Original Article

In vitro assessment of cefoperazone-sulbactam based combination therapy for multidrug-resistant *Acinetobacter baumannii* isolates in China

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Background: Multidrug-resistant *Acinetobacter baumannii* (MDRAB) has emerged as an important pathogen of nosocomial infections. Even though cefoperazone-sulbactam is frequently used to treat MDRAB infections, this single-drug therapeutic approach often results in antibiotic resistance. Thus, combination therapy is preferred over single-drug therapy, particularly in the case of carbapenemase-producing gram negative bacteria. The aim of this study was to investigate the efficacy of cefoperazone-sulbactam combined with either tigecycline or rifampicin against clinical isolates of MDRAB.

Methods: One hundred and three MDRAB bacteria were isolated from patients in two hospitals in China. The Epsilomer test (E test) was used to determine the minimum inhibitory concentration (MIC) values for amikacin, ceftazidime, cefepime, levofloxacin, rifampicin, cefoperazone-sulbactam, meropenem, tigecycline, and gentamicin against MDRAB isolates. *In vitro* effects of various antibiotic combinations were measured and the fractional inhibitory concentration index (FICI) was calculated for each drug combination.

Results: Approximately 17.5% of the isolates were resistant to tigecycline, whereas more than 84.2% isolates were resistant to other antimicrobial agents tested in this study. Cefoperazone-sulbactam revealed remarkable synergistic effects when used in combination with either tigecycline or rifampicin. However, for the isolates with MICs lower than blood peak concentration after combination therapy, the ratio was lower in highly resistant isolates compared to the least resistant bacteria.

Conclusions: *In vitro* cefoperazone-sulbactam in combination with tigecycline or rifampicin showed the highest synergistic or additive activity against MDRAB isolates. However, acquisition of highly antibiotic resistant bacteria may lessen the effectiveness of combination therapy.

Keywords: *Acinetobacter baumannii* (*A. baumannii*); multidrug-resistant *Acinetobacter baumannii* (MDRAB); cefoperazone-sulbactam; tigecycline; rifampicin

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Introduction

Acinetobacter baumannii (*A. baumannii*) is an important pathogen of nosocomial infection and can cause a wide range of infections including bacteremia, pneumonia, urinary tract infections, and wound infections (1,2). Antibiotic use and invasive procedures increase drug resistance and tolerance of *A. baumannii* (3). Particularly, the emergence of multi-drug resistant *A. baumannii* (MDRAB) presents a series of challenges to clinical anti-infection treatment (4,5), including high rate of failure and large costs. In intensive care unit (ICU) patients, the digestive tract is an important epidemiological reservoir for MDRAB infections in hospital outbreaks (6). MDRAB is disseminated worldwide (6,7) and is highly resistant to a number of available antibiotics, including aminoglycosides, quinolones, penicillin, cephalosporin, and carbapenems. At present, colistin and tigecycline have been employed as alternative therapeutic options for MDRAB infections. However, emergence of resistance to these antimicrobial agents has also been reported (8). Notwithstanding, combination therapy has been considered superior to single-drug therapy against MDRAB, with regards to both efficacy and lower risk of adverse reactions and drug toxicity (9-11). Tigecycline based therapy with various combinations such as cefoperazone-sulbactam, carbapenem, quinolone, or aminoglycoside antibiotics, has been adopted for treatment of MDRAB infections (12,13). However, the most effective combination therapy to treat *A. baumannii* infection has yet to be explored.

Cefoperazone is a bactericidal beta lactam antibiotic (14) that is commonly used in combination with a β-lactamase inhibitor, such as sulbactam, to enhance the activity of cefoperazone by irreversible inactivation of β-lactamases (15). In the absence of tigecycline, either cefoperazone-sulbactam or rifampicin is frequently prescribed to treat MDRAB infections, as both provide good antimicrobial effects against such infections (16,17). Tigecycline and rifampicin are good therapeutic options since they have no cross-resistance influence from β-lactam antibiotics. In addition, β-lactamase inhibitors, including sulbactam and tazobactam, are also effective in treating MDRAB infections (18). Moreover, rifampicin and cefoperazone-sulbactam in combination have synergistic effects against *A. baumannii* infections (19). The aim of the present study was to investigate the efficacy of cefoperazone-sulbactam combined with either tigecycline or rifampicin against clinical isolates of A. baumannii.

Methods

Collection and identification of bacteria

MDRAB (n=103) were clinically isolated from patients at Qilu Hospital at Shandong University and at The Second Affiliated Hospital of Shandong University of Chinese Medicine between December 2015 and July 2016. Of the 103 isolates, 38 were isolated from patients in the Department of Respiratory Medicine, 58 were collected from the ICU and 7 were obtained from the Neurosurgery Department. For the 103 isolates, 29% of them were obtained from bronchoalveolar lavage fluid, 2% from blood, and the rest from sputum. The Ethics Committee of Qilu Hospital at Shandong University approved this study [KYLL-2016 (KS)-507]. All participants in this study provided informed consent. All bacteria were identified using BBL Crystal Identification Kit (Becton Dickinson Diagnostics, Sparks, MD., USA) according to the manufacturer's guidelines. Briefly, bacterial cultures were inoculated into the test kit, and then incubated for 4 h at 35 ℃. Catalase, indol-spot, and gram stain tests were analyzed with the Crystal Mind software. MDRAB refers to isolates of *A. baumannii* that are non-susceptible to at least one agent in three or more antimicrobial categories, such as aminoglycosides, carbapenems, fluoroquinolones, penicillin and β-lactamase inhibitors, extended-spectrum cephalosporins, folate pathway inhibitors, polymyxins, and tetracyclines (20,21).

Antibiotic susceptibility testing

Minimum inhibitory concentration (MIC) values were assessed for tigecycline, ceftazidime, cefepime, cefoperazone, gentamycin, meropenem, levofloxacin, rifampicin, and amikacin for multi-drug resistant *A. baumannii* bacteria using the Epsilomer test (E test) method following clinical and laboratory standards institute (CLSI) guidelines. Briefly, 100 μL bacterial suspensions were spread on Muller-Hinton agar plates, E test strips (Sigma) were placed, and the plates were incubated for 24 h at 37 ℃. MIC values were recorded according to CLSI guidelines, where MIC values ≤16/8 and ≥64/32 μg/mL of cefoperazone-sulbactam against *A. baumannii* are considered sensitive and resistant, respectively. The MIC for 90% of MDRAB (MIC_{90}) was also recorded.

Synergy test

Synergy tests were performed using the E test method

Table 1 Antimicrobial susceptibility testing

Antimicrobial agent	MIC_{50}	MIC_{90}	%R
Amikacin*	64	>256	100.0
Ceftazidime*	32	>128	100.0
Cefepime*	32	>128	96.3
Levofloxacin*	8	16	100.0
Rifampicin*	4	16	84.2
Cefoperazone-sulbactam**	32	128	90.8
Meropenem*	32	256	98.3
Tigecycline***	2	8	17.5
Gentamicin*	256	>256	100.0

*, criteria as published by the CLSI [2013]. **, criteria as published by the CLSI [2013] for cefoperazone (CFS) used for cefoperazone-sulbactam: CFP, susceptible ≤16 μg/mL, resistant ≥64 μg/mL. ***, Food and Drug Administration criteria: susceptible MIC <2 mg/L; resistant MIC >8 mg/L); MIC50, minimum inhibitory concentrations for 50% of the organisms; MIC90, minimum inhibitory concentrations for 90% of the organisms; %R, percent resistant.

for each clinical isolate. The combination included: meropenem with rifampicin, amikacin, or cefoperazone-sulbactam; tigecycline with ceftazidime or ciprofloxacin; and cefoperazone-sulbactam with rifampicin. Briefly, strip A and strip B were placed crosswise, with the intersection of the MIC value of each antibiotic. Fractional inhibitory concentration index (FICI) was used to assess the effect of combination therapy. FICI was calculated as (MIC_a combination/MIC_a alone) + (MIC_b combination/MIC_b alone). MIC_a and MIC_b represent the MIC value read from strip A and strip B tests, respectively. A calculated FICI ≤0.5 represented a synergistic effect (22), a value between 0.5–1 represented as an additive effect, a value between 1–4 represented as an indifferent effect, and a value of >4 represented an antagonistic effect (22). Furthermore, the MIC value of each antibiotic was recorded during combination antimicrobial susceptibility tests.

Statistical analysis

The differences in synergistic and additive efficiency among different combination regimens were compared using the chi-square test. In the efficiency analysis of cefoperazone-sulbactam in combination with tigecycline or rifampicin, MDRAB were first grouped according to the extent of resistance to a single antibiotic, then the difference in synergistic and additive efficiency between different groups were tested using the chi-square test. A P value of <0.05 was considered significantly different.

Results

Bacterial identification and susceptibility pattern

All 103 bacteria were characterized as *A. baumannii* by the BBL Crystal Identification Kit and were classified as multidrug resistant. More than 95% of the isolates were resistant to ceftazidime, cefepime, gentamycin, meropenem, levofloxacin, and amikacin. Approximately 17.5% of the isolates were resistant to tigecycline, and the MIC_{50} and MIC_{90} were calculated as 2 and 8 μg/mL, respectively. Nearly 84.2% of the isolates were resistant to rifampicin, and the MIC_{50} and MIC_{90} were calculated as 4 and 16 μg/mL, respectively. However, approximately 90.8% of the isolates were resistant to cefoperazone-sulbactam, and the MIC_{50} and MIC_{90} were calculated as 32 and 128 μg/mL, respectively (*Table 1*).

Evaluation of effective combination therapy against MDRAB

To identify the best drug combination with the highest efficacy, synergy tests were performed using the E test method. Synergistic effects were observed for the tigecycline and cefoperazone-sulbactam combination (66%), followed by rifampicin with cefoperazone-sulbactam (45.7%), and meropenem with cefoperazone-sulbactam (20.4%). No antagonistic effect was observed in any of the antibiotic combinations tested (*Table 2*).

MIC value of tigecycline and cefoperazone-sulbactam in combination

Based on the MIC values of tigecycline, all 103 MDRAB were divided into four groups (≤1, 1–2, 2–4, and >4). The increased synergistic and additive effects of tigecycline and cefoperazone-sulbactam in combination were associated with higher tigecycline MIC values. A decreased MIC value of tigecycline was observed when used in combination. However, in strains with higher resistance, drug combination did not significantly decrease the MIC values below drug max concentration (C_{max}) after combination. Similarly, based on the MIC value of cefoperazone-

Table 2 Evaluation of effects of various drug combinations by E test method

Combination agent	Synergy (%)	Addition (%)	Indifference (%)	Antagonism (%)	%S+A*
MEM+					
SCF	0 (0)	21 (20.4)	82 (79.6)	0 (0)	20.4
AK	0 (0)	3 (2.9)	100 (97.1)	0 (0)	2.9
RIF	0 (0)	0 (0)	103 (100)	0 (0)	0
TGC+					
SCF	20 (19.4)	48 (46.6)	34 (33.0)	0 (0)	66[#]
LEV	0 (0)	0 (0)	103 (100.0)	0 (0)	0
SCF+					
RIF	5 (4.9)	42 (40.8)	62 (54.4)	0 (0)	45.7[#]

*, synergy + addition %; [#], comparison showing statistically significant difference (TGC-SCF and SCF-RIF *vs.* other groups, P<0.05). MEM, meropenem; SCF, cefoperazone-sulbactam; AK, amikacin; TGC, tigecycline; LEV, levofloxacin; RIF, rifampicin.

Table 3 Assessment of antimicrobial activity of tigecycline and cefoperazone-sulbactam

Agent	Alone				Combination of TGC and SCF				
	MIC range	MIC_{50}[#]	MIC_{90}[$]	% < C_{max}	MIC range	MIC_{50}	MIC_{90}	%S + A*	% < C_{max}
TGC									
Total	0.125–16	2	8	13.6	0.0625–16	0.5	4	66.6	54.4
MIC ≤1	0.125–0.5	0.25	0.5	100.0	0.0625–0.5	0.25	0.5	23.4	100.0
1< MIC ≤2	0.5–2	1	2	16.2	1–2	1	2	50.1	74.9[&]
2< MIC ≤4	2–4	2	4	0	2–4	2	4	67.2	19.5[&]
MIC >4	4–16	8	16	0	4–16	4	16	75.3	0
SCF									
Total	32–256	32	128	100.0	4–64	16	64	66.6	100.0
32< MIC ≤64	32–64	32	64	100.0	4–32	8	16	51.9	100.0
64< MIC ≤128	64–128	64	128	100.0	16–64	16	32	66.5	100.0
MIC >128	128–256	128	256	100.0	32–64	64	128	74.3	100.0

*, synergy + addition %; [&], % < C_{max} after combination drugs were significant higher than that alone. MIC50, minimum inhibitory concentrations for 50% of the organisms; MIC90, minimum inhibitory concentrations for 90% of the organisms. TGC, tigecycline; SCF, cefoperazone-sulbactam; MIC, Minimum inhibitory concentration.

sulbactam, all bacterial strains were divided into three groups (32–64, 64–128, and >128). The MIC values of cefoperazone-sulbactam in all groups declined below C_{max} when used in combination (*Table 3*). Therefore, the level of resistance to tigecycline was recognized as the limiting factor for effective tigecycline and cefoperazone-sulbactam combination therapy.

MIC value of rifampicin and cefoperazone-sulbactam in combination

Based on the MIC value of rifampicin, all 103 MDRAB were divided into four groups (≤4, 4–8, 8–16, and >16). Similar to the combination of tigecycline and cefoperazone-sulbactam, higher rifampicin MIC values resulted in better synergistic and additive effects of rifampicin and

Table 4 Assessment of antimicrobial activity of rifampicin and cefoperazone-sulbactam

Agent	Alone				Combination of RIF and SCF				
	MIC range	MIC_{50} #	MIC_{90} $	% < C_{max}	MIC range	MIC_{50}	MIC_{90}	%S+A*	% < C_{max}
RIF									
Total	4–32	4	16	39.8	2–16	4	8	45.7	73.3
MIC ≤4	2–4	2	4	100.0	2–4	2	4	31.4	100.0
4< MIC ≤8	4–8	4	8	100.0	2–8	4	8	36.5	100.0
8< MIC ≤16	8–16	8	16	37.1	4–16	4	16	58.7	89.0&
MIC >16	16–32	16	32	0	8–16	8	16	71.3	40.4&
SCF									
Total	32–256	32	128	100.0	16–128	32	128	45.7	100.0
32< MIC ≤64	32–64	32	64	100.0	16–32	16	32	33.3	100.0
64< MIC ≤128	64–128	64	128	100.0	32–64	32	64	42.1	100.0
MIC >128	128–256	128	256	100.0	64–128	64	128	62.0	100.0

*, synergy + addition %; &, % < C_{max} after combination drugs were significant higher than that alone. MIC_{50}, minimum inhibitory concentrations for 50% of the organisms; MIC_{90}, minimum inhibitory concentrations for 90% of the organisms. TGC, tigecycline; SCF, cefoperazone-sulbactam; MIC, Minimum inhibitory concentration.

cefoperazone-sulbactam in combination. However, strains with higher MIC values for rifampicin had greater difficultly in decreasing the MIC values below C_{max} after combination. Correspondingly, all bacterial strains were divided into three groups (32–64, 64–128, and >128) based on the different levels of resistance to cefoperazone-sulbactam. The MIC values of cefoperazone-sulbactam in all groups decreased below C_{max} when used in combination (*Table 4*). Therefore, the level of resistance to rifampicin was the limiting factor for effective rifampicin and cefoperazone-sulbactam combination.

Discussion

MDRAB has emerged as a serious challenge for clinical anti-infection treatment due to acquired resistance to most of the previously existing antibiotics (4,5). This emerging resistance could be explained by the increased application of single-drug antibiotics. However, the most effective combination therapy to treat *A. baumannii* infection is still unclear. In the present study, tigecycline and cefoperazone-sulbactam combination had the greatest synergistic effect in most MDRAB isolates *in vitro*. The increased synergistic and additive effects of tigecycline and cefoperazone-sulbactam in combination were enhanced by higher tigecycline MIC values.

Tigecycline is a new class of antibiotic that has an ammonia acyl ring element and exerts a strong antibacterial effect against carbapenem-resistant MDRAB (23,24). Because the C_{max} was only 0.72±0.24 μg/mL at the common, normal dose (100 mg initial dose, followed by 50 mg per every 12 h) (25), there is an increased chance that drug resistance will develop with long-term application of tigecycline. Therefore, tigecycline should be used in combination with other antibiotics for treating serious MDRAB infections. In the current study, the combination of tigecycline and cefoperazone-sulbactam showed the best synergetic antimicrobial effect against MDRAB, which is in accordance with reports by Liu *et al.* (4,15), who reported a 29% synergistic effect for the combination therapy. Moreover, tigecycline in combination with cefoperazone-sulbactam showed a more significant effect than tigecycline in combination with sulbactam against MDRAB. It is worth noting that the bacterial drug resistance level significantly impacted the combination effect. Although the synergistic and additive effects of tigecycline and cefoperazone-sulbactam in combination increased with higher tigecycline MIC values, the MIC value was still higher than the C_{max} in the combination therapy. Therefore, the common doses of tigecycline, either administered singularly or in combination, are not sufficient to treat highly resistant bacterial strains (MIC >4).

Rifampicin can be used to effectively treat pneumonia in a mouse model infected with drug resistant *A. baumannii* (26); however, the singular use of rifampicin often results in drug resistance. It is reported that rifampicin alone leads to drug resistance after 24 h treatment of MDRAB infection (27). Thus, rifampicin should be used in combination with other antibiotics. Previous studies showed that combination of rifampicin with colistin or carbapenem produced a synergistic effect when used to treat drug resistant *Pseudomonas aeruginosa*, *Klebsiella bacillus* and *A. baumannii* infections (18,28). Rifampicin in combination was also reported to significantly decrease MIC values (29). In our study, the combination of rifampicin with cefoperazone-sulbactam decreased the synergistic effect more than the combination of tigecycline with cefoperazone-sulbactam. However, these combinations may also be used as alterative option for MDRAB infection, especially for those bacteria with a lower degree of resistance (30,31). The degree of antimicrobial resistance can affect the result of combination effects. The MIC values of tigecycline or rifampicin in combination are still higher than C_{max}, which may explain why the combination is less effective against high drug resistant strains clinically. In addition, the single-drug (tigecycline or rifampicin) MIC value can also be used for predicting prognosis after drug combination. It is worth mentioning that one shortcoming of the study is that it lacks *in vivo* animal experiments. Further research is in progress to evaluate the effect of the cefoperazone-sulbactam based combinations in MDRAB infection animal experiments.

In conclusion, *in vitro* cefoperazone-sulbactam in combination with tigecycline or rifampicin produced the highest synergistic or additive effects against multi-drug resistant *A. baumannii*. However, due to the low C_{max} of tigecycline and rifampicin, these combinations might work better for bacteria with moderate or low drug resistance levels.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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