Case Report

Treatment for severe infections due to carbapenem-resistant Klebsiella pneumoniae in pediatric patients: combination of fosfomycin with carbapenems

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Abstract: The emergence of carbapenem-resistant Klebsiella pneumoniae is considered as a significant global public health challenge, especially in pediatric patients, since the optimal treatment remains undefined. We summarize the therapeutic experience of six cases with carbapenems-resistant Klebsiella pneumoniae infection occurred in pediatric intensive care unit. Related clinical symptoms and examinations indicated that this highly resistant gram-negative bacillus brought about pneumonia with bloodstream infection (3 cases), bloodstream infection (1 case), intra-abdominal infection (1 case), and intra-abdominal infection with bloodstream infection (1 case). The infection induced by K. pneumoniae caused aberrant expression of multiple blood indexes including white blood cell (WBC), C-reactive protein (CRP), procalcitonin (PCT), neutrophils and bilirubin. Carbapenems were frequently used as the first choice such as imipenem and meropenem in all cases. Meanwhile, other antibacterial strategy was employed including amikacin, amoxicillin-clavulanate, Sulfamethoxazole and Trimethoprim and fosfomycin. Particularly, fosfomycin was frequently given with the combination of carbapenems. Clinical cure of the infection due to carbapenems-resistant Klebsiella pneumoniae was observed in all of patients who treated with combination of fosfomycin and carbapenems. In conclusion, combination strategy with fosfomycin and carbapenems should be recommended for the treatment of carbapenems-resistant K. pneumoniae infection. The clinical benefit of antibacterial regimen is limited with carbapenems alone. Combination of antibacterial agents needs to be established in the presence of accumulative and prospective clinical trials.

Keywords: Klebsiella pneumoniae, antibiotic, carbapenems, aminoglycosides, fosfomycin

Introduction

Klebsiella pneumoniae, one of most common nosocomial pathogen, has received considerable attention as it brings about broad spectrum of infections such as pneumonia, bacteremia, septicemia, urinary tract infection (UTI), intra-abdominal infection in human beings [1, 2]. Nowadays, *K. pneumoniae* is well acknowledged to be responsible for approximately 15% of Gram-negative infections in intensive care patients particularly those with compromised immunity [3].

Recently, the prevalence of *carbapenems-resistant K. pneumoniae associated-in*fection shows remarkable increase (6.0% in 2012, vs. 3.2% in 2009) due to drug resistance [4-6].

Unfortunately, treatment option has yet to be established despite the scientific progress. To date, several antibacterial regimens are considered valuable in the treatment of multidrug-resistant (MDR) *K. pneumoniae*, including gentamicin, tigecycline, polymyxin and fosfomycin [7, 8]. Among these antibiotics, tigecycline is considered as an excellent candidate as it shows broad spectrum of antibacterial activity against Klebsiella pneumoniae carbapenemase (KPC)-producing organisms [9]. However, such regimen is not recommended for the treatment of children aged < 8 year-old. Meanwhile, its usage in the management of UTIs and bloodstream infections (BSIs) is also questionable as its low concentration in urine and plasma [10, 11]. Polymyxins are the drugs of choice for the treatment of infection caused by carbapenem-

resistant Gram-negative bacteria, however, the treatment efficacy is directly associated with the serum concentrations and is usually compromised by antibacterial resistance [12]. Meanwhile, the efficacy of polymyxins in pneumonia is also unclear with various clinical outcomes [13]. The use of aminoglycosides is usually limited considering the adverse events involving renal toxicity, neuromuscular blockade and allergic reaction [14]. Furthermore, such antibiotics may not be optimal for the treatment of intra-abdominal infections and abscesses resulting from their low activity in acidic environments [15]. Therefore, further studies are urgently needed to investigate effective antibiotics in pediatric patients with carbapenems-resistant K. pneumoniae infection.

In this study, we presented the therapeutic experience in six pediatric patients with carbapenems-resistant K. pneumoniae infection. Carbapenems generally served as the first choice in all cases. Meanwhile, multiple antibacterial options were also employed, particularly the combination of fosfomycin and carbapenems. Our study provides an alternative option and clinical reference for the treatment of carbapenems-resistant K. pneumoniae associated infections in pediatric patients.

Materials and methods

Design of the study - data collection

Patients with infections caused by carbapenems-resistant K. pneumoniae, who were hospitalized in the pediatric intensive care unit, during the period from 1/January/2013 to 31/August/2015 (PSICU) were identified by the ICU's electronic database, and during the same period in PMICU. The medical records of these patients were reviewed. Data for several variables, including demographic and clinical information, as well as results of laboratory and imaging tests of the patients were collected using a specially designed case report form and entered in a computer database.

Definitions

Carbapenems-resistant Klebsiella pneumoniae strains were defined if resistance of the isolates was observed resistant to carbapenems, such as Imipenem cilastatin and meropenem.

Bacteremia required not only growth of a recognized pathogen from two or more blood specimen cultures but also one of the clinical signs or symptoms relevant to sepsis, such as fever (> 38°C), chills, or hypotension. multiple organ dysfunction.

Infections at other body sites or fluids, such as pneumonia and abdominal infections were defined based on guidelines from the Centers for Disease Control and Prevention [16].

Microbiological testing

Identification of all causative microorganisms was performed by classic microbiologic methods. Susceptibility testing was performed both by the disk diffusion method and according to an automated broth microdilution method (bioMerieux, Vitek II, Hazelwood, MO). The breakpoints were those defined by the Clinical and Laboratory Standards Institute (CLSI) [17]. The MIC breakpoint used to identify bacteria susceptible to Carbapenems was 1 mg/l. Bacteria for which MIC was 1 mg/l or less were considered susceptible while bacteria with MIC 4 mg/l or more were considered resistant.

Results

Six patients were identified to have infection due to Carbapenems-resistant Klebsiella pneumoniae during the study periods. The clinical features of patients, including the isolated Carbapenems-resistant strains, the antimicrobial agents used for the management of the infections, as well as their outcome, are shown in the tables.

Case 1

A male neonate was admitted to our department due to type III esophageal atresia confirmed by esophagography. End-to-end anastomosis was performed 22 days after admission under thoracoscopy via right chest after general anesthesia. After surgery, mechanical ventilation was given and anti-infection was performed with imipenem and cilastatin. Two weeks after treatment, excessive, viscous secretion was observed in the airway. Carbapenem-resistant K. pneumoniae was identified after sputum culture and pleural fluid culture. Chest film indicated pneumonia, particularly in right lung. Progressive elevation was observed in the

white blood cell (WBC, $23.02×10^9$/L) and C-reactive protein (CRP, 81 mg/L). The level of bacterial endotoxin (BE) was 12.53 pg/mL and procalcitonin (PCT) was 13.75 ng/mL. Meanwhile, the patient was diagnosed with liver dysfunction. Anti-infection therapy was performed with fosfomycin and imipenem/cilastatin with hepatic protection, anemia correction using erythrocyte suspension and immune support using gamma globulin. Twenty-four hours later, PCT was decreased to 4.72 ng/mL, and transaminase was less than 3.0-fold of the upper normal limit. Meanwhile, the direct bilirubin was decreased by 50%, and the body temperature dropped below 37.5°C. Twelve days after treatment, mechanical ventilation was terminated. Six days later, antibiotic therapy was terminated and the patient was discharged with satisfactory outcome. Additional information of the patient was summarized in the following tables (**Tables 1**-**3**).

Case 2

A male neonate was admitted to our hospital due to congenital diaphragmatic hernia. The patient was escorted to ICU with tracheal intubation after delivery. Diaphragmatic hernia repair was performed under thoracoscopy. After the surgery, ventilator was used continually for assisted respiration. Five days later, the patient showed accelerated heart rate, pale and swollen in the whole body, freezing temperature in the distal extremities, decreased blood pressure, renal failure and coagulation dysfunction, as well as elevation of PCT (53.81 ng/mL). On this basis, septic shock was suspected, and meropenem was used for anti-infection. Three days later, Carbapenems-resistant *K. pneumonia was cultured in blood.*

On this occasion, anti-infection therapy was performed with meropenem (80 mg/kg per day) and fosfomycin (0.1 g/kg, iv drip, q8h). Two days after such treatment, PCT was decreased to 0.31 ng/mL. Meanwhile, the CRP value, hepatic and renal function were normal. The patient was finally discharged with satisfactory outcome. Additional information of the patient was summarized in the following tables (**Tables 1**-**3**).

Case 3

A 4-year-old girl presented to our department for dermatomyositis and severe pneumonia.

Meropenem (20 mg/kg, q8h) was given by intravenous drip. However, sharp increase (up to 39.5°C) was noticed in the body temperature. Blood culture indicated Carbapenems-resistant *K. pneumoniae* infection. One day later, the patient showed symptoms of shock, including increased heart rate, decreased blood pressure and clammy limbs. Laboratory evaluation revealed white blood cell count was $37.4×10^9$/L, CRP value was 86 mg/L, PCT value was 14.69 ng/mL, and the percentage of neutrophils was 90.4%. Slight elevation was noted in the value of transaminase and total bilirubin. Mild abnormality was found in the function of coagulation. Subsequently, synergetic antibiotic therapy was carried out using amoxicillin/clavulanate potassium (30 mg/kg, iv drip, q6h), fosfomycin (0.1 g/kg, iv drip, q8h), compound sulfamethoxazole (0.48 g, po, q12h) and meropenem (15 mg/kg, iv drip, q6h) together with administration of gamma globulin. Ten days later, the treatment regimen was replaced by amikacin (7.5 mg/kg, iv drip, q12h) plus amoxicillin clavulanate potassium (30 mg/kg, iv drip, q6h). Afterwards, no abnormalities were noticed in the routine blood test and CRP value. However, blood culture was still positive for *K. pneumoniae*. Twelve days later, meropenem (15 mg/kg, iv drip, q6h) and fosfomycin (0.1 g/kg, iv drip, q8h) were used continuously for up to 12 days. Blood culture was negative and the patient was finally cured. Additional information of the patient was summarized in the following tables (**Tables 1**-**3**).

Case 4

A 10 month-old male patient underwent surgery for megacolon under laparoscopy in our department on December 19, 2014. The patient showed fever (up to 39.3°C) 4 days after surgery together with abdominal distension. Liquid in coffee color was observed by gastric drainage. Laboratory examination showed the WBC was $9.67×10^9$/L, CRP level was 52 mg/L, PCT level was 27.78 ng/mL, and the percentage of neutrophils was 70.1%. Initially, imipenem-cilastatin was used for anti-infection therapy. However, fever was still existed 2 days after treatment. Blood culture yielded Carbapenems-resistant *K. pneumoniae*. On this basis, fosfomycin (0.1 g/kg, iv drip, q8h) was added to the initial regimen. Six days later, the levels of WBC and PCT were in the normal

Table 1. Case information

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Specimen source of pathogen culture	Sputum*16 Hydrothorax *1 Deep venous catheter tip *2	Blood*2	Blood *10 Sputum *1 Deep venous catheter tip *2	Deep venous catheter tip *1 Blood *2	Peritoneal drainage fluid *4	Blood *3 Secretion *1 Ascites*1 Sputum *2
Infection diagnosis	Pneumonia, Septicemia	Pneumonia, Septicemia	Pneumonia, Septicemia	Septicemia	Intra-abdominal infection	Intra-abdominal infection, Septicemia
Minimum inhibitory concentrations (MICs) of imipenem/cilastatin (mg/L)	≥ 16	8	≥ 16	≥ 16	4	≥ 16
K. pneumoniae-susceptibility drug	Compound sulfamethoxazole	Susceptibility: Ciprofloxacin, Levofloxacin, Amikacin, Compound sulfamethoxazole Moderate susceptibility: Tobramycin	Compound sulfamethoxazole	Susceptibility: Ciprofloxacin, Levofloxacin, Amikacin, Compound sulfamethoxazole Moderate susceptibility: Tobramycin	Susceptibility: Gentamicin, Ciprofloxacin, Levofloxacin, Amikacin, Compound sulfamethoxazole, Tobramycin	Gentamicin, Compound sulfamethoxazole
Antibacterial strategy before use of fosfomycin (or isepamicin) and carbapenems	Imipenem/cilastatin (20 mg/kg, q8h, iv drip)	Meropenem (20 mg/kg, q8h, iv drip) with single infusion time over than 2 h	Meropenem (20 mg/kg, q8h, iv drip)	Imipenem/cilastatin (20 mg/kg, q8h, iv drip)	Meropenem (15 mg/kg, q6h, iv drip) with the single infusion time ≥ 1 h	Meropenem (30 mg/kg, q8h, iv drip) with the single infusion time of 2 h
Enable time of fosfomycin (or isepamicin) plus carbapenems	Five days ago before positive result of blood culture based on the previous results of sputum and hydrothorax culture	At the same day of positive results of double blood culture	At the same day of positive results of venous catheter tip	At the same day of positive results of double blood culture	At the same day of positive results of peritoneal drainage fluid	Not use
Diameter of inhibition zone of fosfomycin	Sputum 15 Hydrothorax 6 Deep venous catheter 6	Blood 21	Blood 18 Sputum 6 Deep venous catheter 6	Blood 13 Deep venous catheter 24	Peritoneal drainage fluid 19	Blood 6 Ascites 18 Secretion 18 Sputum 17

Table 2. Related clinical information of 6 patients

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Body temperature ≥ ody °C	38°C		39.5°C	39°C	37°C	38.7°C
Respiratory rate was considered to be increased with the value > 70/min in patients of less than one-year old and > 50/min of those above one-year old	Yes (60/min)		Respiratory rate was 45/min in the presence of ventilator (synchronized intermittent mandatory ventilation 18/min)		No (40 /min)	No (35/min)
Dyspnea (spnea (n)) d intermittent depression of chest wall and nares flaring	Yes	Yes	Yes	No	No	Yes
Apnea	No	No	No	No	No	No
Cyanosis	Yes	Yes	Yes	No	No	No
Consciousness disorder	No	No	No	No	No	No
Fraction of inspired oxygen (FiO$_2$) > 0.6; arterial oxygen saturation (SaO$_2$): 0.6; (sea-level)	SaO$_2$ dropped to 75% as the onset of disease		FiO$_2$ was 55% with the intervention of ventilator	No	No	No
Infiltrative range of infection: multiple lobe involvement or the area ≥ 2/3 of total lung	Yes	Yes	Yes	No	Yes	
Pleural effusion or not	Yes	Yes	Yes	No	Pelvic drainage fluid	Yes
Tachycardia	167/min		180/min	160/min	122/min	150/min
Abnormal liver function or not	Yes	Yes	Yes	No	No	Yes
Abnormal renal function or not	No	Yes	Yes	No	No	Yes
Abnormal disseminated intravascular coagulation (DIC) or not	Yes	Yes	Yes	No	Yes	Yes
Use of vasoactive drugs or not	Yes	Yes	Yes	No	Yes	Yes
Use of gamma globulin or not	Yes	Yes	Yes	Yes	Yes	Yes
Blood product support or not	Yes	Yes	Yes	No	Yes	Yes

Table 3. Therapeutic outcome of 6 patients

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Course of treatment with fosfomycin (or isepamicin in case 5) plus carbapenems	18 d	14 d	Two stages including Early treatment: 10 d+ Late treatment: 12 d	Two stages: Early treatment: 12 d+ Late treatment: 10 d	8 d	Not use
Time of negative conversion of blood culture	No reexamination was performed	After 10 d of combined therapy	After 4 d of the second combined therapy	After 10 d of the second combined therapy	No reexamination was performed in drainage fluid	No negative conversion
Time of negative conversion of WBC and CRP	After 25 d of combined therapy*	After 6 d of combined therapy	After 12 d of combined therapy	After 6 d of combined therapy	After 8 d of combined therapy	No negative conversion
Extinction time of multiple organ dysfunction syndrome (MODS)	After 1 d of combined therapy	After 6 d of combined therapy	After 1 d of combined therapy	None	None	No negative conversion
Therapeutic outcome	Cure	Cure	Cure	Cure	Cure	Failure

*indicated the prolonged time (25 d) of negative conversion was induced as the result of delayed reexamination of routine blood and CRP after the improved clinical symptoms.

ranges. Twelve days after treatment, Sulfamethoxazole and trimethoprim and fosfomycin were used to replace the regimen. Nevertheless, the patient showed fever again with the highest body temperature of 38.8°C 4 days after the treatment. Routine blood test was rechecked and the results were: WBC 30.71×10⁹/L, CRP level 39 mg/L, and the percentage of neutrophils 70.5%. Afterwards, compound sulfamethoxazole was replaced by meropenem (20 mg/kg, iv drip, q8h). After 3 days, the baby's temperature gradually returned to normal and the blood culture was negative for *K. pneumoniae*. The treatment was successful. Additional information of the baby was summarized in the following tables (**Tables 1**-**3**).

Case 5

A 3-month-old baby was admitted to our department for lysis of abdominal adhesions, abdominal drainage and percutaneous endoscopic jejunostomy (PEJ). Postoperative diagnosis indicated intestinal obstruction after lysis of abdominal adhesions, anastomotic leakage and peritonitis. After the surgery, the patient was transferred to ICU with insertion of drainage tube in pelvic cavity and hepatonephric recess. Meropenem was given accompanied by immune support using gamma globulin. On the postoperative day 3, laboratory examination results were as follows: WBC 54.9×10⁹/L, CRP 26 mg/L, PCT 2.23 ng/mL, and the percentage of neutrophils 70.2%. The hepatic and renal function was normal. Yellow turbid liquid was observed after pelvic drainage, based on which diffuse peritonitis was considered and septicemia was suspected. Drainage fluid was collected immediately for culture, which indicated Carbapenems-resistant *K. pneumoniae*. On this basis, meropenem was given continuously with increased administration frequency and prolonged infusion time. However, the outcome of this strategy was not satisfactory. Three days later, isepamicin (7.5 mg/kg, ivgtt, q12h) was given. Five days after treatment, no pelvic drained fluid and ascites were noted. Meanwhile, all infectious indices were negative. Anti-infection therapy was successfully performed. Additional information of the patient was summarized in the following tables (**Tables 1**-**3**).

Case 6

A 3-month-old female baby was admitted to out hospital due to infant hepatitis syndrome,

pneumonia and umbilical hernia. The patient received cholangiography and Kasai's operation on May 14, 2013. On postoperative day 15, the patient showed fever with a body temperature of 38.5°C, blood pressure of 66/25 mmHg, respiratory rate of 35/min and heart rate of 121/min. The amount of urine was decreased, and the levels of urea nitrogen and creatinine were increased. The level of transaminase was in the normal range. The total bilirubin was 50.3 umol/L. Meanwhile, the amount of ascites was increased with a daily discharge of 600 mL. On this basis, abdominal and bloodstream infection were suspected. Transfusion of erythrocyte, plasma, human albumin, and gamma globulin was performed together with administration of dopamine to improve the blood circulation. Sputum culture revealed Carbapenems-resistant *K. pneumoniae*. Routine blood test results were as follows: CRP 161 mg/L, WBC 20.74×10⁹/L, platelet (PLT) 17× 10⁹/L. The baby was initially treated with meropenem (20 mg/kg, ivgtt, q8h). Two days later, ascites culture indicated Carbapenems-resistant *K. pneumoniae*. Laboratory reexamination revealed WBC 23.99×10⁹/L, CRP 188 mg/L, PLT 79×10⁹/L, endotoxin 30.94 pg/mL. The ascites (Rivalta test, positive) was yellow and turbid with an amount of 165 mL. Body temperature was 38.2°C. Under this condition, the dosage of meropenem was increased (30 mg/kg, ivgtt, q8h) accompanied by prolonged single infusion duration (2 h). Five days later, no remission was noted in the fever (38.6°C) and abdominal distension. Blood culture also showed carbapenem-resistant *K. pneumoniae*. Meanwhile, routine blood examination revealed WBC 15.27×10⁹/L, CRP 99 mg/L, PLT 47× 10⁹/L. Previous antibiotic regimen was modified with meropenem (20 mg/kg, ivgtt, q8h) plus amoxicillin-clavulanate potassium (30 mg/kg, ivgtt, q6h). However, the condition of patient was terrible such as mental fatigue, abdominal distension, tachypnea and progressive rise in total bilirubin and direct bilirubin. The treatment was terminated with the requirement of her parents. Additional information of the baby was summarized in the following tables (**Tables 1**-**3**).

Discussion

K. pneumoniae is a major cause for a wide range of hospital-infections. Generally, carbapenem has been acknowledged as an effec-

tive antibiotic for these strains. However, carbapenem resistance has been documented worldwide by the carbapenemase production or the loss of major porins plus the expression of extended-spectrum β-lactamases (ESBLs) or AmpC β-lactamases [18, 19]. The strategy of antibiotic combination is preferable with the considerable superiority in the treatment of Carbapenems-resistant *K. pneumoniae* infection [20]. In a retrospective clinical report, the combination of tigecycline and polymyxin was considered to bring out better outcomes than monotherapy for the management of Carbapenems-resistant *K. pneumoniae* associated infection [21]. Also, colistin coupled to rifampin yielded a synergistic antibacterial activity against KPC-producing *K. pneumoniae* isolates [22]. Moreover, the mortality of patients received combination of antibiotics was markedly decreased compared with those with monotherapy (13.3% vs. 57.8%) [23]. In our study, we presented the treatment of 6 pediatric patients with Carbapenems-resistant *K. pneumoniae* infection. For these cases, carbapenems were generally used as the first choice such as imipenem and meropenem. Furthermore, other antibiotic were also given including amikacin, amoxicillin-clavulanate, Sulfamethoxazole and Trimethoprim and fosfomycin. The outcome of the combined strategy was satisfactory in 5 cases with combination of one of carbapenems and fosfomycin.

Carbapenems, a class of β-Lactam antibiotics, possess a broad spectrum of antibacterial activity. Currently, four carbapenems are frequently used in clinical treatment, including imipenem, ertapenem, meropenem and doripenem [24]. Some reports demonstrated that monotherapy with carbapenems should be considered for the treatment of *K. pneumoniae* infections [21]. On the contrary, unsatisfactory treatment was revealed with the intervention of a carbapenem in patients with imipenem-resistant (MIC > 4 µg/mL) KPC *K. pneumoniae* [25]. In our study, all patients were treated with carbapenems since 5 cases were manifested as serious infection. Pathogen culture in all cases yielded Carbapenems-resistant *K. pneumoniae*, among which the MIC of *K. pneumoniae* to imipenem/cilastatin was over than 16 mg/L in 4 cases, MIC of 4 mg/L and 8 mg/L in other two cases, respectively. On this basis, we aim to investigate the clinical benefit of Carba-

penems in the treatment of Carbapenems-resistant *K. pneumonia, and* to investigate if the patient could benefit from increased dosage or continuous infusion? And whether it could improve efficacy with optimized therapeutic strategy should be considered based on the continuous use of carbapenems alone.

The pharmacokinetics/pharmacodynamics (PK/PD) character of carbapenems was in a time-dependent manner with none or mild post-antibiotic effect (PAE). The optimal parameter of PK/PD for carbapenems is the time of the free carbapenem concentration keeping above the MIC (T > MIC) [26]. Optimum killing activity will be achieved when the T > MIC is accounted for 40%~50% of the dosing interval. The antibacterial efficacy is satisfactory once the parameter of T > MIC reaches 60%~70% of dosing interval. In this study, early intervention with routine dosage of imipenem/cilastatin or meropenem was conducted in three cases (case 1, 3 and 4), followed by the implementation of combined therapy in the presence of poor response. For other three patients, the clinical outcomes were also not satisfactory by prolonging single infusion time or increasing antibiotic dosage. All these indicated that monotherapy with carbapenems failed to control infection effectively. Furthermore, the dosing regimen optimization could not bring about satisfactory outcome from the point of PK/PD. To our knowledge, only one patient with BSI was successfully cured using meropenem monotherapy by high-dose continuous infusion for treatment of KPC *K. pneumoniae* (MIC=8 µg/mL) [27]. However, available evidence has suggested that the introduction of carbapenems is considered to be more effective particularly in the combination with other antibacterial agents. For instance, Tumbarello et al indicated that the addition of meropenem significantly decreased the mortality rates in patients with tigecycline plus colistin (12.5% vs 30.4%), and those treated with tigecycline plus gentamicin (50% vs 16.6%). Meanwhile, the survival rate yielded to 86.6% in the presence of meropenem and other combined-drug regimen when the MIC of KPC *K. pneumoniae* to meropenem was less than 4 mg/L. The inclusion of meropenem in a combined therapy brought about a survival rate of 64.7% even if patients with higher meropenem MICs (≥ 16 mg/L) [28]. Another evidence indicated that the 28-day mortality caused by

KPC-producing *K. pneumoniae* was remarkably decreased in the presence of colistin-polymyxin B or tigecycline plus a carbapenem (12.5%) in comparison with patients receiving monotherapy with colistin-polymyxin B or tigecycline (66.7%) [23]. Taken together, the use of carbapenem monotherapy against Carbapenems-resistant *K. pneumoniae* remains controversial. Antibiotic combination containing a carbapenem may provide an alternative therapy for the treatment of Carbapenems-resistant *K. pneumoniae* infection.

Aminoglycosides is generally used for the treatment of gram-negative bacterial infections. Aminoglycosides coupled to β-lactams is well accepted for the treatment of infections induced by ESBL-producing *K. pneumoniae* [29]. Meanwhile, this kind of antibiotics exhibited favorable response to clear carbapenem-resistant *K. pneumoniae* in the urine as compared to that with polymyxin B or tigecycline [30]. Aminoglycosides may provide a therapeutic option particularly in patients infected with aminoglycoside-susceptible *K. pneumoniae*. In this study, four patients (case 2, 4, 5 and 6) were susceptible with aminoglycosides. However, isepamicin was conducted only in case 5 as the part of combined therapy considering the absence of concentration monitoring, and the introduction of this regimen brought about satisfactory outcome. In case 3, poor response was obtained after isepamicin plus amoxicillin clavulanate potassium, which may be associated with the resistance of strains to aminoglycosides.

β-lactamase inhibitors (BLI) have attracted growing concerns with the spread of bacterial resistance by β-lactamase [31]. However, the therapeutic option with β-lactam/BIL is considered to be controversial in the treatment of non-ESBL *K. pneumoniae* infections [32]. The addition of BIL only led to slight decrease in the MICs of other antibiotics, followed by poor clinical outcome [33]. In this study, the second therapeutic strategy with clavulanate potassium plus amikacin was failed against *K. pneumoniae* infection in case 3. Meanwhile, poor response was observed in case 6 received amoxicillin-clavulanate potassium combined with meropenem. Therapeutic failure was noted in this patient in the presence of mental fatigue, abdominal distension, tachypnea and

progressive rise in total bilirubin and direct bilirubin. On this basis, clavulanate potassium coupled to carbapenems is not suitable for the treatment of Carbapenems-resistant *K. pneumoniae* infection.

To our knowledge, most bacterial could produce tetrahydrofolic acid rather than making use of existing folic acid and its derivatives. Nevertheless, *K. pneumoniae* is a typical exception as it could utilize exogenous folic acid and attenuate the susceptibility to sulfonamides. Therefore, the clinical efficacy for the management of *K. pneumoniae* associated infection may not be satisfactory even if *K. pneumoniae* is susceptible to Sulfamethoxazole trimethoprim indicated by drug-susceptibility testing. In our study, all strains isolated from 6 cases were susceptible to compound sulfamethoxazole. Two patients (case 3 and 4) received this therapeutic agent with the combination of other antibiotics. However, such regimen in case 3 was terminated due to the decrease of platelet. The patient's condition of case 4 was recurrent after the implementation of compound sulfamethoxazole plus fosfomycin. On this basis, we were reluctant to recommend this antibiotic for the treatment of infections caused by carbapenem-resistant *K. pneumoniae*.

Fosfomycin, a broad spectrum antibiotic, is considered as a "last-resort: antibiotic for the infections induced by MDR Gram-negative pathogens. Its antibacterial action is mainly associated with the inhibition of UDP-N-acetylglucosamine enolpyruvyl transferase (MurA), an enzyme that catalyses the first step in bacterial cell wall synthesis [34]. Moreover, fosfomycin is a relatively small hydrophilic agent and could penetrate into tissues [35]. Unfortunately, resistance is prone to develop when fosfomycin is given as monotherapy [36]. Thus, combined strategy appears to be favorable in clinical practice for the treatment of serious infections. Currently, accumulating evidence has demonstrated the synergistic activity with the use of fosfomycin in combination with other antibiotics for the therapy of infection with *K. pneumoniae* strains. Samonis et al indicated that synergy of fosfomycin plus imipenem and meropenem was revealed for 74% and 70% against serine carbapenemase-producing *K. pneumoniae* isolates [8]. Another report indi-

cated that fosfomycin coupled to meropenem could be synergistic against 64.7% KPC2-producing *K. pneumoniae* [37].

In our study, combined therapy using fosfomycin was given to 4 patients. For the case 1, the combined modality resulted in satisfactory outcome after the administration of fosfomycin coupled to imipenem/cilastatin for 18 days. The negative blood culture was achieved 10 days after the treatment of fosfomycin plus meropenem in the case 2. In the early stage of treatment (10 d) in case 3, good response was obtained after administration of fosfomycin coupled to meropenem, and then the regimen was replaced by amikacin plus clavulanate potassium. However, blood culture remained positive even though the clinical symptoms and infectious indices were improved after 12 days of new strategy. Afterwards, fosfomycin plus meropenem was given again and satisfactory outcome was finally achieved. In case 4, the patient's condition was stable after receiving imipenem-cilastatin and fosfomycin for 12 days. Then antibiotics was modified with compound sulfamethoxazole and fosfomycin. However, recurrent infection was noted after the implementation of new strategy, possibly resulting from short-course antibiotic treatment of imipenem-cilastatin. Subsequently, favorable response was obtained after the combination of fosfomycin and meropenem after 3 days. For case 5, combination of meropenem and isepamicin was given for 8 days, and the treatment outcome was still satisfactory. Taken together, fosfomycin in combination with other antibiotics is preferable against carbapenem-resistant *K. pneumoniae* strains. Notably, adequate course of combined therapy is needed for the favorable efficacy.

In conclusion, we summarized the therapeutic experience in six pediatric patients with severe infections caused by carbapenem-resistant *K. pneumoniae* strains. The therapeutic outcomes from these cases indicate that available antibiotics should be considered in the drug-susceptibility testing involving fosfomycin, tigecycline and doxycycline. Compound sulfamethoxazole or amoxicillin/clavulanate potassium is not suitable for the treatment of carbapenem resistant *K. pneumoniae* associated infections. Clinical benefit may be limited with carbapenem monotherapy or by prolonging infusion time and enhancing drug dosage. Moreover, the use of tigecycline is not preferentially recommended as the result of age limit and low drug concentration in blood. On this basis, empirical regimen of carbapenem coupled to a susceptible antibiotic such as fosfomycin provides a promising clinical option against carbapenem-resistant *K. pneumoniae* associated infection in pediatric patients. Furthermore, unobstructed drainage in infection site and immunonutrition support are essential to obtain satisfactory outcomes.

Conclusions

Combination strategy with fosfomycin and carbapenems should be recommended for the treatment of carbapenems-resistant *K. pneumoniae* infection. The clinical benefit of antibacterial regimen is limited with carbapenems alone. Definite combination of antibacterial agents needs to be established in the presence of accumulative and prospective clinical trials.

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Disclosure of conflict of interest

None.

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