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Treatment efficacy of tigecycline in comparison to cefoperazone/ sulbactam alone or in combination therapy for carbapenenm-resistant *Acinetobacter baumannii* infections

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Abstract: Tigecycline (TGC) and cefoperazone/sulbactam (CPS) both have been shown good *in vitro* activity against carbapenem-resistant *Acinetobacter baumannii* (CRAB) isolates. We aim to compare the efficacy of TGC versus CPS for CRAB infections. We conducted a retrospective cohort study of patients with CRAB at a single center in China from 2013 to 2015. Outcomes comprised in-hospital mortality, clinical and microbiological response. The method of inverse probability of treatment weighting and multivariable logistic regression analysis incorporated with propensity score were employed to estimate the effect of treatment groups. There were 130 subjects included in our study. The patients in TGC, CPS and TGC plus CPS combination group were 42, 66, and 22, respectively. After adjustment, in-hospital mortality was lower in CPS group than TGC group (weighted OR 0.173; 95% CI 0.06-0.497; P=0.001) but without differences in clinical success and microbiological eradication (P>0.05). TGC monotherapy had a similar outcome with TGC plus CPS combination group. This is the first study comparing the efficacy of tigecycline and cefoperazone/sulbactam for CRAB infections. Cefoperazone/sulbactam appears to be more efficacious than tigecycline during treatment.

Keywords: Carbapenenm-resistant *Acinetobacterbaumannii,* tigecycline, cefoperazone/sulbactam, influencing factors, efficacy.

INTRODUCTION

Nosocomial infections are associated with a high morbidity and mortality, posing a serious threat to the patient's health as well as huge economic losses (Kollef *et al.*, 1997). Over the last decade, *Acinetobacter baumannii* (AB), which has the ability to rapidly spread has emerged as a serious widespread threat (Peleg *et al.*, 2008). Although carbapenems remain the drugs of choice for the treatment of AB infections, the high resistance rate of AB to carbapenems increased from 31% to 66.7% in China from 2005 to 2014 (Hu *et al.*, 2016). This brings a therapeutic challenge as few treatment options are available. Colistin is suggested as a first-line treatment for AB infections. Most studies which have been associated with colistin for treatment of nosocomial infections have shown good results (Viehman *et al.*, 2014). However, the increasing use of colistin has been problematic due to its nephrotoxicity and ithas not been clinically available in China (Pogue *et al.*, 2011). Tigecyline (TGC) and cefoperazone/sulbactam (CPS) show active against CRAB isolates and there exists numerous studies on both antibiotics for treatment of AB (Temocin *et al.*, 2015). Tigecycline is a glycylcycline and its off label use is common in clinical practice when severe infection leaves no other choice (Ye *et al.*, 2011). Cefoperazone/sulbactam is a β-lactam/β-lactamase inhibitor combination. Sulbactam has high intrinsic activity against *Acinetobacter* species and cefoperazone has synergistic antibacterial effect with sulbactam against AB (Ji *et al.*, 2013). In spite of all this, a study on comparing clinical efficacy of TGC versus CPS for CRAB infections is lacking.

Many reports about treatment failures of TGC monotherapy indicate that it might not be sufficient to control severe infection(Cai *et al.*, 2016). Increasing antibiotic resistance rates of AB strains and the current lack of single antimicrobial agents available to treat CRAB infections have forced clinicians to use combination therapies as the only viable treatment option. At present, TGC and CPS combination are considered as an alternative choice for colistin in clinical practice against CRAB infections in China. However, the conclusion that TGC plus CPS combination is superior to TGC monotherapy remains lack clinical support evidence. The aim of this study is to test efficacy for the treatment of TGC and CPS when used alone or in combination with TGC for CRAB infections and to evaluate the influencing factors of drug efficacy.

MATERIALS AND METHODS

This was a single-center retrospective observational study. The information of patients was derived from the First

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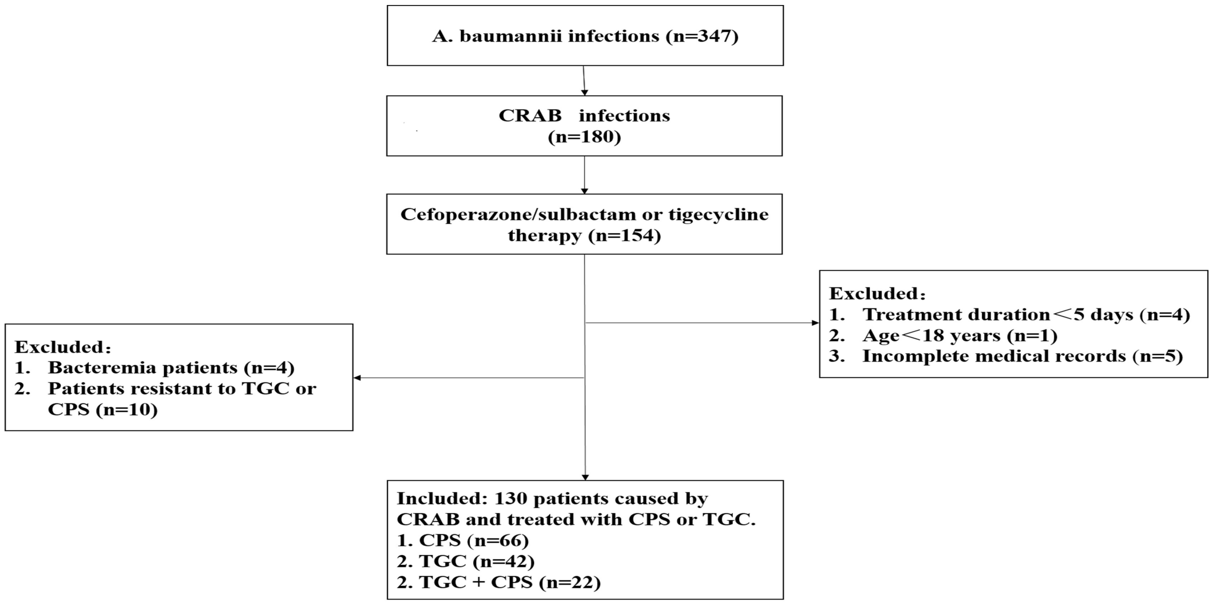

NOTE: CRAB, carbapenem-resistant *Acinetobacter baumannii*; TGC, tigecycline; CPS, cefoperazone/sulbactam.

Fig. 1: Study design of CRAB patients included in the analysis of the impact of tigecycline and cefoperazone/sulbactam between 2013 and 2015

Affiliated Hospital of Xi'an Jiao tong University and their medical records were obtained from hospital computer database. The ethics committee granted a waiver for informed consent to be obtained.

Patients and treatments

We collected patients' information who were admitted to the First Affiliated Hospital of Xi'an Jiao tong University between December 2013 and December 2015. The patient inclusion criteria were (1) patients infected with CRAB and received TGC or CPS treatment; (2) the duration of treatment ≥5 days; (3) aged ≥18 years; (4) patients susceptible to TGC or CPS; and (5) complete medical records. We also excluded patients who infected with bacteremia because tigecycline treatment of bacteremia was controversial. In this study, the main infection type was pneumonia (2/3 of the patients), others included urinary tract infection, skin and soft tissue infection, and intra-abdominal infection. A patient with Pneumonia must have a new or progressive radiographic infiltrate, and at least two of the following characteristics: fever (≥38°C), decline in oxygenation (O_2 saturation <90%), leucocytosis (leucocyte count >12000cells/mm^3) or leucopenia (leucocyte count <4000cells/mm^3), as well as a new onset or a change in purulent sputum characteristics (Ye *et al.*, 2016). Pneumonia infected with CRAB was determined if CRAB isolated from the sputum or tracheal aspirate from 7 days before to 3 days after the first administration of TGC or CPS. Diagnosis of other infections were based on CDC criteria plus the isolation of AB from a usually sterile site (Garner *et al.*, 1988). The dose of TGC was a 100 mg loading, followed by 50mg every 12 hours. The patients in CPS group received cefoperazone/sulbactam 3g (at a ratio 2:1) every 8 or 12 hours.

Microbiology and susceptibility test

The specimen collected from the infection site of each patient was used to perform pathogen identification and susceptibility test. The isolates were identified by routine methods, and *in vitro* susceptibilities to six kinds of antimicrobial agents (β lactam/β lactamase inhibition, quinolones, cephalosporins, carbapenems, aminoglycosides and tigecycline) commonly used in clinic were determined by the Kirby-Bauer disk diffusion method with Mueller-Hinton agar as recommended by the Clinical and Laboratory Standards Institute standards (Tal-Jasper *et al.*, 2016).The resistant breakpoint and susceptible breakpoint for tigecycline were at ≤12 mm and at ≥16 mm, respectively (Jones *et al.*, 2007). The resistant breakpoint and susceptible breakpoint for cefoperazone/sulbactam were at ≤15mm and at ≥21mm (Jean *et al.*, 2015b).

Data collection and definitions

Demographic characteristics including age, gender, infection type, underlying disease, length of hospital stay, invasive procedure, combination therapy, acute physiology and chronic health evaluation (APACHE α score) and et al. Concomitant medication was defined as simultaneously use of different class of antibiotics for at least 3 days. The main outcome endpoint was clinical success. The secondary endpoints were in-hospital mortality and microbiological success. Clinical success was defined by a lessening of the signs and symptoms of AB. In-hospital mortality would be defined as death before discharge. Consistently negative blood culture without recurrence during or after the course of treatment was designated as microbiological eradication.

Table 1: Demographics characteristics and outcomes between (1) tigecycline vs. cefoperazone/sulbactam group, and (2) tigecycline vs. tigecycline plus cefoperazone/sulbactam group

Characteristics	Cefoperazone/ sulbactam(n=66)	Tigecycline (n=42)	Tigecycline Cefoperazone/sulbactam (n=22)	P_1 value	P_2 value
Age (years) [median (IQR)]	66(49-75)	68(55-79)	64(50-75)	0.376	0.822
Male gender [No. (%)]	45(68)	29(69)	17(77)	0.925	0.487
Infection type [No. (%)]					
Pneumonia	50(76)	35(83)	19(86)	0.349	1.000
Urinary tract infection	6(9)	3(7)	0(0)	1.000	0.508
Skin and soft tissue infection	7(11)	1(2)	0(0)	0.225	1.000
Intra-abdominal infection	7(11)	7(17)	2(9)	0.361	0.653
Underlying disease [No. (%)]					
Diabetes mellitus	12(18)	7(17)	3(14)	0.242	1.000
COPD	19(29)	17(40)	11(50)	0.209	0.466
Malignant tumor	11(17)	7(17)	5(23)	1.000	0.800
Shock	8(12)	10(24)	3(14)	0.112	0.526
Sepsis	9(14)	6(14)	2(9)	0.447	0.842
Cerebrovascular	18(27)	18(43)	7(32)	0.094	0.390
Renal dysfunction	16(24)	10(24)	4(18)	0.255	0.842
Liver dysfunction	9(14)	8(19)	4(18)	0.452	1.000
Surgery before antibiotics [No. (%)]	24(36)	30(71)	15(68)	<0.001	0.787
Length of hospital stay (days) [median (IQR)]	21(11-36)	45(34-56)	27(12-42)	0.028	0.001
ICU admission [No. (%)]	42(64)	31(74)	17(77)	0.271	0.046
Surgery before AB infection [No. (%)]	36(55)	18(43)	9(41)	0.236	0.881
Invasive procedures [No. (%)]	34(52)	26(62)	14(64)	0.289	0.892
Mechanical ventilation (days) [median (IQR)]	6(2-9)	21(7-34)	13(6-16)	0.837	<0.001
CRRT [No. (%)]	9(14)	8(19)	3(14)	0.452	0. 0.844
Medication before infection [No. (%)]					
Proton pump inhibitor	64(97)	24(57)	15(68)	<0.001	0.390
Carbapenem	25(38)	28(67)	15(68)	0.004	0.902
Cephalosporin	8(12)	10(24)	2(9)	0.112	0.273
Fluoroquinolones	17(26)	5(12)	2(9)	0.081	1.000
Antifungal agents	46 (70)	31(74)	14(64)	0.645	0.577
Concomitant medication [No. (%)]					
Carbapenem	21(32)	8(19)	9(41)	0.144	0.060
Aminoglycosides	9(14)	2(5)	7(32)	0.246	0.109
Antifungal agents	41(62)	30(71)	15(68)	0.320	0.787
Immunosuppressants	8(12)	0(0)	2(9)	0.052	0.219
Glucocorticoids	41(62)	15(36)	11(50)	0.007	0.269
APACHE α[median (IQR)]	12(8-16)	21(13-26)	21(11-24)	<0.001	0.767
Outcome [No. (%)]					
In-hospital mortality	3(5)	5(12)	6(27)	0.295	0.231
Clinical success	46(70)	26(62)	10(45)	0.402	0.208
Microbiological eradication	30(50)	14(33)	9(41)	0.211	0.549

Note: P_1, Tigecycline vs. Cefoperazone/sulbactam; P_2, Tigecycline vs. Tigecycline + Cefoperazone/sulbactam; COPD, chronic obstructive pulmonary disease; ICU, Intensive Care Unit;AB, *Acinetobacterbaumannii*; CRRT, continuous renal replacement therapy; APACHE II, acute physiology and chronic health evaluation.

Table 2: Comparison of outcomes between (1) tigecycline vs. cefoperazone/sulbactam group, and (2) tigecycline vs. tigecycline plus cefoperazone/sulbactam group by multiple logistic regression analysis and inverse probability of treatment weighting

	Model	Adjusted OR_1 (95% CI)	P_1 value	Adjusted OR_2 (95% CI)	P_2 value
In-hospital mortality	crude	0.352 (0.080-1.560)	0.295	0.360 (0.096-1.354)	0.231
	PS-adjusted multiple logistic	0.115 (0.015-0.890)	0.038	0.346 (0.085-1.415)	0.140
	IPTW	0.173 (0.06-0.497)	0.001	1.024 (0.140-7.495)	0.981
Clinical success	crude	1.415 (0.627-3.196)	0.402	1.950 (0.686-5.545)	0.208
	PS-adjusted multiple logistic	1.360 (0.407-4.540)	0.618	1.540 (0.519-4.570)	0.436
	IPTW	1.191 (0.655-2.166)	0.567	0.392 (0.056-2.770)	0.348
Microbiological eradication	crude	1.667 (0.746-3.724)	0.211	0.722 (0.249-2.095)	0.549
	PS-adjusted multiple logistic	2.073 (0.812-5.291)	0.127	0.723 (0.249-2.103)	0.552
	IPTW	1.710 (0.876-3.339)	0.116	0.634 (0.101-3.980)	0.627

Note: Adjusted $OR_1$and P_1, Tigecycline vs. Cefoperazone/sulbactam; Adjusted OR_2 and P_2, Tigecycline vs. Tigecycline + Cefoperazone/sulbactam; IPTW, inverse probability of treatment weighting; PS, propensity score; OR, odd ratio; CI, confidence interval

Table 3: Univariate and multivariate analyses of the influencing factors for effect during treatment of cefoperazone/sulbactam involving carbapenenm-resistant *Acinetobacter baumannii* infections

characteristics	success	failure	univariate	multivariate	
	n=46	n=20	*P*	*P*	adjusted OR (95% CI)
Age(years) [median (IQR)]	66(48-76)	65(56-74)	0.619		
Male gender [No. (%)]	32(70)	13(65)	0.715		
Infection type [No. (%)]					
Peumonia	30(65)	12(60)	0.686		
Urinary tract infection	6 (9)	4(20)	0.726		
Skin and soft tissue infection	3(7)	3(15)	0.525		
Intra-abdominal infection	4(9)	4(20)	0.377		
Underlying disease [No. (%)]					
Diabetes mellitus	9(20)	3(15)	0.925		
COPD	10(22)	9(45)	0.055		
Malignant tumor	7(15)	4(20)	0.905		
Shock	5(11)	3(15)	0.950		
Sepsis	6(13)	3(15)	1.000		
Cerebrovascular	13(28)	5(25)	0.785		
Renal dysfunction	11(24)	5(25)	1.000		
Liver dysfunction	8(17)	1(5)	0.338		
Surgery before antibiotics [No. (%)]	17(37)	7(35)	0.586		
Hospital stay(days) [median (IQR)]	22(19-42)	13(9-23)	0.006	0.004	0.913 (0.858-0.972)
Surgery before AB infection [No. (%)]	25(54)	10(50)	0.745		
Invasive procedures [No. (%)]	22(48)	11(55)	0.593		
CRRT [No. (%)]	5(11)	4(20)	0.327		
Medication before infection [No. (%)]					
Proton pump inhibitor	41(89)	17(85)	0.638		
Carbapenem	14(30)	10(50)	0.133		
Fluoroquinolones	13(28)	4(20)	0.483		
Antifungal agents	25(54)	11(55)	0.961		
Concomitant medication [No. (%)]					
Carbapenem	10(22)	11(55)	0.010	0.005	0.122 (0.029-0.522)
Aminoglycosides	7(15)	2(10)	0.573		
Immunosuppressants	4(9)	0(0)	0.999		
Glucocorticoids	25(54)	11(55)	0.961		
APACHE α[median (IQR)]	10(8-16)	14(10-20)	0.059		

Note: COPD, chronic obstructive pulmonary disease; AB, *Acinetobacter baumannii*; CRRT, continuous renal replacement therapy; APACHE II, acute physiology and chronic health evaluation; OR, odd ratio; CI, confidence interval.

Ethical approval

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS, version 19 (IBM SPSS Statistics 19.0, Xi'an, China). Continuous variables are presented as medians (interquartile ranges [IQR]) and categorical data are expressed as counts (percentage). Percentages were compared using the chi-squared or Fisher's exact test. Continuous data were calculated using the Mann-Whitney U test, Kruskal-Wallis test or Wilcoxon signed-rank test as appropriate. Decisions regarding antibiotic selection between TGC and CPS were affected by patients' prognostic factors. In order to control the confounders, propensity scores were estimated using multiple logistic regression model where covariates were age, surgery before medication, combination with carbapenem and APACHEα scores. Then, we performed covariable adjustment analysis using the propensity score (PS) and logistic regression model with inverse probability of treatment weighting (IPTW) (Park *et al.*, 2014). The weights for TGC group were the inverse of propensity score and those for CPS group were inverse of 1-propensity scores. After adjustment for clinically related covariates, the average treatment effect between the two group was not significant. To analyze the related factors of therapeutic efficacy of CPS for CRAB infections, a univariable and multivariable regression model were conducted. We combined the covariates with a $P<0.1$ in the univariate analysis into multivariate model. $P<0.05$ was considered significant.

RESULTS

Tigecycline versus cefoperazone/sulbactam therapy study population and baseline characteristics

Of the 347 cases of AB infections during the study period, 130 were met the eligibility criteria, of which 66 (51%) patients had received CPS therapy and 42 (32%) patients had received TGC, whereas the remaining 22 (17%) had received TGC plus CPS combination treatment (fig. 1). All the included patients were infected with CRAB and the strains isolated were susceptible to TGC or CPS.

Table 1 showed the baseline characteristics of the patients. Obviously, there were no significant differences between the groups with regard to age, infection type, underlying disease. Pneumonia was the most common infection type in TGC and CPS group (83% versus 76%). Combination therapy was common: 71% in TGC and 62% in CPS of patients using antifungal agents, 36% and 62% received glucocorticoids, respectively. TGC in this cohort was frequently used to treat postoperative infections. Furthermore, among patients receiving TGC, in particular, severe diseases like cerebrovascular diseases and chronic obstructive pulmonary disease (COPD) were more frequently identified, which manifested as higher APACHE α score and a longer hospital stay. Compared with patients in CPS, carbapenems were widely used as empirical therapy in TGC treatment group. Patients with CPS were much likely to be administered PPIs before the diagnosis of CRAB.

Clinical outcomes in tigecycline and cefoperazone/sulbactam groups

In the unadjusted analysis, there were 26 (62%) patients in TGC group and 46 (70%) in CPS group achieving clinical success. The in-hospital mortality in CPS-treated patients was lower than TGC-treated (5% versus 12%) but its microbiological eradication was higher than TGC-treated patients (50% versus 33%). All the differences were not significant (table 1).

Clinical outcomes after adjustment using propensity scores in tigecycline and cefoperazone/sulbactam groups

To reduce the effect of confounding factors and selection bias. We conducted inverse probability weighted analysis using propensity scores combined with regression adjustment. After weighting, the risk of death was lower in CPS than TGC group (weighted OR 0.173; 95% CI 0.06-0.497; P=0.001). Clinical success and microbiological eradication were not significantly different between the groups (P=0.567; P=0.116, respectively). In addition, we also performed covariable adjustment analysis using the propensity score. This additional analysis showed the same result (table 2).

Tigecycline monotherapy versus tigecycline plus cefoperazone/sulbactam combination therapy
Study population and baseline characteristics

Table 1 showed the baseline characteristics of the patients. There were no significant differences between monotherapy and combination therapy group with regard to age, gender, infection type and underlying disease. The patients treated with TGC had a longer hospital stay (45; IQR, 34-56 versus 27; IQR, 12-42) and duration of mechanical ventilation (21; IQR, 7-34 versus 13; IQR, 6-16) compared with combination therapy group.

Clinical outcomes in tigecycline monotherapy and in combination with cefoperazone/sulbactam group

In terms of clinical response, 26 (62%) clinical success in TGC monotherapy and 10 (45%) in combination group were observed (P=0.208). In-hospital mortality was 12% and 27% in two groups, respectively (P=0.231). The microbiological eradication was higher in combination group than TGC alone (41% versus 33%, P=0.549). However, these differences did not make any sense (table 1).

Clinical outcomes after adjustment using propensity scores in tigecyclinemonotherapy and in combination with cefoperazone/sulbactam therapy

After adjustment, there were no statistically significant differences found between TGC monotherapy and combination group in clinical success in-hospital mortality and microbiological eradication (*P*>0.05) (table 2).

The influencing factors to the clinical efficacy of cefoperazone/sulbactam for CRAB infections

Table 3 shows the baseline characteristics of CPS group patients. A total of 66 patients received CPS. 46 (70%) cases had clinical success while 20 (30%) cases had clinical failure. We individually put baseline characteristics that might have an impact on the clinical success into the univariate regression model. Significant factors were: longer hospital stay (*P*=0.006), avoiding combination with carbapenem (*P*=0.010), and lower APACHE α score (*P*=0.059). A longer hospital stay (adjusted OR, 0.913; 95% CI, 0.858-0.972; *P*=0.004) and avoiding combination with carbapenem (adjusted OR, 0.122; 95% CI, 0.029-0.522; *P*=0.005) were found to be independent influencing factors for efficacy of CPS on multivariable analysis.

DISCUSSION

J. Garnacho introduced to select effective antimicrobial agents based on the susceptibility test of AB isolates for tigecycline or sulbactam (Garnacho-Montero *et al.*, 2015). *In vitro* study indicated that TGC has shown good activity against AB isolates than CPS while comparative clinical efficacy remains unknown (Rizek *et al.*, 2015). The present study demonstrated that clinical and microbiological response were not significantly different between TGC and CPS group. Moreover, TGC group was associated with a higher mortality than CPS. There were a few studies comparing the effect of tigecycline-based and sulbactam-based regemin (Chan *et al.*, 2010, Jean *et al.*, 2015a, Lee *et al.*, 2013). Jean S. S. compared the clinical efficacy between tigecycline plus extended-infusion imipenem and sulbactam plus imipenem against ventilator-associated pneumonia, and suggested that the mortality of tigecyline-based group was significant lower than sulbactam-based therapy (14.3% versus 64.3%, respectively) (Jean *et al.*, 2015a). The reason for a conflicting outcome with us might be due to its small sample size and without exclusion the effect of combination therapy. Jung-Jr Ye reported another study comparing tigecycline-based with sulbactam-based treatment for pneumonia against multidrug-resistant *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex (Ye *et al.*, 2016). It concludes that the patients treated with either tigecycline-based or sulbactam-based treatment had a similar clinical outcome and tigecycline group had a lower microbiological eradiation rate. In agreement with meta-analysis (Cai *et al.*, 2011), TGC in the pooled analysis of different infections showed excess overall mortality. A possible explanation of this observation may be an increased super infections in the TGC group and a growing risk of death especially among patients with VAP (Curcio and Verde, 2011).

It has been reported that TGC monotherapy could make AB isolates develop TGC resistance rapidly (Cai *et al.*, 2016). Combination therapy has become an option to treat infection with MDR bacteria because of the distinct advantage in terms of broad coverage, synergistic effect and prevention of drug resistance development. *In vitro* studies indicated that TGC plus CPS have shown to have synergistic activity against AB (Kim *et al.*, 2016). No convincing evidence was proved to recommend combination therapy in the treatment for AB infections (Garnacho-Montero *et al.*, 2015). Guner R. conducted a study in CRAB patients who treated with TGC alone or in combination therapy (Guner *et al.*, 2011). It turned out that the rate of clinical response in TGC combination group attained 66.7% and it was difficult to compare the outcome between TGC monotherapy versus TGC plus CPS combination since there were only 2 cases in the control group. Our study directly proved that TGC alone and TGC plus CPS combination therapy had similar outcome.

The present study explored the relationship between the efficacy of antibiotic and individual differences to decide the treatment determinants with the purpose of providing a theoretical basis for individualized therapy. We demonstrated that the patients in CPS group who had a longer hospital stay had high probability of treatment success, which might be because of no mortality in patients who had no clinical failure, with the effect of the infection translating into excess length of hospital stay rather than death. We also recommended carbapenems should not be used for severe infections in areas which have a high rate of resistance to this group of antibiotics, which was consistent with J. Garnacho (Garnacho-Montero *et al.*, 2015).

To the best of our knowledge, the present study is the first study comparing the effect of TGC with CPS monotherapy or TGC with TGC plus CPS combination for CRAB infections. To make a precise assessment of the outcome, we applied IPTW and PS-logistic to control the effect of the observed confounders. This study also has several limitations. First, cefoperazone/sulbactam is a widely used antibiotic in China although it is not available in some countries. The conclusion of this study could provide some reference for other β lactam/β lactamase inhibitor combination, like ampicillin/sulbactam or piperacilllin/tazobactam. Second, this is a retrospective, single-center study. CRAB was infected in a rare population and TGC was not available until 2012 in our hospital, resulting in the limited sample size in the present study. Third, on influencing factors analyze, 54% (36/66) of patients in the CPS received combination therapy with more than one agent for CRAB. It was thus difficult to attribute clinical efficacy to CPS alone.

CONCLUSION

In conclusion, our comparison of therapy TGC and CPS therapy for patients with CRAB indicated that in-hospital mortality was higher in TGC group compared with CPS but without differences in clinical success and microbiological eradication. TGC monotherapy had a similar outcome with TGC plus CPS group. The variables independently associated with efficacy in CPS for treatment of patients with CRAB were: longer hospital stay and avoiding combination with carbapenem. Further studies are still warranted.

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