doses were evaluated:

(1) 8 g LD, followed by MD of 8 g infused over 4 hours at 12-hour intervals,
(2) 8 g LD, followed by MD of 8 g infused over 4 hours at 8-hour intervals, and (3) 8 g LD, followed by MD of 8 g infused over 6 hours at 8-hour intervals.

Two continuous infusion regimens for intravenous fosfomycin were also evaluated. Each scenario consisted of a 4 g loading dose infused over 30 minutes and was immediately followed by a continuous infusion maintenance dose administered over a 24-hour time period:

(1) 4 g LD, followed by 16 g continuous infusion administered over 24 hours, and (2) 4 g LD, followed by 24 g continuous infusion administered over 24 hours.

4. Monte Carlo simulation and probability of target attainment

The PK/PD analysis was performed using a 10,000-subject Monte-Carlo simulation (Oracle Crystal Ball) model for parenteral dosage regimens of fosfomycin to calculate %T>MIC and was dependent on the linear pharmacokinetic behavior of the agent. Owing to the difference of the MIC in various health care setting, we also used the MICs of 8, 16, 32, 64, 96, and 128 mg/L in the models to define the optimal dosing regimens for each MIC in the study.

The probability of target attainment (PTA) was described as the likelihood a specific dosage regimen achieved a target PK/PD index and was calculated as the percentage of all 10,000 subjects who had a probability of attaining 70% T>MIC and 100% T>MIC for fosfomycin. Only those dosing regimens that attained a PTA >90% were considered optimal for the treatment of CRE infections [21].

5. Data collection of patients who use fosfomycin for treatment CRE infection

All relevant patient demographics (*i.e.*, age, sex, and comorbidities), concomitant antimicrobial agents, organisms, sources of infection, actual dosage regimen of fosfomycin, and treatment outcomes (*i.e.*, efficacy and safety of fosfomycin therapy) were collected from medical records between July 1st, 2019 and February 29th, 2020.

Microbiological cure or bacterial eradication was defined as culture-negative after treatment with fosfomycin monotherapy or combination with other antimicrobials for 2 weeks. Bacterial persistence was defined as remaining culture-positive after treatment for 2 weeks. Hypernatremia was defined as a serum sodium concentration greater than 145 mEq/L. Hypokalemia was defined as a serum potassium concentration lower than 3.5 mEq/L. Acute kidney injury (AKI) was defined according to the following criteria: (1) increase in serum creatinine by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hours; (2) increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or (3) urine volume <0.5 ml/kg/h for 6 hours [22].

6. Ethics statement

Approval of this study was granted by the Ethical Committee for Clinical Research in Phrae Hospital (No.07/2563). Detailed information was provided to all patients and signed consent was obtained prior to inclusion in this study.

RESULTS

1. MIC of CRE isolates

Throughout the study period, twelve isolates of clinical CRE (nine isolates of *Klebsiella pneumoniae* and three isolates of *Escherichia coli*) were collected from urine, sputum, and pus. The MICs of fosfomycin against CRE ranged from 8 mg/L to 96 mg/L (**Fig. 1**).

2. Probability of target attainment (PTA) of fosfomycin by using Monte Carlo simulation

Table 1 and **Figure 2** present the PTA results of different fosfomycin dosing regimens to achieve 70% T>MIC and 100% T>MIC in critically ill patients with CRE infection. Amongst individuals requiring 70% T>MIC, fosfomycin regimens with a total dose of 4 g to 12 g per
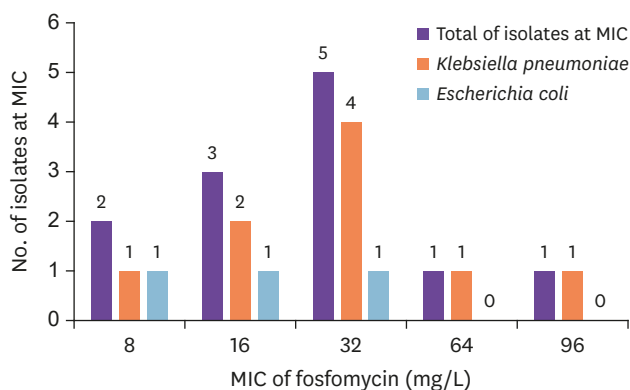

Figure 1. MICs distribution of fosfomycin against CRE isolates.
MIC, minimum inhibitory concentration; CRE, carbapenem-resistant *Enterobacteriaceae*.

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Table 1. PTA for fosfomycin regimens achieving 70% T>MIC and 100% T>MIC at different MICs in patients with infection caused by CRE

Fosfomycin dosing regimen		PTA to achieving 70% T>MIC (%)						PTA to achieving 100% T>MIC (%)					
		MIC (mg/L)						MIC (mg/L)					
Loading[a]	Maintenance[b]	8	16	32	64	96	128	8	16	32	64	96	128
Prolonged infusion													
2 g	2 g infuse 4 h q 12 h	94.26	32.71	0.05	0.00	0.00	0.00	42.67	2.37	0.00	0.00	0.00	0.00
	2 g infuse 4 h q 8 h	100.00	98.67	26.73	0.02	0.00	0.00	99.38	76.83	5.51	0.00	0.00	0.00
4 g	2 g infuse 4 h q 6 h	100.00	99.99	91.13	1.62	0.00	0.00	99.99	99.88	68.38	0.27	0.00	0.00
	4 g infuse 4 h q 8 h	100.00	100.00	98.49	27.09	0.60	0.00	99.99	99.35	75.74	5.52	0.05	0.00
	4 g infuse 6 h q 8 h	100.00	100.00	99.93	47.94	1.49	0.00	100.00	100.00	96.93	21.46	0.38	0.00
	4 g infuse 4 h q 6 h	100.00	100.00	100.00	90.96	27.44	1.78	100.00	100.00	99.86	67.91	10.65	0.49
8 g	8 g infuse 4 h q 12 h	100.00	99.92	94.57	31.78	2.58	0.09	98.63	87.55	42.23	2.48	0.08	0.00
	8 g infuse 4 h q 8 h	100.00	100.00	100.00	98.48	74.86	26.20	100.00	99.98	99.29	76.77	27.62	5.29
	8 g infuse 6 h q 8 h	100.00	100.00	100.00	99.94	92.72	48.57	100.00	100.00	99.98	97.33	66.00	20.95
Continuous infusion													
4 g	16 g infuse 24 h	100.00	100.00	100.00	98.54	45.80	4.19	100.00	100.00	100.00	98.54	45.80	4.19
	24 g infuse 24 h	100.00	100.00	100.00	100.00	98.54	70.84	100.00	100.00	100.00	100.00	98.54	70.84

[a]Loading dose infused for 30 minutes. [b]Maintenance dose was started immediately after loading dose.
PTA, probability of target attainment; T>MIC, the drug concentration exceeds the minimum inhibitory concentration; MIC, minimum inhibitory concentration; CRE, carbapenem-resistant Enterobacteriaceae; q 8 h, every 8 h.

day and 16 g to 24 g per day achieved the PTA target in pathogens with a MIC of 8 mg/L and 32 mg/L, respectively. Moreover, amongst patients who required 100% T>MIC, those fosfomycin regimens consisting of a total dose 4 g to 12 g per day and 16 g to 24 g per day reached the PTA target in pathogens with a MIC of 2 mg/L and 12 mg/L, respectively.

For 70% T>MIC and 100% T>MIC, we found that a 24 g daily dose of fosfomycin administered via a 6-hour infusion achieved the PK/PD target better than the 4-hour infusion regimen for MIC of 96 mg/L and 64 mg/L, respectively. Moreover, we found that administration by continuous infusion additionally improved the PK/PD profile of parenteral fosfomycin.

We observed that in order to achieve T>MIC of at least 70%, the pathogens with higher MIC's required a larger loading dose and maintenance dose of fosfomycin. In fact, a fosfomycin dosing regimen in which 16 g per day was administered as a 4 g LD followed by a 4 g MD administered over 4 hours at 6 hour intervals would be necessary to treat bacteria with a MIC = 64 mg/L. For those bacteria with a MIC = 96 mg/L, only the following prolonged infusion regimen could be utilized: fosfomycin 8 g LD followed by 8 g MD infused over 6 hours at 8 hour intervals for a total daily dose of 24 g.

Similar trends were seen when targeting T>MIC of 100%. To achieve a MIC = 64 mg/L, a prolonged infusion regimen consisting of a fosfomycin 8 g LD followed by an 8 g MD infused over 6 hours and administered every 8 hours was necessary. For bacteria with a MIC = 96 mg/L, only the 24 g per day continuous infusion regimen could be used. However, none of the fosfomycin dosing regimens met the standard for treating CRE organisms with a MIC greater than 96 mg/L.

3. Efficacy and safety of fosfomycin in patients who infected CRE

The characteristics of all patients are exhibited in **Table 2**. The age of patients who received intravenous fosfomycin for the treatment of CRE infection ranged from 58 to 80 years old. Most patients were female, and the most common pathogen isolated was *K. pneumoniae* (nine patients) followed by *E. coli* (three patients). The major source of infection was UTI with sepsis. The three most common comorbidities were diabetes mellitus, chronic obstructive pulmonary disease, and hypertension. Furthermore, most patients did not receive concomitant antimicrobial therapy during the time they received parenteral fosfomycin.
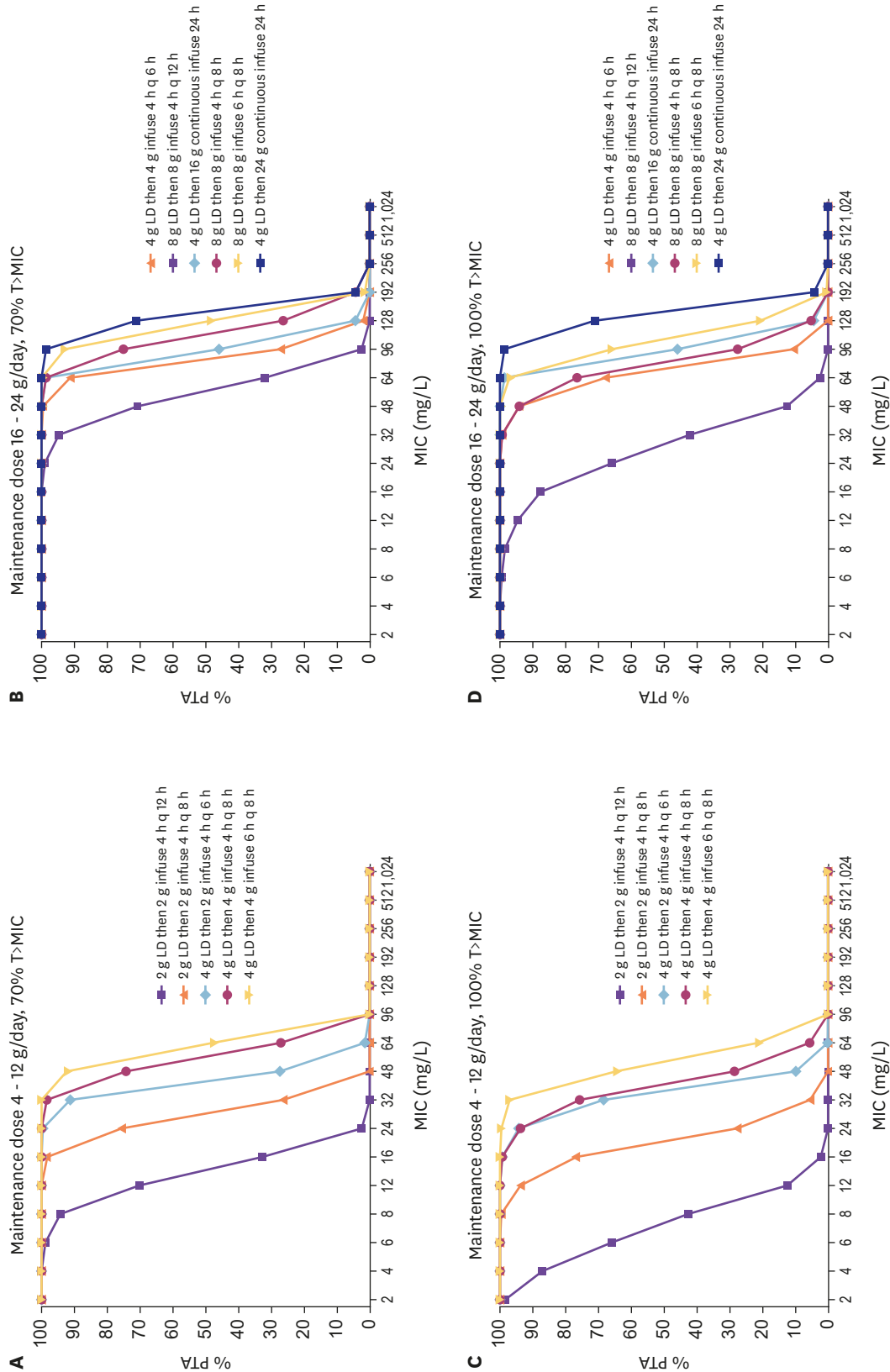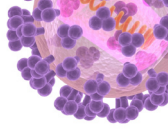
Figure 2. PTA for fosfomycin regimens achieving (A, B) 70% T>MIC and (C, D) 100% T>MIC at different MICs in patients with infection caused by CRE. (A, C): maintain dose 4 - 12 g/day, (B, D): maintain dose 16 - 24 g/day.
PTA, probability of target attainment; MIC, minimum inhibitory concentration; CRE, carbapenem-resistant *Enterobacteriaceae*; LD, loading dose.

Table 2. Characteristic of 12 study patients with infection caused by CRE

Patient no	Sex	Age (year)	Organism	MIC (mg/L)	Source of infection[a]	Fosfomycin dosing regimens	Comorbidity	Concomitant antimicrobial	Treatment outcome	Adverse drug reaction
1	Male	68	*Klebsiella pneumoniae*	32	UTI with sepsis	4 g LD then 2 g infuse 4 h q 6 h	DM type 2, HTN, CKD stage 3b	None	Bacterial eradication	None
2	Male	58	*Escherichia coli*	8	SSI with septic shock	2 g LD then 2 g infuse 4 h q 8 h	GIST, CKD stage 3a	Metronidazole	Bacterial eradication	None
3	Female	61	*Klebsiella pneumoniae*	32	UTI with septic shock	4 g LD then 4 g infuse 6 h q 8 h	DM type 2, CKD stage 3a	None	Bacterial eradication	Hypernatremia
4	Female	71	*Klebsiella pneumoniae*	16	VAP with septic shock	4 g LD then 4 g infuse 6 h q 8 h	COPD, NSTEMI	Colistin	Bacterial eradication and death after 4 weeks	AKI Hypernatremia
5	Female	75	*Klebsiella pneumoniae*	64	UTI with sepsis	4 g LD then 4 g infuse 4 h q 6 h	Schizophrenia, HTN	None	Bacterial eradication	None
6	Male	80	*Klebsiella pneumoniae*	96	VAP with septic shock	4 g LD then 24 g infuse 24 h	COPD, AF, MR, NSTEMI, CKD stage 3b	Colistin, Clindamycin	Bacterial eradication and death after 3 weeks	AKI Hypernatremia
7	Male	73	*Klebsiella pneumoniae*	8	UTI with sepsis	2 g LD then 2 g infuse 4 h q 8 h	DM type 2	None	Bacterial eradication	Hypokalemia
8	Male	59	*Escherichia coli*	16	UTI with sepsis	2 g LD then 2 g infuse 4 h q 8 h	BPH, AF	None	Bacterial eradication	None
9	Female	69	*Escherichia coli*	32	UTI with septic shock	4 g LD then 2 g infuse 4 h q 6 h	Ischemic stroke, AF, DM type 2	None	Bacterial persistence after 2 weeks treatment	Hypokalemia
10	Female	56	*Klebsiella pneumoniae*	32	UTI with septic shock	4 g LD then 4 g infuse 6 h q 8 h	HTN	None	Bacterial eradication	None
11	Female	62	*Klebsiella pneumoniae*	16	VAP with septic shock	4 g LD then 2 g infuse 4 h q 6 h	CKD stage 3a, COPD	Colistin	Bacterial eradication	AKI
12	Female	71	*Klebsiella pneumoniae*	32	UTI with sepsis	4 g LD then 2 g infuse 4 h q 6 h	COPD, HTN, DM type 2	None	Bacterial eradication	Hypokalemia

[a]Sepsis and septic shock were classified according to the Surviving Sepsis Guideline.
CRE, carbapenem-resistant Enterobacteriaceae; MIC, minimum inhibitory concentration; UTI, urinary tract infection; LD, loading dose; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; SSI, surgical site infection; GIST, gastrointestinal stromal tumor; VAP, ventilator-associated pneumonia; COPD, chronic obstructive pulmonary disease; NSTEMI, non-ST-elevation myocardial infarction; AF, atrial fibrillation; MR, mitral regurgitation; BPH, benign prostatic hyperplasia; AKI, acute kidney injury.

Eleven patients received intravenous fosfomycin via prolonged infusion as follows: three patients received intravenous fosfomycin 6 g per day, four patients received intravenous fosfomycin 8 g per day, three patients received intravenous fosfomycin 12 g per day, and one patient received intravenous fosfomycin 16 g per day. The twelfth patient received intravenous fosfomycin 24 g per day via continuous infusion.

Regarding treatment outcomes for patients receiving intravenous fosfomycin, our results demonstrate that eleven of twelve patients (91%) achieved microbiologic cure. Of those, two patients died despite being culture-negative for CRE. The one remaining patient had bacterial persistence, but clinically improved (*i.e.*, afebrile with no signs and symptoms of localized infection) after two weeks of treatment. The most commonly observed adverse drug reactions were hypernatremia (3 cases), hypokalemia (3 cases), and AKI (3 cases).

DISCUSSION

Carbapenems remain the drugs of choice to treat multidrug-resistant gram-negative bacteria, particularly AmpC-producing *Enterobacteriaceae* and Extended-Spectrum Beta-Lactamase (ESBL) producing organisms. These pathogens are known to develop antibiotic resistance through loss of porin or by carbapenemase production. Furthermore, infections caused by CRE organisms remain an important public health concern in many countries throughout the world, including Thailand [7]. For these reasons, proper selection of effective antimicrobial

agents and the use of optimal dosing regimens is essential to reducing morbidity and mortality in patients infected with CRE bacteria [23].

Proper consideration of the PK/PD properties of antibiotics used for the treatment of critically ill patients is essential to achieving optimal outcomes in this population[24]. In this study, every regimen consisted of a 2 - 8 g fosfomycin loading dose which was followed immediately with maintenance dosing to yield optimal PK/PD parameters in prolonged and continuous infusion regimens. The efficacy of fosfomycin was also appraised to determine the treatment effect at steady state plasma concentrations. Previous pharmacodynamic studies of fosfomycin suggested a time-dependent killing effect of the drug on carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli*, hence the selection of the 70% T>MIC target to achieve microbiological success [11, 13, 15, 16]. Another study concluded the bacterial killing effect of fosfomycin on Carbapenem-resistant *E. coli* closely correlated with the area under the concentration-time curve to MIC ratio [25]. Due to the scarce evidence about optimal PK/PD targets for fosfomycin, we decided to use 70% T>MIC and 100% T>MIC as our PK/PD targets. Furthermore, we theorized a 100% T>MIC would be necessary to achieve favorable outcomes in patients with more severe infection [24]. In this study, the range of MIC's of fosfomycin for CRE was between 8 mg/L and 96 mg/L, which was lower than those previously reported [11]. Despite this, 83% of the isolates in this study were susceptible to fosfomycin [14].

The most favorable PK/PD targets for fosfomycin were observed when high doses (16 - 24 g/day) of drug were administered using prolonged or continuous infusion regimens. Consequently, these high-dose regimens could be used to treat bacteria with a MIC range of 32 mg/L to 96 mg/L. In contrast, usual doses (4 - 12 g/day) of fosfomycin could be used for bacteria with MIC's at the lower end of the range, or 8 mg/L to 32 mg/L. Administration of fosfomycin by prolonged or continuous infusion might be more appropriate than the intermittent regimen because it allows for a longer period of drug concentration levels to be above MIC values.

In this study, eleven individuals achieved bacterial eradication and one had bacterial persistence despite two weeks of fosfomycin therapy. Three of the patients who achieved bacterial eradication were being treated for VAP with septic shock and received fosfomycin in combination with colistin. Thus, our results are similar to prior studies which suggest the efficacy of fosfomycin in combination with other antimicrobial agents, particularly colistin, can be improved [5, 8, 20, 26–28]. In fact, synergy found with fosfomycin combination therapy may result in reducing the fosfomycin MIC against CRE isolates [10, 28].

Eight of the twelve patients who achieved bacterial eradication had UTI. The success of fosfomycin in these patients may be due to good penetration of the drug in urine [29]. This finding confirms results from a previous randomized trial which support the use of fosfomycin for treating complicated UTI and acute pyelonephritis [30]. However, the reason for bacterial persistence in one patient after 2 weeks of the treatment remains unclear. If the patient had a urinary catheter in place, it may have been difficult to achieve source control due to the production of a biofilm by CRE on the catheter device [31].

The three relevant adverse effects were hypernatremia, hypokalemia, and AKI. The association of hypernatremia with intravenous fosfomycin may be due to the fact that 1 gram of fosfomycin contains 14.4 mEq of sodium. Thus, parenteral fosfomycin should be diluted with 5% Dextrose in Water. The proposed mechanism for hypokalemia with fosfomycin therapy is that the drug

results in an increase in urinary potassium excretion in the distal tubules [8]. In a previous study in which fosfomycin was given as a 30 to 60 minutes infusion, 26% of patients developed hypokalemia. However, this adverse event was not observed when the infusion time was extended to 4 hours [32]. Because of the adverse effects on serum sodium and serum potassium, electrolyte levels should be monitored regularly in patients receiving fosfomycin. Furthermore, three of twelve patients developed AKI while receiving fosfomycin in combination with colistin. Previous studies have suggested that fosfomycin monotherapy does not cause AKI, and it might even reduce the aminoglycoside-induced AKI [33] Hence, we attribute the AKI observed in this study to colistin as the reported rate of nephrotoxicity can be as high as 20%, 35%, and 40% with the use of low-dose, usual-dose, and high-dose colistin, respectively [34].

This study has several limitations. First, our simulated findings were based solely on plasma pharmacokinetics. We believed this to be appropriate as fosfomycin has good tissue penetration and is almost completely unbound to plasma proteins. In fact, several *in vivo* studies have confirmed the achievement of complete concentration equality between plasma and in-tissue fluid after fosfomycin administration. Furthermore, pharmacokinetic studies of fosfomycin have revealed that the drug distributes equally to various sites, such as urine, skin, and lung, compared to that of plasma [9, 35; 36]. Our findings seem to confirm those results. Another important consideration is that there exist intermittent infusion dosing recommendations for fosfomycin, though we did not evaluate those regimens in this study. Instead, we focused primarily on prolonged or continuous infusion regimens in our simulation as we believed those regimens to be most appropriate for treatment [19]. Another limitation of this study is that fosfomycin PK/PD targets were determined based on limited information. That being the case, we chose our targets by considering PK properties specific to the drug itself, as well as the mechanism by which it inhibits cell wall synthesis in bacteria [37]. Another limitation of this study is that MIC distributions for fosfomycin were based on isolates of the CRE bacteria obtained from a secondary care hospital in Thailand. We acknowledge these findings may be different than isolates taken from patients at other types of hospitals. We must also mention our study did not simulate fosfomycin drug levels in patients with renal impairment. This is important because patients with impaired renal function would achieve higher levels of drug concentrating in tissues, compared to those with normal renal function. As a result, it's possible that lower doses of drug would be necessary to achieve the desired clinical effect [38]. Further complicating matters, we must also consider critically ill patients may have augmented renal clearance. This would have resulted in low levels of drug concentration, especially during the initial phase of a treatment. If true, a higher dose of fosfomycin administered during the initial phase might be more appropriate in critically ill patients [39]. Four patients in this study who achieved bacterial eradication also received concomitant antibiotic therapy. The combination of fosfomycin with other antimicrobials may have contributed to the clinical outcome seen in these patients. Another important consideration is that our study has a small sample size (n = 12). Consequently, a prospective clinical study with a larger sample size would be necessary to determine the clinical efficacy and the safety of various fosfomycin dosing regimens. Despite this fact, eleven of the twelve patients in this study achieved successful bacterial eradication and of those that lived, all clinically improved. Finally, most participants in this study received fosfomycin monotherapy, which might result in an increased likelihood of resistance [40]. Treatment strategies, however, were decided based on clinician's judgment. Because the source of infection for most patients was the urinary tract and because fosfomycin has good distribution and reaches sufficient concentrations in urine [8, 9, 36], we believe fosfomycin monotherapy might be an appropriate treatment option for these patients. Our findings support this hypothesis because amongst patients with UTI, we observed clinical improvement.

It is possible to use fosfomycin as monotherapy when the MIC of fosfomycin against CRE pathogens is known. For patients in whom it is necessary to maintain 70% T>MIC target, such as those with UTI or skin and soft tissue infections, a PTA of ≥90% for fosfomycin at MIC ≤16 mg/L, ≤32 mg/L, ≤64 mg/L and ≤96 mg/L was achieved with: 2 g LD followed by 2 g MD infused over 4 hours and administered at 8-hour intervals, 4 g LD followed by 2 g MD infused over 4 hours and administered at 6-hour intervals, 4 g LD followed by 4 g MD infused over 4 hours and administered at 6-hour intervals, and 8 g LD followed by 8 g MD infused over 6 hours and administered at 8-hour intervals, respectively.

Meanwhile, it is important to note that a T>MIC of 100% might be necessary for treatment of an immunocompromised host or a difficult-to-treat infection (*e.g.*, bacteremia, VAP, or catheter-related infection). For these patients, the PTA of ≥90% for fosfomycin at MIC ≤16 mg/L, ≤32 mg/L, ≤64 mg/L and ≤96 mg/L was reached with: 4 g LD followed by a 2 g MD infused over 4 hours and administered at 6-hour intervals, a 4 g LD followed by a 4 g MD infused over 6 hours and administered at 8-hour intervals, a 8 g LD followed by a 8 g MD infused over 6 hours and administered at 8-hour intervals, and 4 g LD followed by 24 g continuous infusion over 24 h, respectively.

There are several benefits associated with the use of fosfomycin for the treatment of CRE infections. First of all, fosfomycin has a trend to good clinical efficacy when used as monotherapy for the treatment of UTI. Secondly, fosfomycin monotherapy has relatively few adverse effects. Moreover, the cost of therapy is low compared to fosfomycin combination with other antibiotics. Despite these advantages, there still exist legitimate concerns for the development of resistance when the drug is used alone. It is important to note CRE treatment requires the use of antimicrobial combinations to improve clinical outcomes and prevention of fosfomycin resistance [5, 16, 40]. The beneficial synergism of fosfomycin dosed in combination with powerful antimicrobials, such as colistin or tigecycline, might be necessary to attain higher PTA targets and to reduce fosfomycin MIC's against CRE isolates [7, 8]. Therefore, in an immunocompromised host or difficult-to-treat infection, it is likely fosfomycin should be combined with other antibiotics, and 100% T>MIC should be targeted. Additionally, close monitoring of renal function, liver function, and electrolyte levels is necessary for these patients receiving high-dose fosfomycin therapy.

Future research is necessary to better elucidate the efficacy and safety outcomes of fosfomycin against CRE infections in the larger population to confirm the clinical outcomes found in this study. In conclusion, it is important to note fosfomycin monotherapy may yield favorable results when used for treating UTI. Meanwhile, severe infections should be treated using combination therapy and with higher doses of fosfomycin. Dosing regimens for fosfomycin should be tailored according to the source of infection, PK/PD target, and MIC value. Nevertheless, a larger clinical study is required to confirm our suggestions.

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