

A Retrospective Analysis of Polymyxin B Combined with Tigecycline in the Treatment of Multi-Drug Resistance *Klebsiella pneumoniae* Infection: Hypertension Increases the Incidence of Acute Kidney Injury

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Du et al.: Multi-Drug Resistance *Klebsiella pneumoniae* Infection: A Retrospective Analysis

Multidrug resistance *Klebsiella pneumoniae* infection is an essential factor threatening the life of patients with severe infection. Polymyxin B is widely used in treating multidrug resistance *Klebsiella pneumoniae*, but few studies on its efficacy and safety. In our study, 205 patients with multidrug resistance *Klebsiella pneumoniae* infection were admitted to our hospital from January 2017 to December 2020, treated with polymyxin B for antibacterial and selected as the subjects. These patients were divided into two therapy groups: A monotherapy group (polymyxin B) and a combined therapy group (polymyxin B-tigecycline). The efficacy and safety of the two groups were analyzed. Also, the risk factors were analyzed. The changes of cystatin C, beta 2-microglobulin and microalbuminuria in the two groups showed an upward trend during the treatment. The descent degree of procalcitonin, C-reaction protein and white blood cell count in the polymyxin B-tigecycline group was higher than that in the polymyxin B group. The two groups had a similar effective rate, while acute kidney injury incidence in the polymyxin B-tigecycline group was higher than in the polymyxin B group. Blood infection, hypertension, high dose of tigecycline were risk factors for acute kidney injury. It was the first time to report that hypertension is an independent risk factor of acute kidney injury when polymyxin B combined with tigecycline is used to treat multidrug resistance *Klebsiella pneumoniae* infection. Patients with hypertension infected with multidrug resistance *Klebsiella pneumoniae* should avoid accepting the combination therapy of polymyxin B and tigecycline.

Key words: Polymyxin B, infection, *Klebsiella pneumoniae*, acute kidney injury

Klebsiella pneumoniae is the clinically significant opportunistic pathogen, also the common pathogenic bacteria causing the nosocomial infection^[1,2]. It can quickly form the biofilm and readily colonize, easily mutate and have multi-drug resistance^[3]. *Klebsiella pneumoniae*, which is not the common customized bacteria in the human body, generally can be isolated from the skin, nasal mucosa, throat, faeces and other parts of ordinary people^[1,3]. In patients' *Klebsiella pneumoniae* infected rate is higher than 50 %, especially the patients with trauma, mechanical ventilation, catheter, surgery and severe burns^[3,4]. According to the China Antimicrobial Resistance Surveillance System statistics, the incidence of infections caused by *Klebsiella pneumoniae* is increasing year by year,

which is No. 2 of the number of clinically isolated strains in China in 2020 and the leading cause of patient deaths^[5]. For the infection caused by Multidrug Resistance *Klebsiella pneumoniae* (MDR-KP), the primary clinical therapy protocol should combine various antimicrobials^[6,7].

Polymyxin, a narrow-spectrum antibiotic, has good activity against most Gram-Negative Bacteria (GNB) and natural resistance to Gram-Positive Bacteria (GPB), fungi, anaerobic bacteria, some gram-negative cocci (*Neisseria gonorrhoeae*, *Neisseria meningitidis*) and parasites, etc., And it is naturally sensitive to *Pseudomonas aeruginosa* and *Acinetobacter baumannii*^[8,9]. It can also effectively resist *Haemophilus influenzae*, *Escherichia coli*, *Salmonella*, *Shigella*,

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Klebsiella pneumoniae, *Legionella pneumophila*, *Citrobacter* and *Bordetella pertussis*. Polymyxin can kill bacteria rapidly by destroying the integrity of the cell membrane^[10]. It was widely used to treat the GNB clinically, but the narrow antibacterial spectrum, apparent toxic and side effects drive it into replacement gradually^[10,11]. With the increasing infection rate of MDR-GNB globally, polymyxin as the last line of defence for treating GNB infection, people began to value it again^[12]. At present, polymyxin B and polymyxin E are two kinds of polymyxin used in clinical. Compared with polymyxin E, polymyxin B has an excellent pharmacokinetic effect^[10,13]. However, due to limited drug resources, it relatively lacks clinical data and clinical treatment experience for Polymyxin B, especially with tigecycline^[14].

Tigecycline, a low resistance rate to *Klebsiella pneumoniae*, is often combined with other drugs for antibacterial therapy, including carbapenems, cephalosporins, penicillins and bacillosporin^[15,16]. This study aims to investigate the efficacy and safety of polymyxin B and tigecycline combined with MDR-KP by retrospective analysis to provide evidence for doctors' clinical applications.

MATERIALS AND METHODS

Study design:

In this study, 293 patients were selected as the subjects. They had a severe infection and were admitted to our hospital from January 2017 to December 2020. Collected patients' information based on the medical record system in the hospital, including the basic information of the patient (age, gender, clinical diagnosis, inpatient department, etc.); the basic information of medication

(dosage, frequency, time, combined use of antibiotics); the situation and results of bacterial culture; patient infection index (pre-and post-infection signs, White Blood Cell Count (WBC), C-Reaction Protein (CRP), Procalcitonin (PCT) value, etc.,) and the early kidney function index of the patient (Cystatin C (Cyc-C), microalbuminuria (mALB), beta₂-Microglobulin (β₂-MG)). In addition, this study did not directly interfere with the patients and showed the patients, names. In order to improve the accuracy of the analysis, we had strictly controlled the inclusion criteria so that only patients with purity MDR-KP infection could be included in this study. The study would exclude patients with the following conditions: Use other antibiotics except for polymyxin B and tigecycline; <16 y old; had severe liver, brain, kidney diseases; infection time was less than 48 h; combined treatment time was less than 7 d. Assessed the severity of diseases by using the Acute Physiology and Chronic Health Evaluation (APACHE) II scores and Acute Kidney Injury (AKI) risk prediction scores calculated when MDR-KP attacks^[17].

Data analysis:

As shown in fig. 1, according to include and exclude conditions, 205 patients were finally selected as the research object. According to antibiotics, these patients were divided into two groups (Polymyxin B (PB), n=45 and polymyxin B-tigecycline (PB-TGC), n=160); according to AKI occurrence, 160 patients in the PB-TGC group were divided into two groups (kidney injury group, n=70 and kidney non-injury group, n=90). It is worth mentioning that the patients included in this study did not die during the treatment period and because of the patients' active discharge, we could not track and count the recovery of kidney function after treatment.

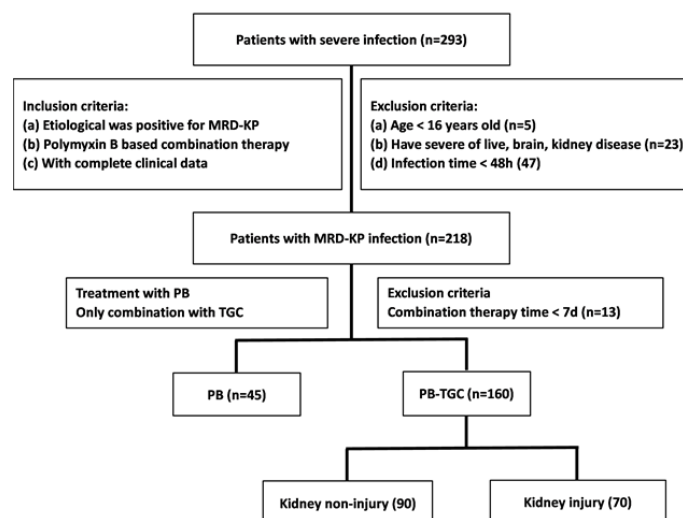


Fig. 1: Flowchart of the case selection process

Microbiological assessment and definition of terms:

The identification and antimicrobial susceptibility of *Klebsiella pneumoniae* were determined by using the Vitek 2 system (bioMérieux, Marcy-l'Etoile, France). MDR-KP onset was defined as the collection date of the first positive biological simple culture. According to the guidelines of the Clinical and Laboratory Standards Institute standards (2015), the definition of carbapenem-nonsusceptibility was a Minimum Inhibitory Concentration (MIC) of ≥ 1 mg/l for ertapenem or ≥ 2 mg/l for imipenem or meropenem^[18]. The US Food and Drug Administration (FDA) breakpoints were used to judge tigecycline and polymyxin B susceptibilities^[19]. The *in vitro* susceptibility test results showed that the pathogenic bacteria isolated from the patients were sensitive to polymyxin B and tigecycline. The MIC of tigecycline and polymyxin B was determined by using standard broth microdilution tests with fresh (<12 h) Mueller–Hinton II Broth (cation-adjusted; Solarbio Science and Technology Ltd., Beijing, People's Republic of China). According to the using dose, the dose of tigecycline was classified into low-dose (loading dose 100 mg, maintenance dose 50 mg/12 h) and high-dose (loading dose ≥ 100 mg, maintenance dose > 50 mg/12 h)^[20] and the dose of polymyxin B was classified into low-dose (<1.5 mg/kg) and high-dose (>1.5 mg/kg)^[21]. The efficacy of antibacterial therapy was defined by the patient's negative etiological examination 3 d after discontinuation.

Statistical analysis:

In this study, statistical analysis used Statistical Package for the Social Sciences (SPSS) 24.0. Mean \pm Standard Deviation (SD) expressed the measurement data and Percentage (%) expressed the count data. Chi-square (χ^2) was used for qualitative data and alpha t-test was used for quantitative data. Variables with $p < 0.05$ in the univariate analysis were used in binary logistic regression. Multivariate analysis was used to identify independent predictors. The correlation analysis between variables, 95 % Confidence Interval (CI), used logistic regression and the R and p value expressed the results. In all analyses, $p < 0.05$ was considered significant.

RESULTS AND DISCUSSION

In this study, 205 patients were finally included, wherein the minimum age was 22 y old; the maximum age was 92 y old; the average age was 60.77 ± 13.22 y old, of which 142 were male (69.2 %). As shown in Table 1, the patients with pulmonary infection account for the majority (103/205, 50.24 %), followed by blood infection (15/205, 26.82 %). In terms of underlying diseases, hypertension accounts for the majority (104/205, 50.7 %) and then diabetes (58/205, 27.8 %). Compared to the demographic and characteristics in the two groups, three projects showed significant differences ($p < 0.001$), namely, skin infections, urinary infections and AKI scores. The incidence of AKI in the PB-TGC group (70/160, 43.8 %) was higher than PB group (8/45, 17.8 %). Two groups had similar antibacterial efficacy (69.1 % vs. 68.8 %, $p = 0.913$). As shown in fig. 2, in the period of antimicrobial therapy, the inflammatory factors of the two groups showed a downtrend, while the descent degree of the PB-TGC group was significantly higher than that of the PB group. The kidney injury-related factors in the early stage of the two groups were within the standard limit, while with the ongoing antimicrobial therapy, the value of Cys-C and mALB in the PB-TGC group was significantly higher than that of the PB group ($p < 0.05$).

In the light of study design conditions, 205 patients were divided into two groups, the PB group (45/205, 22.0 %) and the PB-TGC group (160/205, 78.0 %). The results of the univariate analysis indicated that the factors independently associated with a higher risk of AKI were as follows: Male, age, APACHE II score, blood infection, hypertension, CRP, WBC, mALB and higher dose of PB and TGC. The results of multivariate analysis indicate that the factors independently associated with a higher risk of AKI were as follows: Blood infection (OR=3.527, 95 % CI=1.153-9.201, $p = 0.026$), hypertension (OR=6.727, 95 % CI=1.446-27.206, $p = 0.014$), WBC (OR=3.922, 95 % CI=1.064-14.464, $p = 0.014$), dose of TGC < 0.2 g/d (OR=0.096, 95 % CI=0.032-0.288, $p = 0.001$) and dose of TGC > 0.2 g/d (OR=0.023, 95 % CI=0.006-0.088, $p = 0.001$), as shown in Table 2.

TABLE 1: CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF PATIENTS CAUSED BY MULTI-DRUG RESISTANCE *Klebsiella pneumonia*

Demographic	PB (n=45)	PB-TGC (n=160)	p value
Male, n (%)	30 (66.7)	112 (70)	0.217
Female, n (%)	15 (33.3)	48 (30)	
Age, years, mean±SD	59.60±16.97	61.10±12.17	0.944
APACHE II, score, mean±SD	24.68±8.05	23.57±9.196	0.547
Period of treatment, d, mean±SD	11.89±1.22	9.85±1.21	0.205
Infection site ^a , n (%)	100	100	100
Pulmonary	23 (51.1)	78 (48.8)	0.017
Blood	15 (33.3)	40 (25)	0.44
Abdominal cavity	6 (13.3)	23 (14.4)	0.418
Skin	1 (2.2)	16 (10.0)	<0.001
Urinary	3 (6.7)	3 (1.9)	<0.001
Underlying diseases ^b , n (%)	100	100	100
Hypertension	29 (64.4)	75 (46.9)	0.494
Diabetes	15 (33.3)	43 (26.8)	0.361
Atrial fibrillation	14 (31.1)	38 (23.7)	0.532
Rheumatoid arthritis	2 (4.4)	2 (1.3)	
Prostatic hyperplasia	2 (4.4)	2 (1.3)	
Pancreatitis	0 (0)	2 (1.3)	
AKI score, n (%)	100	100	100
1 grade	8 (17.8)	35 (21.8)	<0.001
2 grade	0 (0)	16 (10.0)	
3 grade	0 (0)	19 (11.9)	
Efficiency %	69.1	68.75	0.913

Note: Data is expressed as numbers (%) unless otherwise stated; ^apatients with multiple-site infections will be counted separately; ^bpatients with multiple underlying diseases will be counted separately, PB: Polymyxin B; PB-TGC: Polymyxin B-Tigecycline

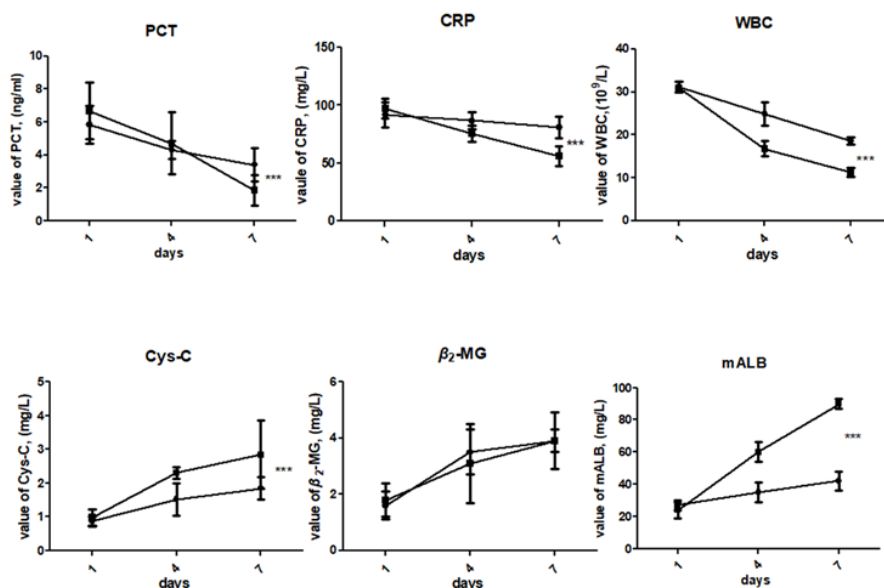


Fig. 2: Inflammatory markers and kidney injury markers of patient, (○) PB; (●) PB-TGC

In the light of study design conditions, 160 patients in the PB-TGC group were divided into two groups, the kidney injury group (70/160, 43.8 %) and the kidney non-injury group (90/160, 56.2 %). As shown in Table 3, the results of the univariate analysis indicated that the factors independently associated with a higher risk of AKI were as follows: APACHE II, period of treatment, blood infection, abdominal cavity infection, skin infection, hypertension, diabetes, atrial fibrillation, WBC, β_2 -MG, mALB and dose of PB and TGC. The results of multivariate analysis indicate that the factors

independently associated with a higher risk of AKI were as follows: APACHE II (OR=1.162, 95 % CI=0.948-1.425, $p<0.001$), period of treatment (OR=1.047, 95 % CI=0.837-1.413, $p<0.001$), blood infection (OR=0.899, 95 % CI=0.283-2.858, $p<0.001$), hypertension (OR=8.732, 95 % CI=2.264-3.366, $p=0.007$), Cys-C (OR=0.942, 95 % CI=0.671-1.323, $p<0.001$), β_2 -MG (OR=1.048, 95 % CI=0.801-1.370, $p<0.001$) and dose of PB ≥ 1.5 mg/kg/d (OR=0.801, 95 % CI=0.587-1.029, $p<0.001$) and dose of TGC ≥ 0.2 g/d (OR=0.854, 95 % CI=0.654-1.115, $p<0.001$).

TABLE 2: ANALYSIS OF RISK FACTORS FOR AKI ALL PATIENTS WITH MDR-KP

	Univariate analysis			Multivariable analysis			
	PB (n=45)	PB-TGC (n=160)	p value	Sig.	EXP (B)	95 % CI for EXP (B)	
						Lower	Upper
Demographic							
Male, n (%)	30 (66.7)	7 (70)	0.046				
Age, years, mean \pm SD	65.68 \pm 18.03	61.10 \pm 12.17	0.015				
APACHE II, score, mean \pm SD	24.68 \pm 8.05	23.57 \pm 9.196	0.012				
Period of treatment, d, mean \pm SD	11.89 \pm 1.22	9.85 \pm 1.21	0.187				
Infection site ^a							
Pulmonary, n (%)	23 (51.1)	78 (48.8)	0.209				
Blood, n (%)	15 (33.3)	40 (25)	0.005	0.026	3.527	1.153	9.201
Seroperitoneum, n (%)	6 (13.3)	23 (14.4)	0.214				
Skin wound, n (%)	1 (2.2)	16 (10.0)	0.226				
Urine, n (%)	3 (6.7)	3 (1.9)	0.606				
Underlying diseases ^b							
Hypertension, n (%)	29 (64.4)	75 (46.9)	<0.001	0.014	6.272	1.446	27.206
Diabetes, n (%)	15 (33.3)	43 (26.8)	0.339				
Atrial fibrillation, n (%)	14 (31.1)	38 (23.7)	0.437				
Rheumatoid arthritis, n (%)	2 (4.4)	2 (1.3)	0.094				
Prostatic hyperplasia, n (%)	2 (4.4)	2 (1.3)	0.976				
Pancreatitis, n (%)	0 (0)	2 (1.3)	0.172				
Inflammatory markers							
PCT, >0.5 ng/ml, n (%)	20 (44.4)	33	0.955				
CRP, >8 mg/l, n (%)	27 (60.0)	64	<0.001				
WBC, >9.5 $\times 10^9$ /l, n (%)	18 (40.0)	37	0.004	0.040	3.922	1.064	14.464
Renal injury markers							
Cys-C, >1.03 mg/l, n (%)	9 (20.0)	23	0.123				
β_2 -MC, >2.4 mg/l, n (%)	7 (15.6)	12	0.940				
mALB, >30 mg/l, n (%)	12 (26.7)	30	0.001				
Polymyxin B							
<1.5 mg/kg/d	11 (24.4)	87 (54.3)	0.742				
≥ 1.5 mg/kg/d	34 (75.6)	73 (45.6)	<0.001				
Tigecycline							
<0.2 g/d	0 (0)	96 (60.0)	<0.001	0.001	0.096	0.032	0.288
≥ 0.2 g/d	0 (0)	64 (40.0)	0.001	0.001	0.023	0.006	0.088

Note: Data is expressed as mean \pm SD unless otherwise stated; ^apatients with multiple-site infections will be counted separately; ^bpatients with multiple underlying diseases will be counted separately, PB: Polymyxin B; PB-TGC: Polymyxin B-Tigecycline

TABLE 3: ANALYSIS OF RISK FACTORS FOR AKI IN PB-TGC GROUP WITH MDR-KP

	Univariate analysis			Multivariable analysis			
	Injury (n=70)	Non-injury (n=90)	p value	Sig.	EXP (B)	95 % CI for EXP (B)	
						Lower	Upper
Demographic	48 (68.2)	61 (67.8)	0.838				
Male, n (%)	66.33±13.32	67.42±12.73	0.589				
Age, years, mean±SD	27.45±10.16	25.66±6.79	<0.001	<0.001	1.162	0.948	1.425
APACHE II, mean±SD	12.63±1.51	7.07±0.91	<0.001	<0.001	1.047	0.837	1.413
Infection site ^a							
Pulmonary, n (%)	34 (48.8)	44 (48.8)	0.160				
Blood, n (%)	18 (25.0)	22 (24.4)	<0.001	<0.001	0.899	0.283	2.858
Abdominal cavity, n (%)	10 (14.8)	13 (14.4)	<0.001				
Skin, n (%)	0 (0)	9 (100.0)					
Urinary, n (%)	0 (0)	3 (100.0)					
Underlying diseases ^b							
Hypertension, n (%)	33 (46.9)	42 (46.7)	<0.001	0.007	8.732	2.264	3.366
Diabetes, n (%)	19 (26.9)	24 (26.7)	<0.001				
Atrial fibrillation, n (%)	17 (23.7)	21 (23.3)	<0.001				
Rheumatoid arthritis, n (%)	0 (0)	2 (100)					
Prostatic hyperplasia, n (%)	0 (0)	2 (100)					
Pancreatitis, n (%)	0 (0)	2 (100)					
Inflammatory markers							
PCT, >0.5 ng/ml, n (%)	20 (28.6)	25 (27.8)	0.191				
CRP, >8 mg/l, n (%)	27 (16.8)	37 (41.1)	0.015				
WBC, >9.5×10 ⁹ /L, n (%)	18 (11.3)	19 (21.1)	<0.001				
Renal injury markers							
Cys-C, >1.03 mg/l, n (%)	9 (5.6)	14 (15.6)	0.003	<0.001	0.942	0.671	1.323
B ₂ -MC, >2.4 mg/l, n (%)	7 (4.3)	5 (5.6)	<0.001	<0.001	1.048	0.801	1.370
mALB, >30 mg/l, n (%)	12 (7.5)	18 (20)	<0.001				
Dose of polymyxin B							
<1.5 mg/kg/d	30 (42.8)	57 (63.3)	0.111				
≥1.5 mg/kg/d	40 (57.1)	33 (36.7)	0.013	<0.001	0.801	0.587	1.092
Dose of tigecycline							
<0.2 g/d	34 (48.5)	62 (68.9)	0.031				
≥0.2 g/d	36 (51.4)	28 (31.1)	<0.001	<0.001	0.854	0.654	1.115

Note: Data is expressed as mean±SD unless otherwise stated; ^apatients with multiple-site infections will be counted separately; ^bpatients with multiple underlying diseases will be counted separately

Currently, polymyxin B is widely used in various severe infections such as pneumonia, urinary tract infection and septicemia caused by *Pseudomonas aeruginosa* and *Acinetobacter baumannii*^[10,13,14]. However, most related studies are carried out *in vitro* and relevant clinical research data is small. Thus the rationality and safety evaluation of combined medication is limited^[10,14,22]. Another reason is that the clinical practice is usually confused with various drugs for antibacterial treatment, so interaction between these drugs has not been known. Therefore, based on the limited number of patients, it is

meaningful to investigate the efficacy of the combined application of polymyxin B and tigecycline to treat MDR-KP by controlling variables. Previous studies have shown that the adverse reactions of polymyxin B are nephrotoxicity and neurotoxicity and other rare side effects include allergic reaction, skin itching and mild irritative cough when inhaling the preparation^[11,14]. It is interesting that, except for the relatively high incidence of AKI, the incidence of other adverse reactions was extremely low, about 1 %. Thus the statistics of those adverse reactions were not performed in this study.

For the highest incidence of adverse reactions, both in the PB group and PB-TGC group, AKI appeared around the fourth day of the beginning of antimicrobial treatment. In order to study the high incidence of AKI, we evaluated patients' characteristics and treatments. Furthermore, we identified the risk factors for AKI through the analysis of intergroup (PB group vs. PB-TGC group) and intragroup (PB-TGC group, kidney injury group vs. kidney non-injury group).

As shown in Table 2 and Table 3, the results indicated that blood infection, hypertension and a high dose of TGC ≥ 0.2 g/d were the high-risk factors for AKI. Severe blood infection often leads to multiple organ failure and shock, with a high mortality rate^[23]. Septic AKI occurs between 15 % and 20 % of all intensive care unit admissions and its mortality ranges from 20 % to 60 %. During the study period, we observed that patients usually had pulmonary infections before blood infection (10/78, 12.8 %) and the probability of blood infection was positively related to the treatment time. For patients whose infection is not resolved by conventional doses of tigecycline, an increased dose is often used, which is an approach that has also been recommended in a recent consensus statement^[20]. There were no reports of kidney injury induced by tigecycline^[19,20]. However, our study results indicated that doses of tigecycline ≥ 0.2 g/d were the high-risk factors for AKI. This might be related to the following facts: tigecycline and polymyxin B were both excreted through the kidney, wherein tigecycline was about 33 %^[24,25] and polymyxin B was about 60 %^[26], the combination of tigecycline and polymyxin B increased the kidney burden of drug metabolism and caused the increased incidence of kidney injury.

It is generally accepted that hypertension is a risk factor for kidney injury^[27,28]. The damage of hypertension to the kidney is not transient but persistent and irreparable^[29]. Furthermore, the kidney itself has a powerful compensatory capacity and under normal circumstances, just 30 % of kidney function can maintain the metabolism demand of the human body. Therefore, kidney injury in the early stage generally does not have clinical symptoms. When the clinical symptoms of kidney injury appeared, the degree of kidney injury had reached more than 70 %. In order to avoid the occurrence of the above situation, we selected Cys-C, β_2 -MG, mALB as the markers of kidney injury in the early-stage^[30]. These indicators were within the standard limit before patients were included in the study to accept antimicrobial therapy. With the

ongoing therapy, their values gradually increased, indicating that Cys-C, β_2 -MG and mALB can be used to diagnose kidney injury. We also observed that the decreasing trend of inflammatory related factors in PB-TGC group was more significant than that in PB group ($p < 0.001$). The above results indicated that for MDR-KP, the therapeutic efficacy of combination application of polymyxin B and tigecycline was better than that of polymyxin B alone, but the relatively higher incidence of kidney injury is worthwhile concerning of clinicians, especially for patients with hypertension. Unfortunately, we do not know why hypertension is an independent risk factor for AKI when polymyxin B and tigecycline are combined for anti-MDR-KP therapy. This issue will be further studied in the future.

The present study is associated with some limitations. Firstly, the sample size of each group in this study is relatively small. Secondly, only acute kidney injury is analyzed and the patients are not followed up for an extended period. Finally, the clinical effect and microbiological subgroup analysis of different combined treatment regimens are not performed in different bacterial groups.

To sum up, we analyzed the efficacy of polymyxin B combined with tigecycline to treat MDR-KP infection in this study. It was found that the combination of polymyxin B and tigecycline in the treatment of MDR-KP infection had a higher incidence of AKI. Through analysis of intergroup and intragroup, blood infection, hypertension and high dose of tigecycline were higher risk factors for acute kidney injury. It was the first time to report that hypertension was an independent risk factor of kidney injury when the combination of polymyxin B and tigecycline was used to treat MDR-KP infection. Therefore, we suggest that people with hypertension who are infected with MDR-KP should avoid using PB-TGC for antimicrobial treatment. This study provided a valuable clinical experience for polymyxin B and tigecycline combination therapy and provided clinical support and basis for patients with MDR-KP infection when choosing appropriate antimicrobial treatment.

Authors' contributions:

Xiao Du and Hanwen Tong have contributed equally to this work. Yunfei Jiang and Binxia Shao are considered as co-corresponding authors.

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Conflict of interests:

The authors declare that no conflict of interest is associated with this work.

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