



Efficacy of tigecycline monotherapy versus combination therapy with other antimicrobials against carbapenem-resistant *Acinetobacter baumannii* sequence type 2 in Heilongjiang Province

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Background: Selecting alternative antibiotic combinations as treatment options may help successfully manage carbapenem-resistant *Acinetobacter baumannii* (CRAB). This study aimed to determine the synergistic effects of tigecycline (TIG) monotherapy versus combination therapy with other antimicrobials against CRAB.

Methods: After performing biochemical identification assays, we detected oxacillin-hydrolyzing (OXA)-type carbapenemase genes in 35 CRAB isolates. The minimum inhibitory concentrations (MICs) and interactions of the test drugs were determined using the checkerboard assay with TIG, colistin (CST) and meropenem (MEM). Static time-kill assays were conducted to validate the synergistic effects of the most efficacious combination.

Results: The chromosomal gene, *bla*_{OXA-51-like}, was tested among all isolates, *bla*_{OXA-23-like} and *bla*_{OXA-24-like} were present in 91.4% and 25.7%, respectively. In the checkerboard assay, the combination of TIG and MEM displayed the highest rate of synergy (30.5%) against the 35 isolates. In contrast, the TIG-CST combination showed a higher indifference interaction rate (36.1%) than that of the TIG-MEM (16.7%) combination. Antagonism appeared in one isolate for the TIG-CST combinations. The static time-kill assays confirmed the superior synergistic effect of CST against the CRAB isolates.

Conclusions: TIG combined with CST exhibited early synergistic activity that was not sustained beyond 12 h. TIG combination therapy can only be recommended when other optimized therapeutics are unavailable.

Keywords: *Acinetobacter baumannii*; tigecycline (TIG); *in vitro*; colistin (CST)

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Introduction

In recent decades, carbapenem-resistant *Acinetobacter baumannii* (CRAB) has become one of the most important causative agents associated with hospital-acquired infections worldwide (1). Developing new antimicrobial agents and therapeutic strategies has been a major challenge in the field of infectious diseases. Various effective antibacterial drugs are available but often exert adverse effects on patients. Currently, tigecycline (TIG) is the best option for treating and controlling CRAB-related infections (2).

TIG is the irreplaceable member of the glycylcycline class of antimicrobial agents, the Food and Drug Administration (FDA) has been approved it to treat complicated skin-structure infections, intraabdominal infections and community-acquired pneumonia (3). TIG inhibits bacterial protein synthesis by acting on the 30S ribosomal subunit and prevents amino acids from incorporating and elongating peptide chains (4). Randomized trials have shown that use TIG alone may increase the risk of death, which further suggests that TIG is best used for combination therapy (5). However, because most of these researches concentrated on multisite infections with multiple pathogens, establishing the effect of TIG as a single agent against CRAB is difficult because of the many confounding factors. Thus, whether TIG is effective in treating CRAB-related infections remains unclear.

Therapeutic choices for treating *Acinetobacter spp.* are usually limited to polymyxins and TIG. Empiric antibiotic therapy for *A. baumannii* should be chosen based on local susceptibility patterns (6). The treatment should contain a broad-spectrum cephalosporin combined with a carbapenem. Fluoroquinolones, aminoglycosides, or colistin (CST) are second-line alternatives. Selecting appropriate alternative treatments with antibiotic combinations may help successfully manage CRAB infections.

Because TIG-based combination therapy is valuable in treating TIG-resistant *Acinetobacter baumannii*, we conducted this study on CRAB to assess the effectiveness of TIG alone or combined with other drugs in treating CRAB and to identify the forecasts of therapy success.

Methods

Collection of patients' clinical data and bacterial strains

Thirty-five CRAB clinical isolates were obtained from the First Affiliated Hospital of Jiamusi University between September 2013 and June 2015. *A. baumannii* was initially

identified by the Vitek 2 system (bioMérieux, Marcy-l'Étoile, France). Clinical characteristics of the CRAB-infected patients were collected, including age, sex, sample type, admission ward, prior antimicrobial use, recovery situation, and outcome. Of the 35 strains, 29 were isolated from sputum, three from cerebrospinal fluid, one from pus, one from blood, and one from wound secretions. *A. baumannii* ATCC 19606 and *Escherichia coli* ATCC 25922 were used as reference strains. The isolates were put away -80°C until use and subcultured on Columbia agar for *in vitro* testing.

Multilocus sequence typing (MLST) and detection of oxacillin-hydrolyzing (OXA)-type carbapenemase genes

β -lactamase-associated genes were amplified via PCR using primers as described previously (7). Table 1 lists several primer sets used to amplify β -lactamases of Ambler classes A, B, C, and D (*bla*_{OXA-23-like}, *bla*_{OXA-24-like}, and *bla*_{OXA-51-like}; <http://pubmlst.org/abaumannii/>) (8).

To estimate the relationship between MLST type and the isolates, isolates were arranged according to the time. Put the same isolates via PCR detected the genes encoding carbapenemases. Adopting BLAST (<http://blast.ncbi.nlm.nih.gov/>) (9) to compared nucleotide sequences gained from PCR sequencing. By PCR and sequencing analysis of seven housekeeping genes to performed MLST. Then compared the nucleotide sequences obtained sequencing with sequences preexisting in the MLST databases to distribute the allelic numbers and sequence types (STs).

Checkerboard assay for synergy testing

The minimum inhibitory concentrations (MICs) for TIG, CST and meropenem (MEM) were defined by agar dilution in accordance with CLSI recommendations. CST used in the research was purchased from Sigma-Aldrich (St. Louis, MO, USA). TIG was purchased from Wyeth Pharmaceutical Co. Ltd., and MEM was from Haibin Pharmaceutical Co., Shenzhen, China. According to the CLSI breakpoint criteria, the MIC results were explained.

In the guidelines, no breakpoints for TIG are used. So adopt the criteria of the United States FDA for Enterobacteriaceae for TIG (susceptibility, $\leq 2\ \mu\text{g/mL}$; resistance, $\geq 8\ \mu\text{g/mL}$) (10). Synergistic testing was performed in 96-well microdilution plates (8). The synergistic effect was assessed by the fractional inhibitory concentration index (FICI), which was calculated as follows:

Table 1 Clinical patient data for carbapenem-resistant *A. baumannii* isolates used and the results of β -lactamase genotyping, MICs and FICIs in this study

Isolate	Clinical sample	Clinical ward	Outcome	β -lactamase genotyping	MIC (μ g/mL)				FICI		
					TIG		MEM		Result	TIG + MEM	Result
					TIG	CST	MEM	CST	TIG + CST	TIG + MEM	Result
ATCC 19606	-	-	-	-	0.5	2	32	-	-	-	-
ATCC 25922	-	-	-	-	0.25	2	64	-	-	-	-
CRAB 02	Sputum	Emergency	Improved	OXA-23, OXA-51, ADC, TEM, OXA-24	0.25	2	64	1.25	Ind	1.125	Ind
CRAB 12	Sputum	Respiratory	Improved	OXA-23, OXA-51, ADC, TEM, OXA-24	0.5	1	32	1.125	Ind	0.625	Add
CRAB 22	PUS	Orthopedic	Cure	OXA-51, ADC, TEM, OXA-24, GES	0.25	2	64	0.625	Add	1.125	Ind
CRAB 33	Sputum	Emergency ICU	Improved	OXA-23, OXA-51, ADC, TEM, OXA-24	0.5	1	32	1.25	Ind	0.375	Syn
CRAB 42	Sputum	Geriatric	Improved	OXA-51, ADC, TEM, OXA-24, GES, SHV	0.5	1	64	1.125	Ind	0.5	Syn
CRAB 44	Sputum	ICU	Improved	OXA-23, OXA-51, ADC, TEM, OXA-24, GES	0.5	2	8	2.0625	Ant	0.625	Add
CRAB 51	CSF	Thoracic surgery	Improved	OXA-23, OXA-51, ADC, TEM	0.25	1	64	1	Add	0.5	Syn
CRAB 52	Sputum	ICU	Improved	OXA-23, OXA-51, ADC, TEM, GES	0.5	2	64	0.75	Add	0.625	Add
CRAB 63	Blood	ICU	Improved	OXA-23, OXA-51, ADC, OXA-24	0.5	1	64	1.125	Ind	0.25	Syn
CRAB 68	Sputum	Emergency ICU	Improved	OXA-23, OXA-51, TEM, OXA-24	0.5	1	128	1.125	Ind	0.25	Syn
CRAB 71	Sputum	Emergency ICU	Die	OXA-23, OXA-51, ADC, TEM, OXA-24	0.25	2	32	1	Add	0.625	Add
CRAB 73	Sputum	Emergency ICU	Die	OXA-23, OXA-51, ADC, TEM	0.25	1	32	1	Add	1.5	Ind
CRAB 75	Sputum	Emergency	Improved	OXA-23, OXA-51, ADC, TEM, GES	0.25	4	64	0.75	Add	0.625	Add
CRAB 77	Sputum	Neurology	Unhealed	OXA-23, OXA-51, ADC, TEM	0.5	4	32	0.375	Syn	0.625	Add
CRAB 82	Sputum	ICU	Improved	OXA-23, OXA-51, ADC, TEM	0.25	1	64	1	Add	0.625	Add
CRAB 84	Sputum	Respiratory	Improved	OXA-23, OXA-51, ADC, TEM	0.5	4	64	0.375	Syn	0.375	Syn
CRAB 101	Sputum	Geriatric	Improved	OXA-23, OXA-51, ADC, TEM	0.5	2	1	1	Add	0.75	Add
CRAB 102	Wounds secretions	Orthopedics trauma	Improved	OXA-23, OXA-51, ADC	0.5	1	64	1	Add	0.25	Syn
CRAB 104	Sputum	Emergency	Cure	OXA-23, OXA-51, ADC, TEM	0.5	2	64	1.25	Ind	1	Add
CRAB 110	Sputum	Emergency ICU	Unhealed	OXA-23, OXA-51, ADC, TEM	0.5	2	16	1.25	Ind	0.25	Syn
CRAB 111	Sputum	ICU	Improved	OXA-23, OXA-51, ADC, TEM	0.5	2	64	1	Add	0.5	Syn
CRAB 114	Sputum	Emergency ICU	Unhealed	OXA-23, OXA-51, ADC, TEM	0.5	2	64	0.75	Add	0.625	Add
CRAB 116	Sputum	Nephrology	Improved	OXA-23, OXA-51, ADC, TEM	0.25	1	32	1.125	Ind	1.5	Ind
CRAB 118	CSF	Neurosurgery	Unhealed	OXA-23, OXA-51, ADC, TEM	0.25	4	16	0.625	Add	0.75	Add

Table 1 (continued)

Table 1 (continued)

Isolate	Clinical sample	Clinical ward	Outcome	β-lactamase genotyping	MIC (µg/mL)			FICI			
					TIG	CST	MEM	TIG + CST	Result	TIG + MEM	Result
CRAB 125	Sputum	ICU	Cure	OXA-23, OXA-51, ADC, TEM	0.25	2	64	1.125	Ind	1	Add
CRAB 126	Sputum	ICU	Die	OXA-23, OXA-51, ADC, TEM	0.25	2	32	0.625	Add	1.25	Add
CRAB 131	Sputum	ICU	Cure	OXA-23, OXA-51, ADC, TEM	0.5	2	64	1.25	Ind	1.125	Add
CRAB 132	Sputum	Emergency ICU	Unhealed	OXA-23, OXA-51, ADC, TEM	0.25	1	64	1.25	Ind	0.625	Add
CRAB 133	Sputum	Neurosurgery	Improved	OXA-23, OXA-51, ADC, TEM	0.25	4	64	0.625	Add	0.625	Add
CRAB 135	Sputum	ICU	Improved	OXA-23, OXA-51, ADC, TEM	1	2	16	0.75	Add	0.625	Add
CRAB 136	Sputum	ICU	Improved	OXA-23, OXA-51, ADC, TEM	0.5	2	64	0.75	Add	0.625	Add
CRAB 137	Sputum	ICU	Improved	OXA-23, OXA-51, ADC, TEM	0.5	1	128	1.25	Ind	0.625	Add
CRAB 138	Sputum	ICU	Improved	OXA-23, OXA-51, ADC, TEM, GES	0.25	2	64	0.5	Syn	0.375	Syn
CRAB 140	Sputum	Emergency ICU	Improved	OXA-51, ADC	1	2	32	0.75	Add	0.625	Add

CSF, cerebrospinal fluid examination; ICU, intensive care unit; MIC, minimum inhibitory concentrations; FICI, fractional inhibitory concentration index; TIG, tigecycline; CST, colistin; MEM, meropenem; syn, synergy; add, additive; ind, indifferent; ant, antagonistic; -, not tested.

$$FICI = MIC_{(a \text{ in combination})} / MIC_{(a)} + MIC_{(b \text{ in combination})} / MIC_{(b)}.$$

The FICI was interpreted as follows: synergistic: FICI is smaller 0.5; antagonistic: FICI greater than 4.0; and indifferent: $0.5 < FICI < 4.0$. Synergy was also defined as an SBPI > 2 as calculated using the checkerboard assay (11).

Time-kill assays

By the CLSI guidelines [2015], the time-kill assays were in progress in triplicate for four representative isolates. In short, concentrations of $1 \times$ and $0.5 \times$ MIC were prepared in Mueller-Hinton broth for TIG alone and combined with CST or MEM. The bacterial suspension was incubated at 37°C with swinging at 160 rpm for 24 h. We also had an antibiotic-free growth control. The predetermined time-points were 0, 4, 8, 12 and 24 h, 100-µL samples were obtained, then diluted, and spread on Mueller-Hinton agar plates to observe the colony-forming units (CFU) per mL. Establish a time-kill curve function relationship, The results are expressed as the difference in Log10 at each time point at 0 to 24 h. Comparing the antibiotics in combination to the most active drug at the stationary time-point, decrease of ≥ 3 Log10 indicated bactericidal, decrease of ≥ 2 Log10 was synergistic effects, while an increase of > 2 Log10 was antagonism (12).

Statement of ethics approval

The study protocol was approved by the Ethics Committee of Jiamusi University Clinical Medical College for research. The committee's reference number is 059. Individual informed consent was waived by the ethics committee listed above because this study used currently existing sample collected during the course of routine medical care and did not pose any additional risks to the patients.

Results

Collection of patients' clinical data and bacterial strains

Table 1 presents the patients' clinical data. Among these isolates, 45.7% were healed and they were from the intensive care unit, of whom, 25.7% were women with a median age of 53 years. The male patients had a median age of 64 years. Of the isolates, 80% were collected from the respiratory tract, with the remainder having been obtained from other sources. All 35 CRAB isolates were susceptible to TIG, while 85.7% and 3.0% were susceptible to CST

Table 2 The mic_{50} and mic_{90} values and susceptibility

Antibiotics	MIC result ($\mu\text{g/mL}$)			Susceptibility (%)
	50%	90%	Range	
Tigecycline	0.5	0.5	0.25–1	100
Colistin	2	4	1–4	85.7
Meropenem	64	64	1–128	3.0

MIC, minimum inhibitory concentrations.

Table 3 Results of the checkerboard synergy test of combination of tigecycline with two different antibiotics against carbapenem-resistant *Acinetobacter baumannii* isolated

Combination	Result			
	Synergy	Additive	indifferent	Antagonist
Tigecycline + Colistin	8.5%	51.5%	37.2%	2.8%
Tigecycline + Meropenem	28.6%	60.0%	11.4%	0.0%

and MEM, respectively. *Table 2* presents the MIC_{50} and MIC_{90} values and susceptibility results.

MLST and OXA carbapenemase gene detection

MLST revealed that all CRAB isolates were ST2. The PCR results showed that several CRAB isolates carried multiple resistance genes. The PCR assay for common carbapenemase genes showed that *bla*_{OXA-23-like} and *bla*_{OXA-24-like} were present in 91.4% and 25.7% of the isolates, respectively, and seven isolates harbored both *bla*_{OXA-23-like} and *bla*_{OXA-24-like} genes. The chromosomal *bla*_{OXA-51-like} gene was detected in all tested isolates (*Table 1*).

Checkerboard synergy analysis

Table 1 shows the checkerboard synergy testing results for the 35 CRAB isolates. The TIG-CST combination showed a synergistic effect against three of the 35 tested isolates (8.5%), an additive effect against 18 isolates (51.5%), and an indifferent effect against 13 isolates (37.2%), with FICI values of 0.375–2.0625. The TIG-MEM combination showed an additive effect against 21 strains (60.0%) and an indifferent effect against four strains (11.4%); 4 of these carried *bla*_{OXA-24-like}, with FICI values of 0.375–1.5. *Table 3* shows the results of the combination checkerboard synergy testing.

Time-kill assays

For the time-kill studies, four isolates with different carbapenem-resistance mechanisms and belonging to the same STs were exposed to TIG alone or in combination at concentrations of 1× or 0.5× the MICs of TIG. At 0.5× the MICs of TIG, the combination with CST showed both synergy and bactericidal activity in two isolates carrying *bla*_{OXA-23-like} and *bla*_{OXA-24-like} (CRAB22 and CRAB52). CRAB42 also carried *bla*_{OXA-24-like}, which showed antagonistic activity at 24 h. All isolates showed antagonistic activity toward MEM (*Figure 1*). The combination of 1× the MIC of TIG with high-concentration CST showed synergy against 75% of the isolates (*Figure 2*). Isolates CRAB52 and CRAB125 carried *bla*_{OXA-23-like} and exhibited synergy. These results indicate that the combination of TIG and CST is effective against CRAB isolates. Furthermore, the combinations of TIG with high or low concentrations of MEM were antagonistic. Compared with the combination antibiotics, the single drug CST had better antibacterial effects, even at low concentrations (4 $\mu\text{g/mL}$).

Discussion

Acinetobacter baumannii is a pathogen in hospitals characterized by inborn and acquired antimicrobial resistance (13). Of main concern is the increased incidence of carbapenem resistance, which has risen markedly in the past decade, and there are few treatment options (14).

Of CRAB isolates, production of acquired carbapenem-hydrolyzing class D β -lactamases, which can confer carbapenem resistance (15), and overproduction of intrinsic class D β -lactamase *bla*_{OXA-51-like} family members are the most prevalent mechanisms of carbapenem resistance. The *bla*_{OXA-23-like}, *bla*_{OXA-24-like} and *bla*_{OXA-58-like} genes and the recently discovered *bla*_{OXA-143-like} and *bla*_{OXA-253-like} genes are globally associated with CRAB emergence (16). *Bla*_{OXA-23-like} is the most prevalent enzyme associated with CRAB infections. Significant associations of the *bla*_{OXA-23-like} gene and carbapenem resistance have been observed, and this phenomenon is consistent with our findings. The chromosomal gene *bla*_{OXA-51-like} was detected in all isolates, and *bla*_{OXA-23-like} was present in 91.4% of the isolates.

Although the clinical role of TIG for treating CRAB infections remains controversial because of limited efficacy and increasing resistance, TIG remains a beneficial option in specific situations such as when given as large-dose therapy or as part of combination regimens (17).

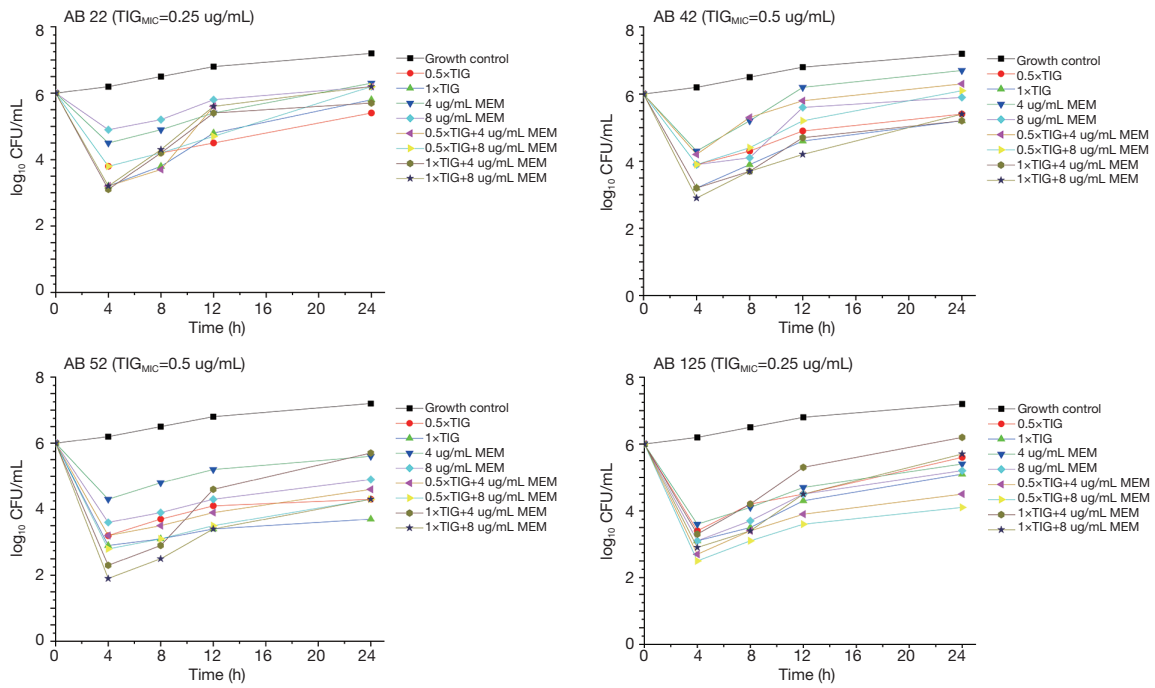


Figure 1 Results of dynamic time-kill experiments with tigecycline alone and in combination with meropenem.

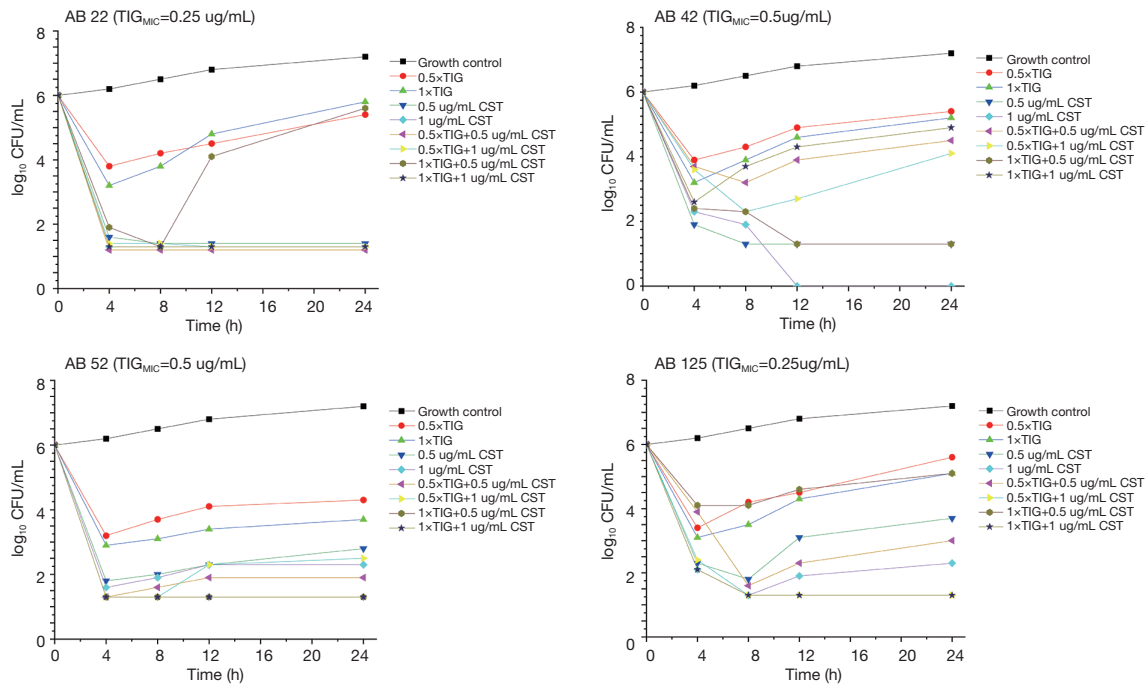


Figure 2 Results of dynamic time-kill experiments with tigecycline alone and in combination with colistin.

The present study demonstrated a difference in the effectiveness of TIG combined with CST or MEM against CRAB isolates from northeastern China, and all CRAB isolates were susceptible to TIG. However, using TIG as a monotherapy promotes the emergence of heteroresistant *A. baumannii* isolates and the development of TIG resistance among other bacterial species. The MICs of the drugs in the combination treatments were reduced compared with the MIC of each drug alone, thereby reducing the required dose. When TIG was used alone, the TIG concentration was very low. The MIC showed that TIG inhibited 94% of the bacteria at less than or equal to 0.5 µg/mL based on the criteria of the United States FDA; thus, all CRAB isolates were sensitive. The MIC results showed that all isolates were sensitive to TIG when they carried the *bla*_{OXA-23-like} or *bla*_{OXA-24-like} genes. In addition, 14.30% of the CRAB isolates were resistant to CST and carried *bla*_{OXA-23-like}.

In this study, 32 isolates carried the *bla*_{OXA-23-like} gene. The TIG-MEM combination showed a low rate of synergy (in 28.1% of strains), and 44.4% of the nine isolates with *bla*_{OXA-24-like} showed synergism. The time-kill study revealed that MEM monotherapy had little discernible effect. Antagonism was dominant in the TIG plus MEM combinations, which may be because the β-lactam antibiotics act within the periplasmic space and primarily pass through the outer membrane (18). TIG plays a part in the cytoplasm by inhibiting the 30S subunit of the ribosome and must through two membranes (19). However, we found that the results for TIG-MEM differed between the checkerboard synergy analysis and the time-kill assays. CRAB42 had a FICI of 0.5 on the checkerboard synergy analysis, representing synergy, but this isolate showed antagonism in the time-kill assays. The difference in this result was due to the time-kill assays; we used clinically achievable concentrations to determine the antibacterial effects. Therefore, the results obtained in our study are more useful for clinical practice. We collected specimens from Heilongjiang Province, which were all ST2 type. These specimens differed from those in Park *et al.*'s study (20); therefore, the results differed, although all specimens contained *bla*_{OXA-23-like}. Thus, the impact of different MLST-typing methods on efficacy requires further verification.

Hagihara *et al.* (21) found that CST was responsible for most of the effect against CRAB isolates tested with CST and TIG. Similar to our observations, TIG monotherapy showed a lack of activity. CST alone achieved more significant bactericidal activity than did TIG, especially

the TIG/CST combination. The results from the present study are consistent with the findings of Rao *et al.* (22), who revealed that CST combined with TIG against CRAB isolates in the time-kill assay resulted in early bactericidal activity within 4 h at concentrations sustained for 24 h. When the CST concentration reached 1 µg/mL at 24 h, three isolates had synergy due to the increased active uptake of TIG into the cell, resulting in sufficient intracellular concentrations to slow bacterial growth by inhibiting protein synthesis. In addition, CST may increase TIG penetration at the action site by permeabilizing the outer bacterial membrane.

This study had several limitations. First, the bactericidal effects of the combinations were only examined for 24 h. Therefore, whether resistance and regrowth occurred after 24 h is unknown. In addition, only four CRAB strains were used in the present study; thus, the representativeness of these results must be further verified with more isolates from other species. However, to our knowledge, this is the first report on TIG combination therapy against *A. baumannii* in Hei Longjiang Province.

Conclusions

TIG combination therapy does not eradicate microbes, but it reduces bacterial loads and adverse drug reactions. CST is currently unavailable on the Chinese market. Therefore, TIG combination therapy may be a reasonable alternative before more optimized treatments become available. However, TIG is a bacteriostatic agent and may not be recommended as a first-line treatment based on current research that does not show a benefit toward the end result. Further studies based on PK/PD parameter combination therapy should be performed to explore the optimal dose, route of administration, and optimal combination of TIG.

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Ethics Committee of Jiamusi University Clinical Medical College for research. The committee's reference number is 059. Individual informed consent was waived by the ethics committee listed above because this study used currently existing sample collected during the course of routine medical care and did not pose any additional risks to the patients.

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