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Original Article

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Prescription Pattern of Intravenous Fosfomycin in a Provincial Hospital in Thailand

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ABSTRACT

Background: In Thailand, active antibiotics against Gram-negative bacteria are limited. The re-emergence of intravenous (IV) fosfomycin is an alternative. IV fosfomycin has broad-spectrum activity, relative safety, and availability. The limitations of the clinical use of IV fosfomycin include the lack of susceptibility reports and unclear dosing. Therefore, this study was designed to examine the prescription pattern of IV fosfomycin in Chonburi Hospital, a provincial hospital in Thailand.
Materials and Methods: A retrospective descriptive study involving in-patients aged ≥18 years who received IV fosfomycin between February 2019 and January 2020. Data were collected from the electronic patient records.
Results: Of 265 patients, 254 (95.8%) and 11 (4.2%) received IV fosfomycin for treatment and prophylaxis, respectively. IV fosfomycin was prescribed for empirical and definitive treatment. All 166 organisms were Gram-negative bacteria (GNB), including *Enterobacterales* (47.0%), *Acinetobacter baumannii* (44.0%), and *Pseudomonas aeruginosa* (9.0%). Moreover, 141 (87.6%) isolates were carbapenem-resistant GNB (CR-GNB). The most commonly used IV fosfomycin regimen contained colistin or aminoglycosides. Furthermore, 35.3% of the combination regimens contained one active antibiotic. The appropriate dosage of IV fosfomycin for treating urinary tract infection was 71.8%. The 14-day all-cause mortality rate in CR-GNB was 45.0%.
Conclusion: IV fosfomycin is reserved for secondary use in treating nosocomial infection with resistant GNB. It is used synergistically with other antibiotics. At least one active antibiotic and the optimal fosfomycin dosage should be considered. An antimicrobial stewardship program should be implemented for the optimal use of fosfomycin.

Keywords: Fosfomycin; Combination therapy; Carbapenem resistance

INTRODUCTION

The rise of drug-resistant pathogens is a worldwide problem [1]. In Thailand, resistant Gram-negative bacteria (GNB) are a major threat [2]. There are few active antibiotics against resistant bacteria; therefore, developing new drugs and renewing old antibiotics should be promoted.

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Fosfomycin was discovered in 1969 and has been shown to inhibit the first step of peptidoglycan synthesis. Fosfomycin has broad-spectrum bactericidal activity against gram-positive and Gram-negative bacteria. While waiting for the development of new drugs, fosfomycin is an alternative for treating infection with drug-resistant organisms. It has two formulations: oral fosfomycin trometamol for lower urinary tract infection and intravenous (IV) fosfomycin disodium for systemic infection. IV fosfomycin is unavailable in the United States but available in many European and Asian countries, including Thailand. IV fosfomycin is widely used in clinical practice because it can penetrate well into various sites of infection. The drug is relatively safe; however, it can cause abnormal sodium and potassium levels. The use of IV fosfomycin has some limitations: first, it only has a breakpoint for urinary tract isolates of *Escherichia coli* and *Enterococcus faecalis* as defined by the Clinical & Laboratory Standards Institute (CLSI) [3]. According to the European Committee on Antimicrobial Susceptibility Testing, IV fosfomycin has a minimum inhibitory concentration (MIC) breakpoint for *Staphylococcus* spp. and *Enterobacterales* [4]. Some microbial laboratories cannot test the MIC value of antibiotics. Second, it should be used with other antibiotics to prevent resistance. Finally, dosage recommendations are wide ranging (12 - 24 g/day) for patients with normal renal function, whereas those for patients with renal impairment are still unclear [5-8].

IV fosfomycin is widely used in Thailand; however, no survey on real-life practice has been conducted. The primary objective was to examine the prescription pattern of IV fosfomycin disodium in Chonburi Hospital to guide the dosage prescription to be more effective and appropriate and to reduce fosfomycin resistance.

MATERIALS AND METHODS

1. Study design and participants

A retrospective descriptive study on the prescription pattern of IV fosfomycin in Chonburi Hospital, a 850-bed provincial hospital in Chonburi, Thailand, was conducted between February 2019 and January 2020. In-patients aged ≥ 18 years who received IV fosfomycin were included. Patients whose data cannot be retrieved from electronic medical records were excluded from this study. The sample size was estimated to be at least 281 patients. According to the proportion sample size calculation method and the fact that 24.4% of patients received fosfomycin in the previous study, this would produce results at 5% significance levels and 5% precision [9].

2. Ethics statement

This study was reviewed and approved by the Institutional Review Board of Chonburi Hospital (Approval No. 97/63/T/h3). This study was conducted according to the Declaration of Helsinki. The need for patient consent was waived because of the retrospective nature of this study.

3. Data collection

Patient data were collected from electronic medical records. The collected data included (1) demographic characteristics, including sex, age, underlying diseases, and creatinine clearance; (2) characteristics of infectious diseases, including admitting ward, type of infection (*i.e.*, community-acquired or nosocomial), site of infection, type of treatment (*i.e.*, empirical or definitive treatment), pathogens, and antimicrobial susceptibility results; (3) prescription pattern of fosfomycin (*i.e.*, drug, dose, duration, infusion time, and solution); and (4) outcomes, including 14-day all-cause mortality in patients who received fosfomycin for definitive treatment.

4. Definitions

Nosocomial infection was defined as the isolation of pathogens from infectious specimens after hospital admission within 48 h after hospital discharge in patients who received IV fosfomycin for treating infection. Empirical treatment was defined as the use of IV fosfomycin for treating infectious diseases before pathogens were identified, and definitive treatment was defined as IV fosfomycin therapy after pathogens were isolated and identified. The hospital laboratory determined antimicrobial susceptibility using the disk diffusion test and interpret the results by CLSI criteria of *E. coli*. Active antibiotics were defined as antibiotics that had activity (susceptible) against pathogens based on the susceptibility report. The sites of infections were determined as diagnosed by the physicians. Creatinine clearance was calculated using the Cockcroft–Gault formula. The appropriate dosage according to the classification of renal function was based on Lexicomp online, a pharmacokinetic-pharmacodynamic study, and a phase 2/3 randomized trial for complicated urinary tract infection [10-12]. The 14-day all-cause mortality was defined as patients who died within 14 days after the onset of infection.

5. Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (version 28, IBM Corp., Armonk, NY, USA). Descriptive statistics were used to represent demographic characteristics, infection characteristics, and prescription patterns of IV fosfomycin. The comparison of categorical variables was conducted using Pearson's Chi-square test or Fisher's exact test. *P*-values ≤0.05 were used to denote statistical significance.

RESULTS

Of the 265 patients who were hospitalized and received IV fosfomycin between February 2019 and January 2020, 163 (61.5%) were admitted to the general internal medicine ward before the administration of IV fosfomycin. Chronic kidney disease and hypertension were the most common comorbidities. Only 11 (4.2%) patients received IV fosfomycin for surgical prophylaxis (**Table 1**). Fosfomycin was commonly used to treat nosocomial infections (96.9%) and respiratory tract infections (46.5%). Carbapenems and piperacillin/tazobactam were commonly used before the administration of IV fosfomycin (n = 41, 42.7% and n = 10, 10.4%, respectively). The highest fosfomycin dose administered was 16 g/day (**Table 2**). The appropriate dosage of IV fosfomycin for patients with creatinine clearance ≥50, 30 to <50, 15 to <30, and <15 mL/min was 20.0%, 56.3%, 60.7%, and 53.3%, respectively. The appropriate dosage of IV fosfomycin for patients with urinary tract infection with creatinine clearance ≥ 50, 30 to <50, 15 to <30, and <15 mL/min was 71.2%, 75.0%, 100.0%, and 50.0%, respectively.

Mostly, IV fosfomycin was used synergistically with other agents for treatment. IV fosfomycin plus colistin was the most common combination regimen for empirical (n = 59, 51.8%) and definitive treatments (n = 73, 51.4%). The combination regimen of IV fosfomycin plus aminoglycosides was more common for definitive treatment (n = 32, 22.5%) than for empirical treatment (n = 9, 7.9%) (**Table 3**).

Mono-microbial infections were reported more than polymicrobial infections (82.1% *vs.* 17.9%, respectively). Enterobacterales and *Acinetobacter baumannii* were the most common isolates (47.0% and 44.0%, respectively). Of all isolates, 141 (87.6%) were carbapenem-resistant organisms. Fosfomycin susceptibility was reported in 87 isolates. Fosfomycin-sensitive

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Table 1. Baseline characteristics and prescription pattern with patients received intravenous fosfomycin

Characteristics (N = 265)	N (%)
Male	142 (53.6)
Age, mean ± standard deviation, years	59.6 ± 17.7
Comorbidity	
Hypertension	62 (23.4)
Diabetes	53 (20.0)
Cardiovascular disease	39 (14.7)
Chronic kidney disease	147 (55.5)
Solid tumor	24 (9.1)
Hematologic malignancy	22 (8.3)
Ward	
Critical care ward	26 (9.8)
General internal medicine ward	163 (61.5)
Critical surgery ward	8 (3.0)
Surgical wards	68 (25.7)
Surgical prophylaxis	11 (4.2)
Treatment	254 (95.8)
Infusion drip 1 hour	265 (100)
Solution	
0.9% sodium chloride	133 (50.2)
Dextrose 5% in water	132 (49.8)

Table 2. Prescription pattern of intravenous fosfomycin for the treatment of infections

Characteristics (N = 254)	N (%)
Nosocomial infection	246 (96.9)
Site of infection	
Respiratory tract infection	118 (46.5)
Urinary tract infection	53 (20.9)
Skin and soft tissue infection	29 (11.4)
Bloodstream infection	24 (9.4)
Intraabdominal infection	7 (2.8)
Central nervous system infection	1 (0.4)
Bone and joint infection	1 (0.4)
Unknown source	21 (8.3)
Type of treatment	
Empirical treatment	112 (44.1)
Definitive treatment	140 (55.1)
Empirical and definitive treatment	2 (0.8)
IV Fosfomycin daily dose based on site of infections; grams/day	
Respiratory tract infection	2 – 16
Urinary tract infection	2 – 12
Skin and soft tissue infection	1 – 12
Bloodstream infection	2 – 12
Intraabdominal infection	2 – 12
Febrile neutropenia	8 – 12
Central nervous system infection	8
Bone and joint infection	4
Duration of IV fosfomycin therapy	
<7 days	147 (57.9)
7 – 14 days	81 (31.9)
>14 days	26 (10.2)

organisms were observed in 60 (69.0%) isolates. Intermediate and resistance to fosfomycin was observed in 16 (18.4%) and 11 (12.6%) isolates, respectively (**Table 4**).

Of all definitive fosfomycin monotherapies, 50.0% were used to treat urinary tract infection. The combination regimen of IV fosfomycin with colistin was used to treat respiratory tract infections (55.0%), urinary tract infections (50.0%), and bacteremia (54.0%) (**Fig. 1A**).

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Table 3. Intravenous fosfomycin – based regimens for the treatment of infections

Fosfomycin – based regimens	N (%)	
	Empirical treatment	Definitive treatment
Fosfomycin monotherapy	10 (8.8)	6 (4.2)
Fosfomycin – colistin	59 (51.8)	73 (51.4)
Fosfomycin – aminoglycosides	9 (7.9)	32 (22.5)
Fosfomycin – tigecycline	1 (0.9)	1 (0.7)
Fosfomycin – carbapenem	5 (4.4)	3 (2.1)
Fosfomycin – levofloxacin	2 (1.8)	2 (1.4)
Fosfomycin – ampicillin/sulbactam	–	2 (1.4)
Fosfomycin – ceftazidime	2 (1.8)	–
Fosfomycin – colistin – ampicillin/sulbactam	8 (7.0)	9 (6.3)
Fosfomycin – colistin – carbapenem	9 (7.9)	3 (2.1)
Fosfomycin – colistin – aminoglycosides	–	3 (2.1)
Fosfomycin – colistin – levofloxacin	4 (3.5)	3 (2.1)
Fosfomycin – colistin – piperacillin/tazobactam	1 (0.9)	–
Fosfomycin – colistin – tigecycline	–	1 (0.7)
Fosfomycin – colistin – cotrimoxazole	–	1 (0.7)
Fosfomycin – aminoglycosides – tigecycline	–	1 (0.7)
Fosfomycin – aminoglycosides – meropenem	2 (1.8)	–
Fosfomycin – meropenem – levofloxacin	1 (0.9)	1 (0.7)
Fosfomycin – meropenem – piperacillin/tazobactam	1 (0.9)	–
Fosfomycin – aminoglycosides – trimethoprim-sulfamethoxazole	–	1 (0.7)

Table 4. Antimicrobial susceptibility for Gram-negative pathogens

	% Sensitivity											
	3GC	ETP	IPM	MEM	FOF	SAM	GEN	AMK	TMP/SMX	LVX	CIP	TGC
Acinetobacter baumannii	0	–	0	0	28.0%[a] I = 56%	1.4%	2.7%	8.2%	13.7%	0	0	78.7%[b]
Pseudomonas aeruginosa	38.5%	–	8.3%	8.3%	100%[c]	–	50.0%	66.7%	–	30.8%	30.8%	–
Klebsiella pneumoniae	0	25.0%	25.4%	27.1%	80.5%[d] I = 4.9%	–	74.1%	57.9%	12.1%	11.9%	5.1%	33.3%[e]
Escherichia coli	5.9%	31.3%	35.3%	41.2%	92.9%[f]	–	41.2%	88.2%	17.6%	0	5.9%	71.4%[g]

No colistin sensitivity report.
[a]Report 25 isolates; [b]Report 47 isolates; [c]Report 7 isolates; [d]Report 41 isolates; [e]Report 51 isolates; [f]Report 14 isolates; [g]Report 14 isolates.
3GC, third generation cephalosporins; ETP, ertapenem; IPM, imipenem/cilastatin; MEM, meropenem; FOF, fosfomycin; SAM, ampicillin-sulbactam; GEN, gentamicin; AMK, amikacin; TMP/SMX, trimethoprim/sulfamethoxazole; LVX, levofloxacin; CIP, ciprofloxacin; TGC, tigecycline.

Moreover, the combination regimen of IV fosfomycin plus colistin was most commonly prescribed for *A. baumannii*. The combination regimen of colistin or aminoglycosides plus IV fosfomycin was most commonly used for Enterobacterales and *Pseudomonas aeruginosa*. Aminoglycosides were used in aminoglycoside-sensitive GNB. Regarding combination treatments, 10 (14.3%) and 42 (56.8%) regimens contained one active agent against *A. baumannii* and *Enterobacterales*, respectively (**Table 5**, **Fig. 1B-1D**). The 14-day all-cause mortality rate of patients infected with Gram-negative pathogens was 45.0%. Moreover, the 14-day all-cause mortality rate of patients infected with *A. baumannii*, *P. aeruginosa*, and *Enterobacterales* was 54.8%, 26.7%, and 39.7%, respectively. The 14-day mortality rate was higher in patients who received the combination regimen of IV fosfomycin plus colistin than in patients who received the combination regimen of IV fosfomycin plus aminoglycoside (53.7% *vs.* 30.6; $P = 0.016$).

Of the patients who received IV fosfomycin for surgical prophylaxis, eight (72.7%) were allergic to penicillins or cephalosporins, and all patients received IV fosfomycin monotherapy. One patient received a single dose of IV fosfomycin before surgery, and the others continued for ≥2 days.

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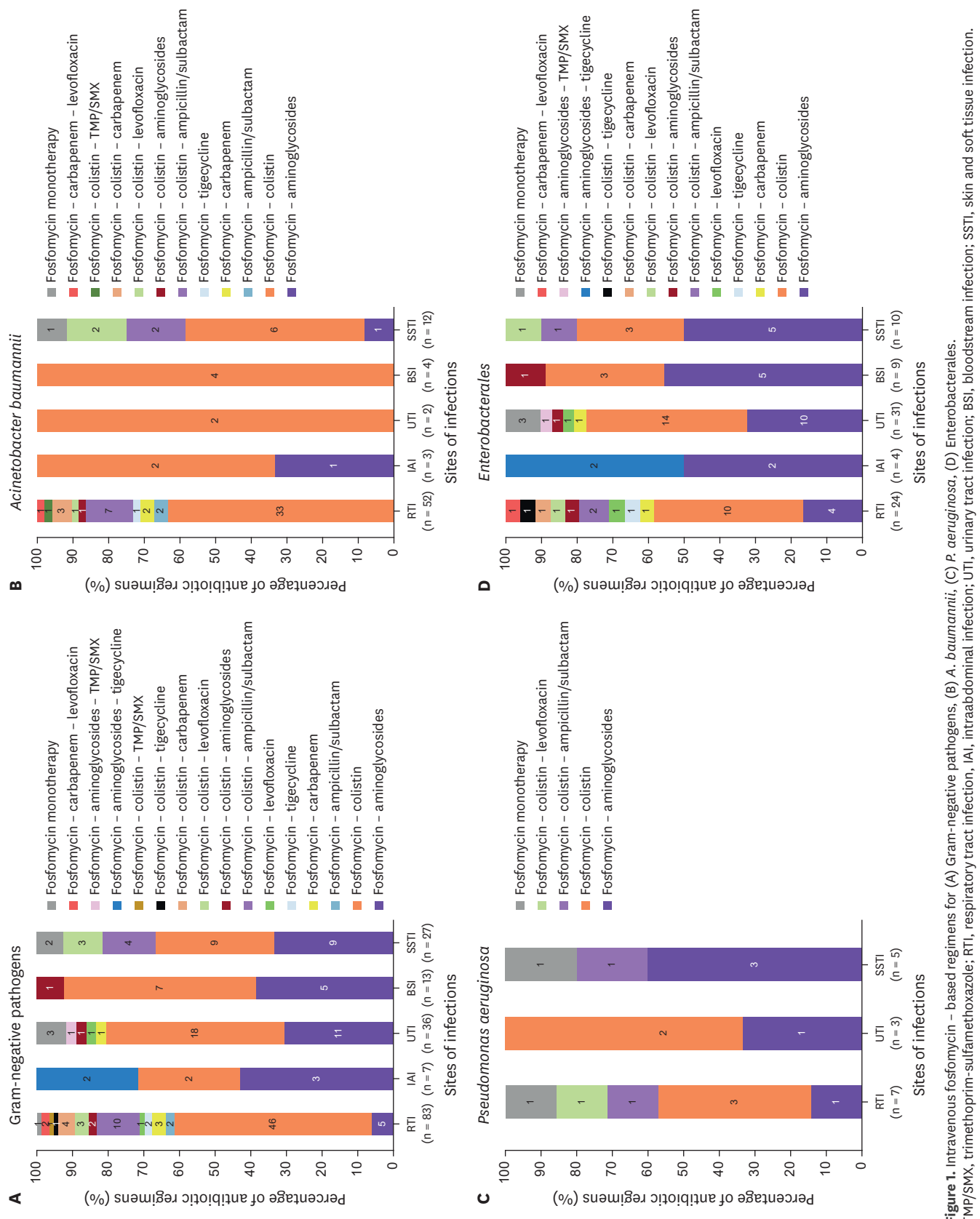

Figure 1. Intravenous fosfomycin – based regimens for (A) Gram-negative pathogens, (B) *A. baumannii*, (C) *P. aeruginosa*, (D) Enterobacterales.
TMP/SMX, trimethoprim-sulfamethoxazole; RTI, respiratory tract infection, IAI, intraabdominal infection; UTI, urinary tract infection; BSI, bloodstream infection; SSTI, skin and soft tissue infection.

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Table 5. Intravenous fosfomycin – based regimens for the Gram-negative pathogens

Fosfomycin – based regimens	N (%)		
	Acinetobacter banumannii	*Pseudomonas aeruginosa*	*Enterobacterales*
Fosfomycin monotherapy	1 (1.4)	2 (12.5)	3 (3.8)
Fosfomycin – colistin	47 (64.4)	5 (33.3)	30 (38.5)
Fosfomycin – aminoglycosides	2 (2.7)	5 (31.3)	26 (33.3)
Fosfomycin – tigecycline	1 (1.4)	–	1 (1.3)
Fosfomycin – carbapenem	2 (4.1)	–	2 (2.6)
Fosfomycin – levofloxacin	–	–	2 (2.6)
Fosfomycin – ampicillin/sulbactam	2 (2.7)	–	–
Fosfomycin – colistin – ampicillin/sulbactam	9 (12.2)	2 (12.5)	3 (3.8)
Fosfomycin – colistin – aminoglycosides	1 (1.4)	–	3 (3.8)
Fosfomycin – colistin – tigecycline	–	–	1 (1.3)
Fosfomycin – colistin – carbapenem	3 (4.1)	–	1 (1.3)
Fosfomycin – colistin – levofloxacin	3 (4.1)	1 (6.3)	2 (2.6)
Fosfomycin – colistin – cotrimoxazole	1 (1.4)	–	–
Fosfomycin – carbapenem – levofloxacin	1 (1.4)	–	1 (1.3)
Fosfomycin – aminoglycosides – tigecycline	–	–	2 (2.6)
Fosfomycin – aminoglycosides – trimethoprim-sulfamethoxazole	–	–	1 (1.3)
Number of active antibiotics in combination regimens			
No active antibiotic[a]	60 (85.7)	6 (50.0)	13 (17.6)
One active antibiotic	10 (14.3)	3 (25.0)	42 (56.8)
Two active antibiotics	–	3 (25.0)	18 (24.3)
Three active antibiotics	–	–	1 (1.4)

[a]Colistin containing regimens; *A. baumannii* 57 isolates, *P. aeruginosa* 5 isolates, *Enterobacterales* 3 isolates.

DISCUSSION

Few studies have examined the use of IV fosfomycin in real practice. This study observed the current prescription pattern of IV fosfomycin in Thailand for patients with infections. In this study, IV fosfomycin was commonly prescribed for carbapenem-resistant GNB (CR-GNB). In Europe, IV fosfomycin is used for Gram-positive and Gram-negative pathogens and anaerobes. Only 24.4% were multidrug-resistant organisms [13]. In India, the most common isolate was *K. pneumoniae* and one was suspected to have carbapenem resistance [14]. This could be because in Thailand, Gram-positive bacteria remained susceptible to beta-lactam and vancomycin. Thus, the use of IV fosfomycin should be reserved for CR-GNB, which is an important problem [2]. A systematic review reported that studies on fosfomycin for treating multidrug-resistant Gram-negative organisms were published after 2010 [15]. In this study, fosfomycin showed good activity against *K. pneumoniae* and *E. coli.* However, only approximately half of the pathogens had fosfomycin susceptibility. In Thailand, fosfomycin is less active against carbapenem-resistant *A. baumannii, P. aeruginosa*, and *K. pneumoniae* and remains active against carbapenem-resistant *E. coli* [11, 16-18]. Therefore, if susceptibility could not be confirmed, IV fosfomycin is not the main antibiotic for treating CR-GNB, especially for *A. baumannii.*

IV fosfomycin was prescribed for treating all sites of infections. The respiratory system and urinary tract are the most common sites of nosocomial infections. In a meta-analysis, no significant difference in the clinical efficacy was observed between fosfomycin monotherapy or combination and other antibiotics; however, resistance development during fosfomycin monotherapy was only 3.4% [15]. Combination regimens contain the following: (1) two to three active antibiotics and (2) active and inactive antibiotics. In this study, IV fosfomycin was commonly prescribed with other antibiotics for synergy. The synergistic activity of fosfomycin with several other antibiotics, particularly carbapenems, aminoglycosides, and

colistin, against GNB was found in several studies [17, 19-23]. Among the combination regimens for treating CR-GNB, IV fosfomycin with aminoglycosides or polymyxin was the most common [24]. Regimens containing fosfomycin and colistin had higher mortality than those containing fosfomycin and aminoglycosides. Regimens containing fosfomycin and aminoglycosides contained at least one active drug; however, regimens containing fosfomycin and colistin did not know the exact number of active drugs. Colistin susceptibility has not been reported because the CLSI recommends broth microdilution for colistin susceptibility testing [3]. The combination regimen of IV fosfomycin plus colistin was the common treatments for carbapenem-resistant *A. baumannii* and higher mortality rate of carbapenem-resistant *A. baumannii* infection. In addition to severity, immune status, inappropriate treatment, time to appropriate treatment, *A. baumannii* infection was associated mortality [25-27]. *A. baumannii* infection had higher mortality than other GNB in accordance with a previous study [28] and the 14-day all-cause mortality rate of patients infected with *A. baumannii* and *Enterobacterales* was higher in previous studies [26, 29].

According to the guidelines of the Infectious Diseases Society of America, IV fosfomycin is not recommended for treating CR-GNB because IV fosfomycin is unavailable in the USA. Ampicillin–sulbactam monotherapy or combination is the preferred treatment for infections with carbapenem-resistant *A. baumannii*; however, IV fosfomycin is not recommended because of insufficient supporting evidence, only *in vitro* studies and preliminary study and low susceptibility rate [17, 21, 30, 31]. For carbapenem-resistant *Enterobacterales*, the choice of antibiotics depends on the type of carbapenemase [32]. Metallo-beta-lactamases and oxacillinase are common in Thailand [26, 33]. Aztreonam and cefiderocol are currently unavailable, and ceftazidime–avibactam is the agent of choice for carbapenem-resistant *Enterobacterales* carrying $bla_{\text{OXA-48}}$ [34]. Therefore, when ceftazidime–avibactam cannot be used, old antibiotics remain the treatment option for carbapenem-resistant *Enterobacterales*. Fosfomycin is one of the antibiotics in combination regimens [26, 35]. IV fosfomycin has been fairly used for treating infections with *P. aeruginosa.* Although *P. aeruginosa* is not sensitive to carbapenems, it is often sensitive to other beta-lactams [32]. When ceftolozane–tazobactam cannot be used, the combination of fosfomycin with colistin or aminoglycosides is an option for difficult-to-treat resistant *P. aeruginosa.* Colistin with aminoglycosides increases the risk of nephrotoxicity. In selecting antibiotic regimens, the following factors should be considered: disease severity, site of infections, safety, and sensitivity results. Two active antibiotics should be considered first. If two active agents are unavailable, at least one active should be considered. In this study, the most commonly used combination regimens contained one active drug if reported the susceptibility result.

The recommended dose of fosfomycin for treating infections with GNB was 16 - 24 g/day [10, 36]. In this study, a low rate of appropriate fosfomycin dosing was observed according to creatinine clearance. The maximum daily dose was 16 g for patients with normal renal function and critically ill patients. The number of beds is limited in the intensive-care unit at this center. Fosfomycin breakpoint for *E. coli* urinary tract isolates was 64 μg/mL. A Monte Carlo simulation of fosfomycin dosing in critically ill patients showed that the doses that provided at least 90% probability of the ratio of the area under the curve to the MIC >21.5 for carbapenem-resistant Enterobacterales at MICs of 64 and 128 μg/mL was 16 and 24 g, respectively [11]. Similar to 70% and 100% free time over MIC for carbapenem-resistant *Enterobacterales* at MICs of 64 and 128 μg/mL, daily dosing of at least 16 g and 24 g, respectively, reached the probability of target attainment [37]. For carbapenem-resistant *A. baumannii* at MICs of 64 and 128 μg/mL, dosing of at least 12 and 16 g, respectively, exceeded the 90%

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probability of 100% free time over MIC [21]. In critically ill patients with severe infections, those with central nervous system infections, those with unknown susceptibility, and unsusceptible patients, a dosage of 24 g/day should be used. In this study, the fosfomycin doses administered to half of the patients were lower than the recommended dose, except for those administered for treating urinary tract infections [5, 10, 11].

For surgical prophylaxis, the guidelines recommend alternative agents (*i.e.*, clindamycin, vancomycin, aminoglycosides, and fluoroquinolone) for patients allergic to beta-lactams, and these agents should not be continued for more than 24 h [38]. No difference in the efficacy of surgical prophylaxis was observed between IV fosfomycin and cephalosporins [39, 40]. IV fosfomycin was unnecessary for preventing postoperative infection.

This study has several limitations. First, this was a retrospective descriptive study; some data were not evaluated, including clinical cure, microbiological eradication, and safety outcomes. The most common adverse drug reactions associated with fosfomycin are hypernatremia and hypokalemia [13]. Many patients had chronic kidney disease, hypertension, and heart disease, and approximately half of the patients used 0.9% sodium chloride solution. Therefore, 5% dextrose in water solution is recommended if not contraindicated. Fosfomycin should be administered for 1 h. Infusion for >1 h can decrease hypokalemia, and prolonged infusion can increase target attainment of fosfomycin [13, 21]. Second, palliative care patients were not excluded from this study, and confounding factors, including dosing of antibiotics, severity of patients, and severe underlying diseases, were eliminated. Third, susceptibility results of fosfomycin and colistin were not determined. The optimal fosfomycin combination regimen remains unclear. Fourth, as there was no interpretation of the susceptibility criteria for *A. baumannii* and *P. aeruginosa*, the susceptibility criteria for *E. coli* in the urinary tract was used instead.

In conclusion, the mortality rate of patients infected with CR-GNB is high. IV fosfomycin is an alternative add-on antibiotic for combination regimens in hospitalized patients infected with CR-GNB. The combination of fosfomycin with aminoglycosides or colistin is common. Inactive antibiotics and suboptimal fosfomycin dosage have been identified. An antimicrobial stewardship program should be implemented for the optimal use of fosfomycin. The MIC of antibiotics, therapeutic effects, and adverse effects of each drug regimen should be studied.

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