Retrospective analysis of fosfomycin combinational therapy for sepsis caused by carbapenem-resistant *Klebsiella pneumoniae*

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Abstract. The aim of the present study was to compare the efficacy and safety of fosfomycin combinational therapy with other antibiotics for the treatment of infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP). This retrospective cohort study examined 104 cases of sepsis caused by CRKP occurring between January 2012 and November 2014 in Shanghai Tenth People's Hospital. Three categories of patient outcome were assessed: Survival/mortality, duration of intensive care unit stays and duration of medical ventilation. Univariate ordinal analyses were adopted to evaluate the correlations between outcome and treatment. A total of 104 patients with physician-diagnosed CRKP were involved in the study. The overall mortality rate was 25.0%. The majority of the infections (84; 80.8%) were hospital acquired. Critical infections received more than one active antibiotic as therapy. Patients treated with fosfomycin combinational therapy were less likely to fail therapy (OR: 4.71, 95% CI: 1.03-21.65, P=0.034) and tended to have a shorter duration of mechanical ventilation. Gender (OR: 4.35, 95% CI: 1.08-3.60, P=0.037), history of chronic obstructive pulmonary disease (OR: 9.35, 95% CI: 0.06-0.19, P=0.007) and peripheral catheter use (OR: 3.00, 95% CI: 0.07-0.19, P=0.002) are risk factors for clinical outcome. Therefore, the use of fosfomycin combinational therapy for treatment of infection due to CRKP appears to be associated with improved survival rate.

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Introduction

Infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) have been a serious problem due to limited therapeutic options all around the world (1). Few optimal therapy strategy are available for the infections, making its treatments extremely difficult and leading to poor therapeutic outcomes with the reported mortality rates ranging from 39-72% (2-4). The core issue of managing CRKP infection is to find an effective antibiotic regimen, as carbapenem resistance is often accompanied by resistance to other families of first-line antibiotics, such as beta-lactam inhibitors, quinolones and 3rd/4th generation cephalosporin. Optional antibiotics are usually limited to polymyxins, aminoglycosides, gentamicin, colistin and tigecycline (5,6).

Recently, a study reported that treatment with tigecycline or an aminoglycoside can generate positive outcomes (7). In addition, there are reports indicating that the use of carbapenems in combination with other active agents could contribute to a lower mortality, particularly when the strains have low levels of *in vitro* resistance to those antimicrobials (8). Furthermore, a number of reports suggest that combinational therapies are often more effective than monotherapies (9,10). Therefore, the goal of this retrospective study was to analyze the effect of combinational therapy of fosfomycin and carbapenemase on mortality from sepsis due to CRKP.

Patients and methods

Patients. The retrospective study was conducted in a teaching hospital of Tongji University (Shanghai, China). From January 2012 to November 2014. All CRKP isolates were collected from the database of the Microbiology Service of the Shanghai Tenth People's Hospital of Tongji University. The clinical records of patients with CRKP isolates were reviewed. The enrollment criteria were as follows: i) Clinical evidence of sepsis, severe sepsis or septic shock due to CRKP; ii) meropenem or imipenem were used within 72 h after CRKP cultured from urine, blood, phlegm or drainage liquid; iii) the administration of meropenem therapy lasted for at least 72 h; and iv) >18 years old.

Admission to intensive care unit (ICU) was defined as a stay of 24 h before or after diagnosis of the severe sepsis.

Predictors of the primary outcomes included age, sex, underlying diseases [diabetes mellitus, history of chronic obstructive pulmonary disease (COPD), heart failure, hepatic failure, renal failure, gastrointestinal surgery, solid malignancies, hematologic malignancies], special treatments (central venous catheter, peripheral catheter, foley catheter, Nasogastric tube, mechanical ventilation ≥3 days, gastric acidity-lowering agents, immunosuppressive therapy, total parenteral nutrition), prior use of antibiotics and bacteremia. Clinical outcome contained length of ICU stay, mortality or cure, and duration of mechanical ventilation. The patients with recurrent CRKP isolated from the blood or urine were defined as microbiological failure at least 7 days after their index culture. Patients who had a negative culture were defined as treatment success.

Statistical analysis. Quantitative variables are expressed as the mean ± standard deviation and qualitative variables are depicted as percentages of the group to which they belonged. Differences between patients treated with fosfomycin and meropenem and other antibiotics were analyzed by univariate logistic regression. Risk factors correlated with clinical outcome and microbiological failure was analyzed using stepwise multiple logistic regression analyses. The odds ratio (OR) was calculated with 95% confidence interval (CI). All statistical tests were two-tailed and utilized a 0.05 significance level. Analyses were performed using SPSS software, version 20.0 (IBM SPSS, Armonk, NY, USA).

Results

Clinical characteristics of the patients. A total of 104 unique cases of bacteremia with CRKP were identified during the experimental period. The demographics and clinical characteristics of the cases are shown in Table I. The ages of the 104 patients, 79 male and 25 female, ranged from 28 to 95 years, with a median of 67.2 years. The majority of the infections (84; 80.8%) were hospital acquired. All but one patient had been admitted to the hospital within a year prior to the episode of bacteremia, with a majority of them (87; 83.7%) having been admitted to an ICU. Patients that received ineffective empirical antimicrobial therapy before the susceptibility results became available are in the majority and 80 patients (76.9%) received mechanical ventilation. The majority of patients had underlying diseases, had undergone invasive procedures, and had been admitted to ICUs or received medical services.

Antimicrobial susceptibility. Colistin exerted the highest susceptibility rate with 93.3% (Table II). Tigecycline and minocyline were active against 68 (65.4%) and 79 (76.5%) isolates, respectively. With regard to fosfomycin, 40 isolates (38.5%) were susceptible, 54 (51.9%) showed intermediate susceptibility and 10 (9.6%) were resistant. A less marked susceptibility to amikacin (28, 26.9%) and gentamicin (14, 13.5%) was observed.

Antibiotic treatment. All patients received targeted antibiotic treatment. Targeted treatment was optimal in 78 patients (75.0%). The targeted antibiotics used were shown in Table III. A total of 10 patients were infected with a fosfomycin-resistant CRKP strain. This combination treatment group consisted of 24 patients (23.1%) that were administered a dose of 12 mg/24 h and were not administered fosfomycin as monotherapy. In the fosfomycin combinational therapy group, 16 patients were administered meropenem (1 g every 8 h) following with fosfomycin with the other 8 patients received fosfomycin, meropenem, tigecycline or (and) minocyline. Those patients received fosfomycin combination were less likely to fail therapy (OR: 4.71, 95% CI: 1.03-21.65, P=0.030). However, no difference between length of ICU stays and duration of mechanical ventilation was observed in these two groups (Table I). The primary characteristics of the patients who received fosfomycin combinational therapy are shown in Table IV. According to the result, the number of patients that underwent prior use of minoglycosides and carbapenems differed between the two groups. Compared with other regimens (10.2±11.0 vs. 13.0±11.2), fosfomycin combination group tends to have shorter duration of mechanical ventilation, however the difference did not display statistical significance. An interesting thing is that the age of fosfomycin combinational therapy group is older than other treatments group (68.7±14.6 vs. 62.0±18.3, P=0.065), which might give us a hint that fosfomycin combinational therapy is safer and more suitable to be applicable to aged people. The fosfomycin combinational therapy group has an overall mortality of 8.3% with one case died of pneumonia and another died of the infection of the central nervous system (Table V).

Taking the difference in prior use of aminoglycosides into consideration, the effect of fosfomycin in combination with meropenem and with other regimens treatment was compared (Table VI). This combinational therapy group has 16 patients. Compared with other therapy, a significant difference was observed (Table VI, P=0.010) when compared with treatment by using 3rd/4th generation (monotherapy or combinational therapy).

Risk factors for mortality. Differences between cases of mortality and survival was observed using univariate analysis (Table I). Peripheral catheter and history of COPD have a negative influence on survival rates (P=0.01 and P=0.016). Meanwhile, compared with female patients, male patients have a higher mortality. Fosfomycin combinational therapy (7.7 vs. 24.6%) was associated with lower mortality (Table I). Compared with other targeted therapy, target treatment with fosfomycin exerted preponderance (P=0.034, OR: 4.71 [1.03-21.65]). The survival analysis performed using Kaplan-Meier curves showed that patients treated with fosfomycin combinational therapy had higher survival rates at 45 days after diagnosis (Fig. 1, log-rank test t=3.96, P=0.047). However, in a multivariate analysis, no correlation between fosfomycin combination and outcome was observed (Table VII, P=0.141).

Discussion

CRKP has become a major hospital pathogen worldwide, and infections due to this organism have been associated with high mortality (9,11-13). The increasing prevalence and the high mortality associated with the organism underscore the importance of effective antimicrobial therapy for these serious infections. However, optimal treatment for infections caused by CRKP has not yet been defined (14).

Table I. Baseline characteristics of 104 patients with severe infection caused by carbapenem-resistant *Klebsiella pneumoniae*. Univariate analysis of factors associated with clinical outcome, N (%).

Demographic variables	Total (104)	Mortality (26)	Survivors (78)	P-value	OR (95% CI)
Age (mean ± SD)	67.2±15.7	68.4±15.5	66.8±15.9	0.641	
Gender					
Male	79 (76.0)	16 (61.5)	63 (80.8)	**0.047**	**2.63 (1.00-6.93)**
Female	25 (24.0)	10 (38.5)	15 (19.2)		
Underlying disease					
Diabetes mellitus	43 (41.3)	13 (50.0)	30 (38.5)	0.301	0.63 (0.26-1.53)
History of COPD	29 (27.9)	12 (46.2)	17 (21.8)	**0.016**	**0.32 (0.13-0.83)**
Heart failure	24 (23.1)	8 (30.8)	16 (20.5)	0.282	0.58 (0.21-1.58)
Hepatic failure	7 (1.9)	3 (11.5)	4 (5.1)	0.363	0.41 (0.09-1.99)
Renal failure	24 (23.1)	8 (30.8)	16 (20.5)	0.293	0.58 (0.21-1.58)
Gastrointestinal surgery	9 (8.7)	3 (11.5)	6 (7.7)	0.687	0.64 (0.15-2.76)
Solid malignancies	14 (13.5)	4 (15.4)	10 (12.8)	0.746	0.81 (0.23-2.84)
Hematologic malignancies	0 (0)	0 (0)	0 (0)		
Special treatments total					
Central venous catheter	72 (69.2)	17 (65.4)	55 (70.5)	0.624	1.27 (0.49-3.25)
Peripheral catheter	43 (41.3)	18 (69.2)	25 (32.1)	**0.001**	**0.21 (0.08-0.55)**
Foley catheter	86 (82.7)	21 (80.8)	65 (83.3)	0.765	1.19 (0.38-3.73)
Nasogastric tube	78 (75.0)	22 (84.6)	56 (71.8)	0.295	0.46 (0.14-1.50)
Mechanical ventilation ≥3 days	70 (68.0)	19 (73.1)	51 (66.2)	0.518	0.72 (0.27-1.94)
Gastric acidity-lowering agents	98 (94.2)	25 (96.2)	73 (93.6)	1.00	0.58 (0.07-5.24)
Immunosuppressive therapy	29 (27.9)	4 (15.4)	25 (32.1)	0.132	2.59 (0.81-8.33)
Total parenteral nutrition	44 (42.3)	10 (38.5)	34 (43.6)	0.647	1.24 (0.50-3.06)
Prior use of antibiotics					
β-lactam inhibitors	52 (50.0)	17 (65.4)	35 (44.9)	**0.070**	**0.43 (0.17-1.08)**
Quinolones	42 (40.4)	14 (53.8)	28 (35.9)	0.106	0.48 (0.20-1.18)
3rd/4th Generation cephalosporin	72 (69.2)	17 (65.4)	55 (70.5)	0.624	1.27 (0.49-3.25)
Aminoglycosides	21 (20.6)	2 (7.7)	19 (25.0)	**0.060**	**4.0 (0.86-18.53)**
Fosfomycin	6 (5.8)	0 (0)	6 (7.7)	0.333	0.74 (0.65-0.83)
Imipenem	14 (13.5)	1 (3.8)	13 (16.7)	0.097	5.00 (0.62-40.25)
Type of infection					
CAP	28 (26.9)	6 (23.1)	22 (28.2)	0.610	1.31 (0.46-3.69)
HAP	84 (80.8)	21 (80.8)	63 (80.8)	1.000	1.00 (0.32-3.08)
Urinary tract infection	17 (16.3)	5 (19.2)	12 (15.4)	0.646	0.76 (0.24-2.42)
Surgical site infection	11 (10.6)	2 (7.7)	9 (11.5)	0.581	1.57 (0.32-7.76)
Intra-abdominal infecton	4 (3.8)	1 (3.8)	3 (3.8)	1.000	1.04 (1.00-1.08)
Primary bacteraemia	9 (8.7)	3 (11.5)	6 (7.7)	0.546	0.64 (0.15-2.76)
Central venous catheter bacteraemia	0 (0)	0 (0)	0 (0)		
Ventilator associated pneumonia	1 (1.0)	0 (0)	1 (1.3)	1.000	0.75 (067-0.83)
Targeted treatment					
Monotherapy	32 (30.8)	11 (42.3)	21 (26.9)	0.141	0.50 (0.20-1.27)
Combination therapy	72 (69.2)	15 (57.7)	57 (73.1)		
Fosfomycin combination	**24 (23.1)**	**2 (7.7)**	**22 (28.2)**	**0.034**	**4.71 (1.03-21.65)**
Other treatment regimens	**65 (61.9)**	**16 (24.6)**	**49 (75.4)**		
Length of ICU stays		15.2±10.5	17.6±12.2	0.355	
Duration of mechanical ventilation		10.7±10.6	10.9±10.9	0.958	

Values in bold are statistically significant. SD, standard deviation; COPD, chronic obstructive pulmonary disorder; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

Table II. Antimicrobial susceptibility test result of 104 patients with severe infection caused by carbapenem-resistant *Klebsiella pneumoniae*.

Drug	Sensitive	Intermediary	Resistance
Tigecycline	68 (65.4)	1 (1.0)	35 (33.7)
Minocyline	79 (76.0)	17 (16.3)	8 (7.7)
Colistin	97 (93.3)	0 (0)	7 (6.7)
Gentamicin	14 (13.5)	0 (0)	91 (86.5)
Amikacin	28 (26.9)	0 (0)	76 (73.1)
Meropenem	1 (1.00	0 (0)	103 (99.0)
Imipenem	1 (1.00	0 (0)	103 (99.0)
Ertapenem	1 (1.00	0 (0)	103 (99.0)
Cefepime	9 (8.7)	0 (0)	95 (91.3)
Fosfomycin	40 (38.5)	54 (51.9)	10 (9.6)

Table III. Target antibiotics used in 104 patients with severe infection caused by carbapenem-resistant *Klebsiella pneumoniae,* N (%).

Target antibiotic	Total	Mortality	Survivors
Target monotherapy	32 (30.8)	11 (42.3)	21 (26.9)
Pipercillin/sulbactam	4 (12.5)	1 (9.1)	3 (14.3)
Aminoglycosides	5 (15.6)	1 (9.1)	4 (19.0)
3rd/4th Generation cephalosporin	13 (40.6)	6 (54.5)	7 (33.3)
Quinolones	4 (12.5)	0 (0)	0 (0)
Meropenem	7 (21.9)	3 (27.3)	4 (19.0)
Imipenem	1 (3.1)	0 (0)	1 (4.8)
Tigecycline	1 (3.1)	0 (0)	1 (4.8)
Minocyline	1 (3.1)	0 (0)	1 (4.8)
Target combination therapy	72 (69.2)	15 (57.7)	57 (73.1)
Fosfomycin+meropenem	16 (19.4)	1 (6.7)	15 (24.6)
Fosfomycin+meropenem+ Tigecycline/minocyline/ amikacin	8 (11.1)	1 (6.7)	7 (12.2)
Tigecycline+meropenem	4 (5.6)	1 (5.3)	3 (1.2)
Tigecycline+meropenem+ amikacin	6 (8.3)	1 (5.3)	5 (8.8)
Tigecycline+minocyline	3 (4.2)	0 (0)	3 (5.3)
Tigecycline+minocyline+ meropenem	1 (1.4)	0 (0)	1 (1.8)
Minocyline+carbapenems	4 (5.6)	2 (13.3)	2 (3.5)
Minocyline+pipercillin/ sulbactam	1 (1.4)	1 (5.3)	0 (0)
Gentamicin+meropenem	2 (2.8)	0 (0)	2 (3.5)
Amikacin+meropenem	3 (4.2)	0 (0)	3 (5.3)
Amikacin+cefepime	3 (4.2)	0 (0)	3 (5.3)
Amikacin+pipercillin/ sulbactam	1 (1.4)	0 (0)	1 (1.8)
Cefepime+amoxicillin/ sulbactam	1 (1.4)	0 (0)	1 (1.8)
Cefepime+pipercillin/ sulbactam	1 (1.4)	0 (0)	1 (1.8)
Cefepime+sulfamethoxazole	2 (2.8)	2 (13.3)	0 (0)
Cefepime+aztreonam	1 (1.4)	0 (0)	1 (1.8)
Cefoperazone/sulbactam+ carbapenems	4 (5.6)	0 (0)	4 (7.0)
Cefoperazone/sulbactam+ quinolones	2 (2.8)	1 (5.3)	1 (1.8)
Carbapenems+quinolones	5 (6.9)	3 (20.0)	2 (3.5)
Pipercillin/sulbactam+ carbapenems	4 (5.6)	2 (13.3)	2 (3.5)

The present retrospective study involved 104 unique patients with bacteremia due to CRKP with overall mortality rate of 25%, which is substantially lower than the rates reported for CRKP in previous studies (11,15,16). Alternatively, the difference may be resulted from unrecognized confounding variables. Nonetheless, the mortality still remains considerably higher than for bacteremia due to CRKP (17).

We identified gender, peripheral catheter and history of COPD as independent clinical risk factors for mortality. The present study demonstrated that survival in patients with CRKP was significantly improved when combinational therapy rather than monotherapy was administered. Fosfomycin combinational therapy is successful in the present study compared with other monotherapy and combination regimens. Alternatively, as monotherapy, fosfomycin could drive resistance develops rapidly (18). In the present study, no patients were included that received fosfomycin monotherapy. Fosfomycin is a broad spectrum antibiotic that inhibits peptidoglycan synthesis (19). Fosfomycin inhibits bacterial cell wall biogenesis by inactivating the enzyme UDP-N-acetylglucosamine-3-enolpyruvyltransferase which is also known as MurA (20). This enzyme is able to catalyze the committed step in peptidoglycan biosynthesis, namely the ligation of phosphoenol pyruvate to the 3'-hydroxyl group of UDP-N-acetyl glucosamine (20), which may provide a route for meropenem to enter the bacteria. It can be administered in combination with some other antimicrobial agents, since there is low level of or no cross resistance (21). This agent is well tolerated and has a few side effects. It has an increased role as a therapeutic option against multidrug-resistant Enterobacteriaceae (19,20,22,23). Cumulative susceptibility of fosfomycin against ESBL positive Enterobacteriaceae is reported as 87.7% according to CLSI criteria (24). However, lower susceptibility rates (<50%) was showed in some studies, and in a study this agent was shown to be active against only 50% of *Klebsiella* (22,25).

Qureshi *et al* (3) reported that either colistin-polymyxin B or tigecycline in combination with a carbapenem appeared to be effective. These combination regimens were more successful than monotherapy with either colistin-polymyxin B or tigecycline, even when *in vitro* testing confirmed susceptibility to the respective antimicrobials. While the mechanisms underlying the effectiveness of these combinations are not known, synergistic activity between carbapenems and colistin has been observed *in vitro* among their CRKP isolates, which is consistent with the clinical observation, at least for this particular combination.

Table IV. Analysis of clinical variables in 24 patients that received fosfomycin combination therapy, N (%).

Demographic variable	Total	Fosfomycin combination (n=24)	Other regimens (n=80)	P	OR (95% CI)
Age (mean ± SD)	67.2±15.7	68.7±14.6	62.0±18.3	0.065	
Gender					
Male	79 (76.0)	20 (83.3)	59 (73.8)	0.422	1.78 (0.55-5.81)
Female	25 (24.0)	4 (16.7)	21 (26.2)		
Underlying disease					
Diabetes mellitus	43 (41.3)	6 (25.0)	37 (46.2)	0.064	0.39 (0.14-1.08)
History of COPD	29 (27.9)	4 (16.7)	25 (31.2)	0.201	0.44 (0.14-1.42)
Heart failure	24 (23.1)	2 (8.3)	22 (27.5)	0.057	0.24 (0.05-1.11)
Hepatic failure	7 (6.0)	0 (0)	7 (8.8)	0.197	0.75 (0.67-0.84)
Renal failure	24 (23.1)	3 (12.5)	21 (26.2)	0.268	0.40 (0.11-1.49)
Gastrointestinal surgery	9 (8.7)	1 (4.2)	8 (10.0)	0.681	0.39 (0.05-3.30)
Solid malignancies	14 (13.5)	2 (8.3)	12 (15.0)	0.513	0.52 (0.11-2.48)
Hematologic malignancies	0 (0)	0 (0)	0 (0)		
Special treatments total					
Central venous catheter	72 (69.2)	17 (70.8)	55 (68.8)	0.846	1.10 (0.41-3.00)
Peripheral catheter	43 (41.3)	9 (37.5)	34 (42.5)	0.663	0.81 (0.32-2.07)
Foley catheter	86 (82.7)	18 (75.0)	68 (85.0)	0.256	0.53 (0.18-1.61)
Nasogastric tube	78 (75.0)	17 (70.8)	61 (76.2)	0.591	0.76 (0.27-2.10)
Mechanical ventilation ≥3 days	70 (68.0)	15 (62.5)	55 (68.0)	0.513	0.73 (0.28-1.90)
Gastric acidity-lowering agents	98 (94.2)	23 (95.8)	75 (93.8)	1.00	1.53 (0.17-13.80)
Immunosuppressive therapy	29 (27.9)	10 (41.7)	19 (43.7)	0.086	2.29 (0.88-6.00)
Total parenteral nutrition	44 (42.3)	13 (54.2)	31 (38.8)	0.139	1.80 (0.74-4.69)
Prior use of antibiotics					
β-lactam inhibitors	52 (50.0)	15 (62.5)	37 (46.2)	0.163	1.94 (0.76-4.94)
Quinolones	42 (40.4)	7 (29.2)	35 (43.8)	0.202	0.53 (0.20-1.42)
3rd/4th Generation cephalosporin	58 (55.2)	23 (57.5)	35 (53.8)	0.715	1.16 (0.52-2.57)
Aminoglycosides	**21 (20.6)**	**10 (45.5)**	**11 (13.8)**	**0.001**	**5.23 (1.82-15.00)**
Fosfomycin	6 (5.8)	3 (12.5)	3 (3.8)	0.134	3.67 (0.6-19.51)
Carbapenems	**14 (13.5)**	**8 (33.3)**	**6 (7.5)**	**0.001**	**6.17 (1.88-20.24)**
Type of infection					
CAP	28 (25.7)	6 (22.5)	22 (27.7)	0.809	0.88 (0.31-2.50)
HAP	84 (80.8)	19 (79.2)	65 (81.2)	0.820	0.88 (0.28-2.73)
Primary bacteraemia	9 (8.7)	4 (16.7)	5 (6.2)	0.206	3.00 (0.74-12.22)
Central venous catheter bacteraemia	0 (0)	0 (0)	0 (0)		
Ventilator associated pneumonia	1 (1.0)	1 (4.2)	0 (0)	0.381	1.03 (0.98-1.08)
Urinary tract infection	17 (16.3)	3 (12.5)	14 (17.5)	0.756	0.67 (0.18-2.57)
Surgical site infection	11 (10.6)	4 (16.7)	7 (8.8)	0.273	2.09 (0.56-7.84)
Intra-abdominal infecton	4 (3.8)	1 (4.2)	3 (3.8)	1.000	1.12 (0.11-11.25)
Length of ICU stays		17.4±11.1	15.6±14.2	0.515	
Duration of mechanical ventilation		10.2±11.0	13.0±11.2	0.264	

Values in bold are statistically significant. SD, standard deviation; COPD, chronic obstructive pulmonary disorder; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; ICU, intensive care unit.

It is considered that treatment with fosfomycin is free from the nephrotoxicity that characterizes treatment with aminoglycosides. A previous animal study demonstrated that fosfomycin has a protective effect against nephrotoxicity as a result of treatment with aminoglycosides by inhibiting aminoglycoside-induced histamine release from mast-cell destruction (26).

The present study is limited by its observational nature and relatively small number of cases, since we limited the analysis to cases with bacteremia only. In conclusion, mortality associ-

Table V. Characteristics of patients with severe infection caused by carbapenem-resistant *Klebsiella pneumoniae* treated with targeted fosfomycin combination; N=24.

Characteristic	N (%)
Overall mortality	2/24 (8.3)
Mortality by infection site	
Pneumonia	1/24
Urinary tract infection	0/24
Surgical wound infection	0/24
Intra-abdominal infection	0/24
Catheter-related bacteraemia	0/24
Infection of the CNS	1/24 (4.2)
Treatment regimens	
Fosfomycin+meropenem	16/24 (66.7)
Fosfomycin+meropenem+tigecycline/ minocyline/amikacin	8/24 (33.3)

CNS, central nervous system.

Table VI. Comparison of patients treated with fosfomycin combination therapy against other treatment regimens, N (%).

Treatment	Total (104)	Mortality (26)	Survival (78)	P	OR (95% CI)
Fosfomycin+meropenem	16 (15.4)	1 (3.8)	22 (28.2)		
Monotherpy and in combination					
Tigecycline/minocyline	21 (20.2)	2 (7.7)	19 (24.4)	0.371[a]	0.26 (0.04-1.50)
Aminoglycosides	12 (11.5)	1 (3.8)	11 (14.1)	1.000[a]	0.73 (0.04-13.05)
β-lactam inhibitors	8 (7.7)	2 (7.7)	6 (7.7)	0.249[a]	0.14 (0.03-0.75)
Quinolones	8 (7.7)	2 (7.7)	6 (7.7)	0.249[a]	0.20 (0.02-2.64)
3rd/4th Generation	21 (20.2)	10 (38.5)	11 (14.1)	**0.010[a,b]**	**0.07 (0.01-0.66)**

Carbapenems+quinolones [a]compared with fosfomycin and meropenem group. [b]Other combination therapy including: Cefepime or cefoperazone/sulbactam in combination with carbapenems/β-lactam inhibitors. Values in bold are statistically significant.

Table VII. Multivariate models of risk factors for mortality in patients with carbapenem-resistant *Klebsiella pneumoniae* sepsis.

	Unstandardized Coefficients		Standardized Coefficients		95% CI	
Variable	B	Std. Error	Beta	Sig	Up	Down
(Constant)	1.371	0.592	5.369	0.020		
Gender	1.279	0.614	4.349	0.037	3.594	1.080
History of COPD	-1.644	0.608	7.311	0.007	0.193	0.059
Peripheral catheter	-1.660	0.543	9.345	0.002	0.190	0.066
Fosfomycin combination	1.202	0.817	2.167	0.141	3.326	0.671

COPD, chronic obstructive pulmonary disorder.

ated with bacteremia due to CRKP continues to be high. The use of combinational therapy, with fosfomycin combinational therapy in particular, seems to have a survival benefit in this critically ill population.

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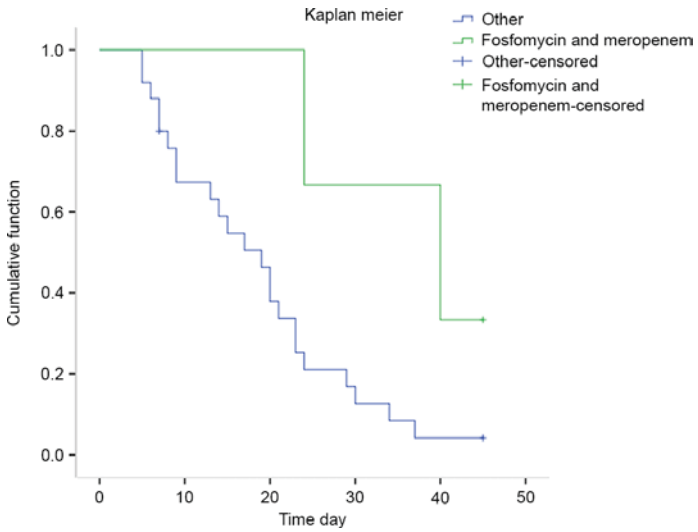

Figure 1. Kaplan-Meier curves showing the impact of targeted treatment with fosfomycin on survival at 45 days in patients with severe infection caused by carbapenem-resistant and colistin-resistant *Klebsiella pneumonia* (log-rank test, t=3.96, P=0.047).

81000311 and 81270831).

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