In vitro Activity of Different Antibacterial Agents in Combination with Each Other against Multidrug-resistant *Acinetobacter baumannii*

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To the Editor: *Acinetobacter baumannii* is a major cause of nosocomial infections associated with high morbidity and mortality, primarily in immunocompromised patients in Intensive Care Units. Multidrug-resistant (MDR) and extensively drug resistant (XDR) *A. baumannii* had become a serious widespread threat to nosocomial infections.[1] There are limited effective antimicrobial agents against these strains. Moreover, the mortality rate of *A. baumannii* infections was associated with inappropriate antimicrobial treatment.[1,2] It is critical to use effective antimicrobials for treating these *A. baumannii* infections. Meanwhile, discovering new antimicrobials and useful combinations of approved drugs against these strains is urgent. Thus, in this study, we discussed the *in vitro* activity of different antibacterial agents, including imipenem (IMI), meropenem (MEM), amikacin (AMK), ciprofloxacin (CIP), cefoperazone/sulbactam (CPS), and sulbactam (SUL) in combination with each other against MDR *A. baumannii* isolated from different provinces of China.

Nonduplicate *A. baumannii* strains were collected from hospitals in different provinces of China. All strains had been identified using microbial identification system. Minimum inhibitory concentrations (MICs) had been determined by the agar dilution method as described by the Clinical and Laboratory Standards Institute protocol. We considered a strain as MDR if it was resistant to two or more antibiotic classes.[1] Moreover, we strictly selected 116 MDR *A. baumannii* strains, which were all resistant to MEM, IMI, AMK, and CIP based on the MICs surveillance results, to evaluate the *in vitro* activities of combinations agents using agar checkerboard dilution method.[3] The combination test involved six clinically, commonly used agents, including imipenem (Merck, USA), meropenem (DSM Pharm., Suzhou, China), amikacin (Xudong Haipu, Shanghai, China), ciprofloxacin (Shangyu Xinyao, Zhejiang, China), cefoperazone/sulbactam (Pfizer, USA), and sulbactam (NICPBP, Beijing, China). The dose of each agents ranges from 1/32 MIC to 4 MIC. Freshly prepared cation-supplemented Mueller-Hinton agar and Mueller-Hinton Broth (Oxoid, Thermo Fisher, British) were used for this study. Results were interpreted by the fractional inhibitory concentration index (FICI).[3] The FICI was calculated for each combination using the following formula: FICI = FICA + FICB, where FICA = MIC of drug A in combination/MIC of drug A alone, and FICB = MIC of drug B in combination/MIC of drug B alone. The FICI was interpreted as follows: synergy, FICI ≤0.5; indifference, 0.5 <FICI ≤4.0; antagonism, FICI >4.0. *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as internal quality control strains.

The *in vitro* antibacterial activities of each combination are compared in Table 1. In the synergy studies, the combination of carbapenem (IMI or MEM) with amikacin (AMK) exhibited the best activity, which showed synergistic against about 50% of tested strains. And the following were SUL plus AMK and SUL plus carbapenem (IMI and MEM). The only antagonism effect happened in the combination between AMK and CIP. We found that antimicrobial agents in combination with AMK would have relative higher synergy response while the combination with CIP primarily produces indifferent response.

The ideal therapy approach to microbial infections should be based on the evaluation of individual isolate susceptibility pattern. Considering carbapenem-resistant *A. baumannii* strains were usually resistant to all classes of antimicrobials other than tigecycline and colistin, the overall treatment strategy generally depended on the susceptibility of carbapenems. For those carbapenem-resistant *A. baumannii*, colistin, tigecycline, and rifampicin may be the alternatives; however, these agents were generally considered as the last choice for MDR *A. baumannii* and they also had obvious limits as described previous.[1,2] The combination of different antimicrobial agents was another strategy to overcome these

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Table 1: The percentage of the FICI of the six antimicrobial agents combination with each other against 116 MDR *Acinetobacter baumannii*

Antibacterial agents	Synergy FIC ≤0.5	Indifference 0.5< FIC ≤4.0	Antagonism FIC >4.0
IMI + AMK	47.41 (55/116)	52.59 (61/116)	–
IMI + CIP	1.72 (2/116)	98.28 (114/116)	–
IMI + CPS	15.52 (18/116)	84.48 (98/116)	–
IMI + SUL	22.41 (26/116)	77.59 (90/116)	–
MEM + AMK	57.76 (67/116)	42.24 (49/116)	–
MEM + CIP	0.86 (1/116)	99.14 (115/116)	–
MEM + CPS	6.90 (8/116)	93.10 (108/116)	–
MEM + SUL	17.24 (20/116)	82.76 (96/116)	–
CIP + CPS	3.45 (4/116)	96.55 (112/116)	–
CIP + SUL	5.17 (6/116)	94.83 (110/116)	–
AMK + SUL	39.66 (46/116)	60.34 (70/116)	–
AMK + CIP	–	82.76 (96/116)	17.24 (20/116)

Data are shown as % (*n*/*N*). IMI: Imipenem; MEM: Meropenem; AMK: Amikacin; CIP: Ciprofloxacin; CPS: Cefoperazone/sulbactam; SUL: Sulbactam; FICI: Fractional inhibitory concentration index; MDR: Multidrug-resistant; FIC: Fractional inhibitory concentration.

MDR *A. baumannii*. On the one hand, combination of agents with different antimicrobial mechanisms may exert an enhanced pharmacodynamic effect, namely synergism. On the other hand, to a certain extent, combination treatment would prevent emergence of resistance.[4]

Our study found that AMK in combination with carbapenems (IMI and MEM) would produce relative higher synergy response, the following combination were SUL plus AMK and SUL plus carbapenems. The previous survey had shown that combinations of IMI or MEM with SUL or ampicillin/sulbactam were potential choice for the treatment of carbapenem-resistant strains. At present, clinical data about combination therapy was relative less.[5] The ideal therapy approach to infections should be initially based on the evaluation of *in vitro* susceptibility surveillance. In this study, we provided valuable *in vitro* data for clinicians' strategy against MDR *A. baumannii* infections through studying the synergy effect of six commonly used agents on large-scale samples, which partly represent the characteristics of China strains. Further studies to investigate *in vivo* effect for its clinical significance are needed.

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Conflicts of interest

There are no conflicts of interest.

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