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Original Article

In vitro activity of cefiderocol, cefepime/enmetazobactam, cefepime/zidebactam, eravacycline, omadacycline, and other comparative agents against carbapenem-non-susceptible *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolates associated from bloodstream infection in Taiwan between 2018–2020

Po-Yu Liu [a], Wen-Chien Ko [b], Wen-Sen Lee [c,d], Po-Liang Lu [e], Yen-Hsu Chen [e], Shu-Hsing Cheng [f,g], Min-Chi Lu [h], Chi-Ying Lin [i], Ting-Shu Wu [j], Muh-Yong Yen [k], Lih-Shinn Wang [l,m], Chang-Pan Liu [n,o], Pei-Lan Shao [p], Yu-Lin Lee [q,r], Zhi-Yuan Shi [a], Yao-Shen Chen [s,t], Fu-Der Wang [u,t], Shu-Hui Tseng [v], Chao-Nan Lin [w,x], Yu-Hui Chen [y], Wang-Huei Sheng [z], Chun-Ming Lee [aa,ab], Hung-Jen Tang [ac], Po-Ren Hsueh [z,ad,ae,*]

[a] *Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan*
[b] *Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan*
[c] *Division of Infectious Diseases, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan*
[d] *Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[e] *Department of Internal Medicine, Kaohsiung Medical University Hospital, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[f] *Department of Internal Medicine, Taoyuan General Hospital, Ministry of Health and Welfare, Taoyuan, Taiwan*

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* Corresponding author. Department of Laboratory Medicine, China Medical University Hospital, No. 2, Yude Road, North District, Taichung 404394, Taiwan.
E-mail address: hsporen@gamil.com (P.-R. Hsueh).

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[g] *School of Public Health, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan*
[h] *Department of Microbiology and Immunology, School of Medicine, China Medical University, Taichung, Taiwan*
[i] *Department of Internal Medicine, National Taiwan University Hospital Yunlin Branch, Yunlin, Taiwan*
[j] *Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan*
[k] *Division of Infectious Diseases, Taipei City Hospital, National Yang-Ming University, School of Medicine, Taipei, Taiwan*
[l] *Division of Infectious Diseases, Department of Internal Medicine, Buddhist Tzu Chi General Hospital, Hualien, Taiwan*
[m] *Tzu Chi University, Hualien, Taiwan*
[n] *Division of Infectious Diseases, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan*
[o] *MacKay Medical College, New Taipei City, Taiwan*
[p] *Department of Pediatrics, Hsin-Chu Branch, National Taiwan University Hospital, Hsin-Chu, Taiwan*
[q] *Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan*
[r] *Institute of Genomics and Bioinformatics, National Chung Hsing University, Taichung, Taiwan*
[s] *Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*
[t] *School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[u] *Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[v] *Center for Disease Control and Prevention, Ministry of Health and Welfare, Taiwan*
[w] *Department of Veterinary Medicine, College of Veterinary Medicine, National Pingtung University of Science and Technology, Pingtung, Taiwan*
[x] *Animal Disease Diagnostic Center, College of Veterinary Medicine, National Pingtung University of Science and Technology, Pingtung, Taiwan*
[y] *Infection Control Center, Chi Mei Hospital, Liouying, Taiwan*
[z] *Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*
[aa] *Department of Internal Medicine, St Joseph's Hospital, Yunlin County, Taiwan*
[ab] *MacKay Junior College of Medicine, Nursing, and Management, Taipei, Taiwan*
[ac] *Department of Medicine, Chi Mei Medical Center, Tainan, Taiwan*
[ad] *Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*
[ae] *Departments of Laboratory Medicine and Internal Medicine, China Medical University Hospital, School of Medicine, China Medical University, Taichung, Taiwan*

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Eravacycline

Abstract *Background/purpose:* This study aimed to investigate the *in vitro* susceptibilities of carbapenem-non-susceptible *Pseudomonas aeruginosa* (CNSPA) and *Acinetobacter baumannii* (CNSAB) isolates to cefiderocol, novel β-lactamase inhibitor (BLI) combinations, new tetracycline analogues, and other comparative antibiotics.
Methods: In total, 405 non-duplicate bacteremic CNSPA (n = 150) and CNSAB (n = 255) isolates were collected from 16 hospitals in Taiwan between 2018 and 2020. Minimum inhibitory concentrations (MICs) were determined using the broth microdilution method, and susceptibilities were interpreted according to the relevant guidelines or in accordance with results of previous studies and non-species-related pharmacokinetic/pharmacodynamic data.
Results: Among the isolates tested, cefiderocol demonstrated potent *in vitro* activity against CNSPA ($MIC_{50/90}$, 0.25/1 mg/L; 100% of isolates were inhibited at ≤4 mg/L) and CNSAB ($MIC_{50/90}$, 0.5/2 mg/L; 94.9% of isolates were inhibited at ≤4 mg/L) isolates. More than 80% of CNSPA isolates were susceptible to cefiderocol, ceftazidime/avibactam, ceftolozane/tazobactam, and amikacin, based on breakpoints established by the Clinical and Laboratory Standards Institute. Activities of new BLI combinations varied significantly. Tetracycline analogues, including tigecycline ($MIC_{50/90}$, 1/2 mg/L; 92.5% of CNSAB isolates were inhibited at ≤2 mg/L) and eravacycline ($MIC_{50/90}$, 0.5/1 mg/L; 99.6% of CNSAB isolates were inhibited at ≤2 mg/L) exhibited more potent *in vitro* activity against CNSAB than omadacycline ($MIC_{50/90}$, 4/8 mg/L).
Conclusions: The spread of CNSPA and CNSAB poses a major challenge to global health.

Significant resistance be developed even before a novel agent becomes commercially available. The development of on-site antimicrobial susceptibility tests for these novel agents is of great clinical importance.

Introduction

Carbapenems constitute the mainstay of therapy against infections caused by gram-negative bacilli.[1,2] However, the increased resistance to carbapenem, particularly in non-fermenting gram-negative bacilli,[3] greatly limits therapeutic options.[4,5] Carbapenem resistance is closely associated with increased mortality from *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infections.[6,7] The mortality rate could be as high as 30% and 80% in individuals infected with carbapenem-resistant *P. aeruginosa* and *A. baumannii*, respectively.[8,9] Prior inappropriate antimicrobial therapy is associated with a higher risk of mortality in individuals infected with both *P. aeruginosa* and *A. baumannii*.[6,10] Moreover, carbapenem resistance could serve as a primary cause for incorrect treatment and result in substantially worse outcomes.[11]

Carbapenem-resistant bacteria pose a threat worldwide; thus, the development of new antimicrobial agents is essential.[12] Novel antibacterial agents, such as cefiderocol, new β-lactamase inhibitor (BLI) combinations (cefepime/enmetazobactam, cefepime/zidebactam, cefoperazone/sulbactam, ceftazidime/avibactam, and ceftolozane/tazobactam), and new tetracycline analogues (eravacycline and omadacycline) have been used clinically over the past few years.[13,14] However, most of these novel agents are not globally available, and their geographic availability varies greatly.[15] In addition, commercial devices used for testing the antimicrobial susceptibilities of these new agents are not readily available in most clinical laboratories.[16] It is evident that these geographic variations have substantial effects on the trends in antimicrobial resistance.[17] Thus, it is crucial to conduct antimicrobial resistance surveillance in different regions.[18]

A nationwide surveillance study on monitoring resistance development against clinically significant bacteria isolated from hospitals throughout Taiwan, called the Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART), were conducted since 2002. Here, we investigated the *in vitro* susceptibilities of carbapenem-non-susceptible *P. aeruginosa* (CNSPA) and *A. baumannii* (CNSAB) clinical isolates, selected for analysis using the SMART program data for 2018–2020, to cefiderocol, new β-lactam/β-lactamase inhibitors, new tetracycline analogues, and relevant comparative agents.

Materials and methods

Bacterial isolates

The *P. aeruginosa* and *A. baumannii* isolates tested in this study were selected using the SMART program data between 2018 and 2020, via interregional coordination by Taiwan's Centers for Disease Control. Sixteen hospitals (11 medical centers and five regional hospitals) located in different parts of Taiwan (eight, four, three, and one from North, Central, South, and East Taiwan, respectively) participated in the surveillance study. Non-duplicated blood isolates were collected and stored at −70 °C in Tryptic Soy Broth (Difco Laboratories, Detroit, MI, USA) supplemented with 15% glycerol prior to testing. Species identification was performed at each site and confirmed by the central laboratory using matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Biotyper™, Bruker Daltonik GmbH, Bremen, Germany). *P. aeruginosa* (n = 150) and *A. baumannii* (n = 255) isolates were chosen based on their carbapenem-non-susceptible phenotype (imipenem minimum inhibitory concentration (MIC) > 2 mg/L), which was identified using the VITEK 2 system (bioMérieux, Marcy-l'Étoile, France).

Antimicrobial susceptibility testing

The broth microdilution method specified by the Clinical and Laboratory Standards Institute (CLSI) was used to determine the MICs for the following antimicrobial agents: cefiderocol, cefepime/enmetazobactam, cefepime/zidebactam, ceftazidime/avibactam, ceftolozane/tazobactam, cefoperazone/sulbactam, piperacillin/tazobactam, eravacycline, omadacycline, tigecycline, ceftazidime, cefepime, ciprofloxacin, levofloxacin, imipenem, meropenem, doripenem, amikacin, colistin, and polymyxin B (Table 1).[19] The Sensititre microbroth dilution method (Thermo Fisher Scientific, Waltham, MA, USA) was used to determine the MICs of all tested agents except cefiderocol, for which iron-depleted cation-adjusted Mueller-Hinton broth (ID-CAMHB) was used.[19] The MIC of cefiderocol was determined to be equal to the concentration in the first panel well, in which isolate growth was significantly reduced (i.e., its appearance was similar to a button < 1 mm in diameter or slightly turbid), relative to the concentration in the ID-well showing CAMHB control growth, which indicated that significant growth had occurred (i.e., a colony ≥ 2 mm in diameter was formed).[13,19]

The MICs of other antimicrobial agents were defined as the lowest concentrations that inhibited the visible growth of microorganisms. Enmetazobactam, avibactam, and tazobactam were present at concentrations of 8 mg/L, 4 mg/L, and 4 mg/L in the cefepime/enmetazobactam, ceftazidime/avibactam, and ceftolozane/tazobactam and piperacillin/tazobactam combinations, respectively. Cefepime/zidebactam and cefoperazone/sulbactam were present in a 1:1 ratio. The MICs of BLI combinations were reported only for the β-lactam co-drug. The quality control

strains used for each day of testing included *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853.

CLSI interpretive criteria, when available, were used to interpret the MICs of tested comparative agents.[19] For comparison, the CLSI *P. aeruginosa* criteria for cefepime alone (susceptible/intermediate/resistant: 8/16/32 mg/L) were applied to cefepime-enmetazobactam and cefepime-zidebactam, in accordance with the results of previous studies and non-species-related pharmacokinetic/pharmacodynamic data.[20] Currently, the CLSI and European Committee on Antimicrobial Susceptibility Testing do not assign breakpoints for eravacycline and omadacycline. The US Food and Drug Administration has assigned eravacycline and omadacycline breakpoints for selected microorganisms. The MIC values of eravacycline and omadacycline used against *P. aeruginosa* and *A. baumannii* were evaluated in this study.

Results

The *in vitro* activities of cefiderocol and the comparative agents used against 405 CNSPA and CNSAB isolates are summarized in Table 1. Among the 150 imipenem-non-susceptible *P. aeruginosa* isolates, 66.7% were not susceptible to meropenem, and ≥80% were susceptible to cefiderocol, ceftazidime/avibactam, ceftolozane/tazobactam, and amikacin. Cefiderocol concentrations of 0.25 and 1 mg/L inhibited 50% (MIC_{50}) and 90% (MIC_{90}) of CNSPA, respectively (Fig. 1). The MIC range of cefiderocol, used against CNSPA, was 0.064 mg/L, with all tested isolates falling within the susceptible category, according to current CLSI criteria. Moreover, 96% and 98.7% of the isolates were inhibited at concentrations of ≤1 and ≤ 2 mg/L, respectively. Amikacin ($MIC_{50/90}$, 4/8 mg/L; 96.6% of isolates were susceptible), ceftazidime/avibactam ($MIC_{50/90}$, 4/32 mg/L; 81.3% of isolates were susceptible), and ceftolozane/tazobactam ($MIC_{50/90}$, 2/8 mg/L; 81.3% of isolates were susceptible) were also active, whereas ceftazidime ($MIC_{50/90}$, 8/128 mg/L), cefepime ($MIC_{50/90}$, 8/32 mg/L), levofloxacin ($MIC_{50/90}$, 4/32 mg/L), and ciprofloxacin ($MIC_{50/90}$, 1/32 mg/L) were less active.

Cefepime and companion BLI combinations exhibited variable anti-bacterial activities against CNSPA isolates. MICs for cefepime/enmetazobactam ($MIC_{50/90}$, 8/32 mg/L) ranged from 0.5% to 32 mg/L, with 58% of isolates being inhibited at ≤ 8 mg/L and 38.7% being inhibited at ≤ 4 mg/L (Fig. 2). Cefepime/zidebactam had an $MIC_{50/90}$ value of 4/8 mg/L for this set of isolates, with MICs ranging from 0.5 to 128 mg/L, and they inhibited 94.7% of isolates at concentrations of ≤8 mg/L. The application of a breakpoint of 8 mg/L rendered 58% and 94.7% of CNSPA isolates susceptible to cefepime/enmetazobactam and cefepime/zidebactam, respectively.

Overall, widely available antibiotics, including ceftazidime ($MIC_{50/90}$, >128/>128 mg/L), cefepime ($MIC_{50/90}$, 128/>128 mg/L), levofloxacin ($MIC_{50/90}$, 16/128 mg/L), ciprofloxacin ($MIC_{50/90}$, >128/>128 mg/L), and amikacin ($MIC_{50/90}$, >64/>64 mg/L), demonstrated limited activity against CNSAB. A single isolate remained susceptible to meropenem, with an MIC of 2 mg/L; the MICs of all other antibiotics ranged from 4 to ≥64 mg/L. Doripenem was active with an MIC of ≤2 mg/L for 2/255 isolates; all other compounds exhibited MICs ranging from 8 to ≥64 mg/L.

Cefiderocol was the most active compound tested against CNSAB, with $MIC_{50/90}$ values of 0.5/2 mg/L. In addition, 83.1% and 94.9% of the isolates were inhibited at ≤1 and ≤ 4 mg/L, respectively (Fig. 1). In contrast, cefepime ($MIC_{50/90}$, 128/>128 mg/L), meropenem ($MIC_{50/90}$, >64/>64 mg/L), ciprofloxacin ($MIC_{50/90}$, >128/>128 mg/L), and amikacin ($MIC_{50/90}$, >64/>64 mg/L) were active against only 4.3%, 0.4%, 7.5%, and 17.2% of isolates, respectively, at the current CLSI susceptibility breakpoint (Table 1).

Among the 255 isolates of CNSAB, cefepime/enmetazobactam, cefepime/zidebactam, and ceftolozane/tazobactam had similar activity levels, with $MIC_{50/90}$ values of >64/>64, 32/64, and 64/>64 mg/L, respectively (Fig. 3). Tigecycline ($MIC_{50/90}$, 1/2 mg/L; 92.5% of isolates were inhibited at ≤2 mg/L) and eravacycline ($MIC_{50/90}$, 0.5/1 mg/L; 99.6% of isolates were inhibited at ≤2 mg/L) exhibited more potent *in vitro* activity against CNSAB than omadacycline ($MIC_{50/90}$, 4/8 mg/L) (Fig. 4).

Discussion

The global spread of carbapenem non-susceptibility has become a major threat in clinical and public health settings.[21,22] CNSPA and CNSAB are often multi-drug-resistant; thus, therapeutic options are limited.[23] The development and improvement of novel antibiotics represents a solution.[24] However, resistance to a novel antibiotic may exist even before it becomes commercially available.[25] Hence, antimicrobial stewardship policies must be optimized, to control the rapid emergence and spread of resistance to novel agents.[26] Antimicrobial resistance surveillance, at both the local and global scale, would not only provide valuable data to guide empiric therapy and antimicrobial stewardship measures, but also benefit the field of antibiotic research and development.[12,18]

In this study, we demonstrated the potent activity of cefiderocol against CNSPA (MIC50/90, 0.25/1 mg/L) and CNSAB (MIC50/90, 0.5/2 mg/L). Cefiderocol, a novel siderophore cephalosporin, forms an extracellular complex with free ferric iron, which results in its transport through the outer cell membrane, after which it exhibits bactericidal activity via the inhibition of cell wall synthesis.[27] During a surveillance study in Taiwan during 2016–2017, the MICs of cefiderocol were found to be ≤ 1 mg/L for 91% of imipenem-resistant *P. aeruginosa* isolates and ≤4 mg/L for 88% of imipenem-resistant *A. baumannii* isolates.[13] These findings are consistent with data from other geographic regions worldwide, suggesting that cefiderocol consistently exhibits a high level of potency against CNSPA and CNSAB.[28]

The activities of new BLI combinations varied significantly according to the regimen. More than 80% of CNSPA isolates were susceptible to ceftazidime/avibactam (81.3%) and ceftolozane/tazobactam (81.3%). Cefepime/enmetazobactam inhibited 84% of CNSPA isolates at an MIC of ≤16 mg/L, whereas cefepime/zidebactam inhibited 94.7% of CNSPA isolates at an MIC of ≤8 mg/L. Ceftolozane/tazobactam retained a significant level of activity against *P. aeruginosa* with an elevated efflux, derepressed

Table 1 *In vitro* activities of cefiderocol, novel β-lactamase inhibitor combinations, new tetracycline analogues, and other comparative antibiotics against bacteremic and carbapenem-non-susceptible *P. aeruginosa* and *A. baumannii* isolates.

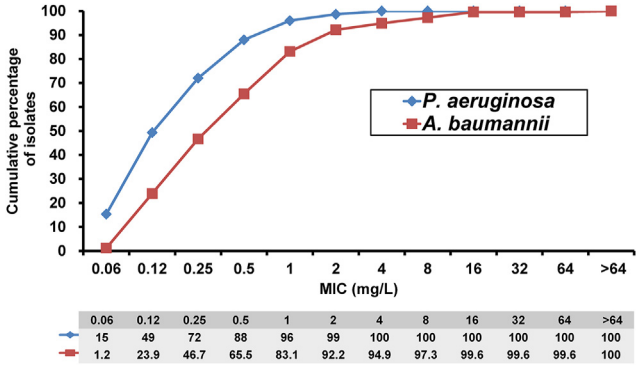
Species (no. of isolates)/agent	MIC (mg/L)			No. (%) of isolates and their susceptibility category[a]		
	Range	MIC_{50}	MIC_{90}	S	I	R
***P. aeruginosa* (*n* = 150)**						
Cefiderocol	0.06 to 4	0.25	1	150 (100)	0	0
Ceftazidime/avibactam	1 to > 64	4	32	122 (81.3)	0	28 (18.7)
Cefepime/enmetazobactam[b]	0.5 to > 64	8	32	87 (58.0)	39 (26.0)	24 (16.0)
Cefepime/zidebactam[b]	0.5 to > 128	4	8	142 (94.7)	6 (4.0)	2 (1.3)
Ceftolozane/tazobactam	0.5 to > 64	2	8	122 (81.3)	13 (8.7)	15 (10.0)
Cefoperazone/sulbactam	4 to > 64	32	>64	NA	NA	NA
Piperacillin/tazobactam	2 to > 128	32	>128	73 (48.7)	21 (14.0)	56 (37.3)
Eravacycline	0.5 to 32	8	16	NA	NA	NA
Omadacycline	4 to > 32	>32	>32	NA	NA	NA
Ceftazidime	1 to > 128	8	128	80 (53.3)	10 (6.7)	60 (40)
Cefepime	1 to > 128	8	32	81 (54.0)	28 (18.7)	41 (27.3)
Levofloxacin	0.25 to > 128	4	32	63 (42)	10 (6.7)	77 (51.3)
Ciprofloxacin	0.06 to 128	1	32	73 (48.7)	12 (8.0)	65 (43.3)
Imipenem	4 to > 128	16	32	0	35 (23.3)	115 (76.7)
Doripenem	0.25 to > 64	4	16	59 (39.3)	37 (24.7)	54 (36.0)
Meropenem	0.12 to > 64	4	16	50 (33.3)	30 (20.0)	70 (46.7)
Amikacin	≤1 to > 64	4	8	145 (96.6)	1 (0.7)	4 (2.7)
Colistin	0.25 to > 64	2	2	0	140 (93.3)	10 (6.7)
Polymyxin B	0.25 to > 64	2	2	0	143 (95.3)	7 (4.7)
***A. baumannii* (*n* = 255)**						
Cefiderocol	0.06 to > 64	0.5	2	242 (94.9)	6 (2.4)	7 (2.7)
Cefepime/enmetazobactam	≤0.03 to > 64	>64	>64	NA	NA	NA
Cefepime/zidebactam	1 to >128	32	64	NA	NA	NA
Ceftolozane/tazobactam	≤0.03 to > 64	64	>64	NA	NA	NA
Cefoperazone/sulbactam	4 to > 64	>64	>64	NA	NA	NA
Tigecycline	0.06 to 8	1	2	NA	NA	NA
Eravacycline	≤0.03 to 4	0.5	1	NA	NA	NA
Omadacycline	0.12 to 32	4	8	NA	NA	NA
Ceftazidime	4 to > 128	>128	>128	11 (4.3)	8 (3.2)	236 (92.5)
Cefepime	2 to > 128	128	>128	11 (4.3)	8 (3.2)	236 (92.5)
Levofloxacin	0.12 to > 128	16	128	20 (7.8)	9 (3.5)	226 (88.7)
Ciprofloxacin	0.12 to > 128	>128	>128	19 (7.5)	0	236 (92.5)
Imipenem	4 to > 128	64	128	0	2 (0.8)	253 (99.2)
Doripenem	1 to > 64	64	>64	2 (0.8)	0	253 (99.2)
Meropenem	2 to > 64	>64	>64	1 (0.4)	1 (0.4)	253 (99.2)
Amikacin	≤1 to > 64	>64	>64	44 (17.2)	15 (5.9)	196 (76.9)
Colistin	0.25 to > 64	1	2	0	243 (95.2)	12 (4.8)
Polymyxin B	0.25 to > 64	1	2	0	244 (95.7)	11 (4.3)

[a] Susceptibilities, when available, were determined according to MIC breakpoints established by CLSI.
[b] Susceptibility was determined in accordance with previous studies and non-species-related PK/PD data.
MIC, minimum inhibitory concentration; S, susceptible; I, intermediate; R, resistant; NA, not applicable.

AmpC, or loss of OprD, which suggests the existence of resistance mechanisms in CNSPA isolates.[29] A previous study in Taiwan demonstrated that the overproduction of active efflux pumps and variations in OprD were the main mechanisms for the development of imipenem resistance in *P. aeruginosa*.[30] The trends and implications of resistance development after the introduction of a novel agent into clinical settings needs further investigation. Our results are comparable with those of a previous study on carbapenem-resistant *P. aeruginosa* isolates in the U.S., which demonstrated that cefepime/zidebactam inhibits 77% of CNSPA isolates at an MIC of ≤8 mg/L.[31]

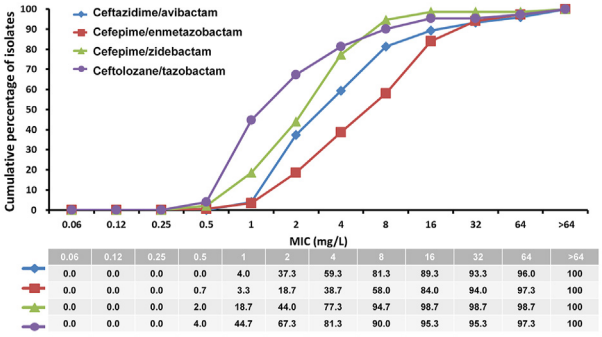
Cefepime/enmetazobactam, cefepime/zidebactam, and ceftolozane/tazobactam exhibited MIC_{90} values of ≥64 mg/L against CNSAB isolates. Similar findings have shown that the MICs of cefepime/enmetazobactam, cefepime/zidebactam, and ceftolozane/tazobactam increased in tandem with an increase in the CNSAB concentration.[29,31,32] Notably, certain β-lactamases were associated with higher MICs. For example, the presence of OXA-23 and OXA-24/40 in *A. baumannii* was associated with higher MICs for cefepime/enmetazobactam.[32]

Tetracycline analogues demonstrated comparable levels of activity against CNSAB. Tigecycline (MIC50/90, 1/



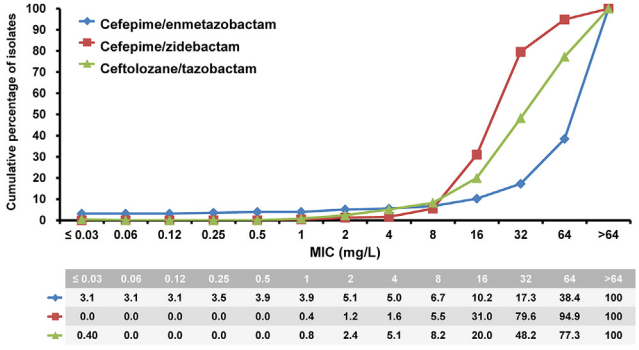
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
P. aeruginosa	15	49	72	88	96	99	100	100	100	100	100	100
A. baumannii	1.2	23.9	46.7	65.5	83.1	92.2	94.9	97.3	99.6	99.6	99.6	100

Figure 1. Cumulative percent distribution of isolates of carbapenem-non-susceptible *P. aeruginosa* and *A. baumannii* isolates in the presence of cefiderocol



	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ceftazidime/avibactam	0.0	0.0	0.0	0.0	4.0	37.3	59.3	81.3	89.3	93.3	96.0	100
Cefepime/enmetazobactam	0.0	0.0	0.0	0.7	3.3	18.7	38.7	58.0	84.0	94.0	97.3	100
Cefepime/zidebactam	0.0	0.0	0.0	2.0	18.7	44.0	77.3	94.7	98.7	98.7	98.7	100
Ceftolozane/tazobactam	0.0	0.0	0.0	4.0	44.7	67.3	81.3	90.0	95.3	95.3	97.3	100

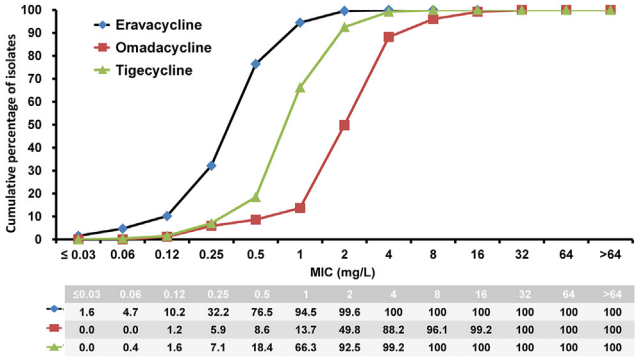
Figure 2. Cumulative percent distribution of minimum inhibitory concentrations (MICs) of ceftazidime/avibactam, cefepime/enmetazobactam, cefepime/zidebactam, and ceftolozane/tazobactam among carbapenem-non-susceptible *P. aeruginosa*.



	≤ 0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Cefepime/enmetazobactam	3.1	3.1	3.1	3.5	3.9	3.9	5.1	5.0	6.7	10.2	17.3	38.4	100
Cefepime/zidebactam	0.0	0.0	0.0	0.0	0.0	0.4	1.2	1.6	5.5	31.0	79.6	94.9	100
Ceftolozane/tazobactam	0.40	0.0	0.0	0.0	0.0	0.8	2.4	5.1	8.2	20.0	48.2	77.3	100

Figure 3. Cumulative percent distribution of minimum inhibitory concentrations (MICs) of cefepime/enmetazobactam, cefepime/zidebactam, and ceftolozane/tazobactam among carbapenem-non-susceptible *A. baumannii*.

2 mg/L), eravacycline (MIC50/90, 0.5/1 mg/L), and omadacycline (MIC50/90, 4/8 mg/L) inhibited 92.5%, 99.6%, and 88.2% of isolates at concentrations $\leq$ 2 mg/L, $\leq$ 2 mg/L, and $\leq$4 mg/L, respectively. It has been reported that omadacycline (MIC50/90, 2/4 mg/L) and eravacycline



	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Eravacycline	1.6	4.7	10.2	32.2	76.5	94.5	99.6	100	100	100	100	100	100
Omadacycline	0.0	0.0	1.2	5.9	8.6	13.7	49.8	88.2	96.1	99.2	100	100	100
Tigecycline	0.0	0.4	1.6	7.1	18.4	66.3	92.5	99.2	100	100	100	100	100

Figure 4. Cumulative percent distribution of minimum inhibitory concentrations (MICs) of eravacycline, omadacycline, and tigecycline among carbapenem-non-susceptible *A. baumannii*.

(MIC50/90, 0.5/1 mg/L) inhibited 91.5% and 92.5% of *A. baumannii* isolates, respectively, at $\leq$4 mg/L, regardless of carbapenem susceptibility.[33,34] A similar pattern of activity between carbapenem-non-susceptible and carbapenem-susceptible *A. baumannii* could be the result of independent mechanisms for the development of carbapenem resistance.[35]

The generation of accurate antimicrobial susceptibility test reports by clinical laboratories in a timely manner is the cornerstone of successful drug-resistant infection management and every antimicrobial stewardship program.[36,37] However, there is a significant lag between the launch of novel antimicrobials and wide availability of commercial antimicrobial susceptibility testing solutions.[16,38] This lag is greater in developing countries, where the infectious disease burden and resistance rate are also high.[39,40] Our data support the need for on-site antimicrobial susceptibility tests for these novel agents. Furthermore, further investigations are needed to decipher the underlying mechanisms of resistance to these novel antimicrobials. For example, 10% of CNSPA isolates were resistant to ceftolozane/tazobactam in our study. We need to further study whether metallo-β-lactamases, GES carbapenemase, or VEB extended-spectrum β-lactamases occurred in these isolates[29]

The current study has several limitations. First, the genetic background of CNSPA and CNSAB isolates is unknown. This would hamper the analysis and interpretation of complicated results. Second, the genospecies of *A. baumannii* were not available; thus, inter-genospecies differences in resistance profiles could not be observed.[41] Third, in this study, we used imipenem to phenotypically define carbapenem-non-susceptibility. Some strains may still be susceptible to meropenem. Finally, in the absence of clinical details, the significance of the development of resistance in clinical outcomes remains unknown.

In conclusion, the spread of CNSPA and CNSAB poses a major challenge to global health. There is a great need to optimize antimicrobial stewardship programs while simultaneously developing novel antimicrobial agents. The development of on-site antimicrobial susceptibility tests for these novel agents is of great clinical importance.

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Ethics approval

This study was approved by the research ethics committees or institutional review boards of the 16 participating hospitals. The requirement of informed consent from each patient was waived.

Declaration of competing interest

The authors declare no conflict of interest.

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