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In vitro activity of cefiderocol and comparator antibiotics against multidrug-resistant non-fermenting Gram-negative bacilli

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Background: This study evaluated the *in vitro* activity of cefiderocol, ceftazidime/avibactam, and aztreonam/avibactam against clinically important multidrug-resistant non-fermenting Gram-negative bacilli.

Methods: Bacteraemic isolates of 126 multidrug-resistant *Acinetobacter baumannii* (MDRAB), 110 imipenem-resistant *Pseudamoas aeruginosa* [including 14 difficult-to-treat resistant *P. aeruginosa* (DTRPA)], 45 beta-lactam-non-susceptible *Burkholderia cepacia* complex (BCC), 47 levofloxacin or trimethoprim/sulfamethoxazole-non-susceptible *Stenotrophomonas maltophilia* and 22 ciprofloxacin-non-susceptible *Elizabethkingia* spp. collected between 2019 and 2021 were subjected to MIC determination for cefiderocol, ceftazidime/avibactam and aztreonam/avibactam.

Results: The $MIC_{50/90}$s of cefiderocol for drug-resistant *A. baumannii*, *P. aeruginosa*, BCC, *S. maltophilia* and *Elizabethkingia* spp. were 0.25/2, 0.25/1, ≤0.06/≤0.06, ≤0.06/0.25 and >32/>32 mg/L, respectively. Cefiderocol inhibited 94.4% (119/126) of MDRAB, 100% of imipenem-resistant *P. aeruginosa*, 100% of DTRPA and 100% of BCC at an MIC ≤4 mg/L, and 97.9% (46/47) of *S. maltophilia* at ≤1 mg/L. Ceftazidime/avibactam inhibited 76.4% (84/110) of imipenem-resistant *P. aeruginosa*, 21.4% (3/14) of DTRPA and 68.9% (31/45) of BCC at an MIC ≤8 mg/L. Aztreonam/avibactam had $MIC_{50/90}$s of 16/>32, 8/16 and 4/8 mg/L for imipenem-resistant *P. aeruginosa*, BCC and *S. maltophilia*, respectively. At ≤8 mg/L, aztreonam/avibactam inhibited 7.1% (1/14) of DTRPA and 93.6% (44/47) of *S. maltophilia* isolates. *Elizabethkingia* spp. demonstrated high MICs for cefiderocol, ceftazidime/avibactam and aztreonam/avibactam, with all MIC_{50}s and MIC_{90}s > 32 mg/L.

Conclusion: Cefiderocol may serve as an alternative treatment for multidrug-resistant *A. baumannii*, *P. aeruginosa*, BCC and *S. maltophilia* when other antibiotics have been ineffective or intolerable. The role of ceftazidime/avibactam and aztreonam/avibactam in the management of BCC or *S. maltophilia* infections warrants further investigation.

Introduction

Non-fermenting Gram-negative bacilli (NFGNB) are important healthcare-associated pathogens that cause human diseases and can spread in hospital environments. Among NFGNB, *Pseudamoas aeruginosa* and *Acinetobacter baumannii* are the most common microorganisms causing nosocomial infections. Other less common bacteria, such as *Stenotrophomonas maltophilia* and *Burkholderia* spp., may also result in serious infection in vulnerable hosts.[1]

Treatment of NFGNB infections is challenging because they are intrinsically resistant to many antibiotics through beta-lactamase production, drug efflux or decreased permeability.[2] Among these issues, beta-lactamase production is of special concern. In recent years, newer beta-lactam-beta-lactamase inhibitor combinations, such as ceftazidime/avibactam and aztreonam/avibactam, and a novel siderophore cephalosporin, cefiderocol, have been introduced to combat carbapenem-resistant GNB.[3] The addition of avibactam overcomes the bacterial-resistance to ceftazidime and aztreonam.[4] Cefiderocol binds to extracellular iron and is transported across the outer membrane through the iron transport system. These agents have shown a broad spectrum of activities against NFGNB.[3] Recent data regarding the activities of cefiderocol and ceftazidime/avibactam have mainly focused on *A. baumannii*, *S. maltophilia* and/or *P. aeruginosa*.[5,6] Data on the efficacy of these newer

antimicrobial agents, including aztreonam/avibactam, against other NFGNB species are limited.

To address this unmet medical need, in the present study, we investigated the susceptibilities of clinical important multidrug-resistant NFGNB to cefiderocol, ceftazidime/avibactam and aztreonam/avibactam.

Methods

Non-duplicate blood isolates of multidrug-resistant NFGNB collected from patients at National Taiwan University Hospital during 2019–2021 were included and subjected to *in vitro* susceptibility testing. Five NFGNB spp. were selected: (i) multidrug-resistant *A. baumannii* (MDRAB), defined as *A. baumannii* that showed non-susceptibility to ≥1 agent in ≥3 antimicrobial categories,[7] (ii) imipenem-resistant *P. aeruginosa* (IRPA), (iii) ceftazidime- and meropenem-non-susceptible *B. cepacia* complex (BCC), (iv) levofloxacin- or trimethoprim-sulfamethoxazole (TMP/SMX)-non-susceptible *S. maltophilia* and (v) ciprofloxacin non-susceptible *Elizabethkingia* spp. *P. aeruginosa* that is non-susceptible to piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem, ciprofloxacin and levofloxacin is defined as 'difficult-to-treat' resistant *P. aeruginosa* (DTRPA).[8] Identification for resistance to traditional antibiotics was performed using the VITEK-2 system (bioMérieux, Inc., Hazelwood, MO, USA). Species identification was performed using the matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Corporation, Billerica, MA, USA).

The MICs of cefiderocol, ceftazidime/avibactam and aztreonam/avibactam were determined using the broth microdilution method and interpreted according to CLSI guidelines.[9] Cefiderocol and avibactam were provided by Shionogi & Co., Ltd (Osaka, Japan). Ceftazidime and aztreonam were obtained from the United States Pharmacopeia and Sigma-Aldrich (MO, USA), respectively. As aztreonam/avibactam does not have approved susceptibility breakpoints for *P. aeruginosa*, the CLSI susceptible breakpoint for aztreonam (MIC ≤8 mg/L) for *P. aeruginosa* was taken as the reference to interpret the results with a fixed concentration of avibactam at 4 mg/L. All IRPA isolates were assessed for carbapenemase production using the modified carbapenem inactivation method per CLSI method.[9] Pulsed-field gel electrophoresis was performed on *Elizabethkingia* isolates as described protocol.[10] Isolates with 80% similarity in banding patterns were considered identical pulsotypes.

Differences in susceptibility between antimicrobial agents were compared using the chi-squared test or Fisher's exact test with Stata software (v.11; StataCorp, College Station, TX, USA). A two-tailed significance level of 0.05 was applied for all analyses.

Results

Between 2019 and 2021, 350 multidrug-resistant NFGNB isolates were collected, consisting of 126 MDRAB, 110 IRPA (including 14 DTRPA), 45 ceftazidime and meropenem-non-susceptible BCC, 47 levofloxacin or TMP/SMX-non-susceptible *S. maltophilia* and 22 ciprofloxacin-non-susceptible *Elizabethkingia* (21 *E. meningoseptica* and 1 *E. miricola*). The susceptibilities of these isolates to traditional antibiotics are shown in Table S1 (available as Supplementary data at *JAC-AMR* Online). None of the *P. aeruginosa* expressed a positive modified carbapenem inactivation method test result.

Table 1 presents the MIC results. Among MDRAB, cefiderocol exhibited an MIC range of ≤0.06 to >32 mg/L, with an MIC_{50} of 0.25 mg/L and an MIC_{90} of 2 mg/L. In addition, 94.4% of the MDRAB isolates were inhibited at ≤4 mg/L. Because ceftazidime/avibactam and aztreonam/avibactam are known to be inactive against carbapenem-resistant *A. baumannii* (CRAB),[1,3] the MICs of these two agents were determined for only 30 randomly selected MDRAB isolates. Both ceftazidime/avibactam and aztreonam/avibactam displayed high MICs against tested MDRAB. The 110 IRPA were 100% susceptible to cefiderocol. Among them, 14 DTRPA and the remaining 96 IRPA isolates showed the same MIC_{50} (0.25 mg/L) and MIC_{90} (1 mg/L) values. Overall, 76.4% (84/110) of IRPA were inhibited at ceftazidime/avibactam MIC ≤8 mg/L. Compared with 14 DTRPA isolates, the remaining 96 non-DTRPA had lower MIC_{50} values for ceftazidime/avibactam (16 versus 8 mg/L) and aztreonam/avibactam (32 versus 16 mg/L), and higher susceptibility rates to ceftazidime/avibactam (21.4% versus 84.4%, $P<0.001$) and aztreonam/avibactam (7.1% versus 43.8%, $P=0.013$).

For BCC isolates, the cefiderocol MICs ranged from ≤0.06 to 0.125 mg/L, with both the MIC_{50} and MIC_{90} being ≤0.06 mg/L. Compared with cefiderocol, ceftazidime/avibactam and aztreonam/avibactam showed much higher MIC_{50}/MIC_{90} values (8/32 mg/L and 8/16 mg/L, respectively) for these BCC isolates. Using the CLSI MIC breakpoints for *P. aeruginosa* as a reference, the susceptibility rates of BCC isolates to cefiderocol, ceftazidime/avibactam and aztreonam/avibactam would be 100%, 68.9% and 86.7%, respectively. Nine BCC isolates showed concurrent resistance to levofloxacin and TMP/SMX; all (9/9) of them had a cefiderocol MIC ≤4 mg/L.

Among *S. maltophilia* isolates that were non-susceptible to levofloxacin or TMP/SMX, 97.9% (46/47) were susceptible to cefiderocol. The cefiderocol MICs ranged from ≤0.06 to 2 mg/L, with an MIC_{50} ≤0.06 mg/L and an MIC_{90} of 0.25 mg/L. The MICs of ceftazidime/avibactam and aztreonam/avibactam for *S. maltophilia* ranged from 2 to >32 mg/L and from 1 to 16 mg/L, respectively. At ≤8 mg/L, aztreonam/avibactam inhibited 93.6% (44/47) of the *S. maltophilia* isolates. *Elizabethkingia* spp. demonstrated high MICs for cefiderocol, ceftazidime/avibactam and aztreonam/avibactam, with all MIC_{50} and MIC_{90} values >32 mg/L. Pulsed-field gel electrophoresis analysis of *Elizabethkingia* isolates revealed different pulsotypes with a dominant cluster of eight isolates (Figure S1). The distribution of the cefiderocol, ceftazidime/avibactam and aztreonam/avibactam MICs for five NFGNB spp. are shown in Figure 1, and Figures S2 and S3, respectively. Overall, drug-resistant BCC and *S. maltophilia* had lower MIC distributions of cefiderocol compared with drug-resistant *P. aeruginosa* and MDRAB.

Discussion

This *in vitro* study demonstrated low cefiderocol MICs for MDRAB, DTRPA, drug-resistant BCC and *S. maltophilia*. Ceftazidime/avibactam inhibited 76.4% of IRPA and 68.9% of beta-lactam non-susceptible BCC at an MIC ≤8 mg/L. Aztreonam/avibactam had MIC_{50} values of 16, 8 and 4 mg/L for IRPA, drug-resistant BCC and *S. maltophilia*, respectively.

The high susceptibility rate for cefiderocol against MDRAB was consistent with previous investigations.[5] However, the cefiderocol MICs were widely distributed, highlighting the importance of obtaining the MIC result of the target isolate when initiating cefiderocol therapy. Treatment-emergence resistance of cefiderocol has been reported in CRAB.[11] In addition, cefiderocol for treatment of CRAB infections was associated with higher mortality

Table 1. MICs of cefiderocol, ceftazidime/avibactam, and aztreonam/avibactam for five multidrug-resistant NFGNB

Bacteria (no.)	Antibiotic	MIC (mg/L)			Percentage susceptible (breakpoint, mg/L)
		MIC range	MIC_{50}	MIC_{90}	
MDRAB (126)	CFD	≤0.06 to >32	0.25	2	94.4 (≤4)
	CZA	32 to >32	>32	>32	NA
	AZA	16 to >32	>32	>32	NA
Imipenem-resistant PA (110)	CFD	≤0.06–4	0.25	1	100 (≤4)
	CZA	0.5 to >32	8	32	76.4 (≤8/4)
	AZA[a]	0.125 to >32	16	>32	12.7 (≤8/4)
Imipenem-resistant PA, excluding DTR strains (96)	CFD	≤0.06–4	0.25	1	100 (≤4)
	CZA	0.5 to >32	8	16	84.4 (≤8/4)
	AZA[a]	0.125 to >32	16	>32	43.8 (≤8/4)
DTRPA (14)	CFD	0.125–4	0.25	1	100 (≤4)
	CZA	4 to >32	16	>32	21.4 (≤8/4)
	AZA[a]	4 to >32	32	>32	7.1 (≤8/4)
BCC, CAZ- and MEM-non-susceptible (45)[b]	CFD	≤0.06–0.125	≤0.06	≤0.06	100 (≤4)
	CZA	2 to >32	8	32	68.9 (≤8/4)
	AZA	8 to >32	8	16	86.7 (≤8/4)
S. maltophilia, LEV or TMP/SMX-non-susceptible (47)	CFD	≤0.06–2	≤0.06	0.25	97.9 (≤1)
	CZA	2 to >32	>32	>32	NA
	AZA	1–16	4	8	NA
Elizabethkingia species, CIP-non-susceptible (22)	CFD	2 to >32	>32	>32	NA
	CZA	>32 to >32	>32	>32	NA
	AZA	>32 to >32	>32	>32	NA

AZA, aztreoman/avibactam; BCC, *Burkholderia cepacia* complex; CAZ, ceftazidime; CFD, cefiderocol; CIP, ciprofloxacin; CZA, ceftazidime/avibactam; DTR, difficult-to-treat resistance; LEV, levofloxacin; MDRAB, multidrug-resistant *A. baumannii*; MEM, meropenem; MIN, minocycline; NA, not applicable; PA, *P. aeruginosa*; TMP/SMX, trimethoprim-sulfamethoxazole.

[a]Susceptibility interpretations of AZA were based on CLSI aztreonam interpretive criteria against *P. aeruginosa* with a fixed concentration of avibactam at 4 mg/L.

[b]The susceptibility interpretations of cefiderocol, CZA and AZA were based on same interpretive criteria against *P. aeruginosa*.

than the best available therapy.[12] These findings have raised concerns about the efficacy of cefiderocol monotherapy against CRAB, and experts suggest using cefiderocol in combination with other agents to treat CRAB infections.[8]

Among IRPA, DTRPA had lower susceptibility to ceftazidime/avibactam and aztreonam/avibactam than non-DTRPA, but all were 100% susceptible to cefiderocol. A previous study on MDR *P. aeruginosa* also reported a higher susceptibility rate to cefiderocol (97.3%) than to ceftazidime/avibactam (48.4%).[13] Although cefiderocol was more potent against extensive-resistant *P. aeruginosa* than ceftazidime/avibactam, to our knowledge, there are no direct comparisons of clinical efficacy between these two agents for *P. aeruginosa*.

Earlier studies showed that cefiderocol inhibited 92.3%–95.5% of BCC isolates at an MIC ≤4 mg/L and 98.6%–100% of *S. maltophilia* isolates at ≤1 mg/L.[6,14] However, reports on clinical use of cefiderocol in the treatment of BCC or *S. maltophilia* infections were still limited. Aztreonam/avibactam has been shown to inhibit 88.2%–97.9% of *S. maltophilia* at 8 mg/L,[4,15] and treatment with aztreonam/avibactam successfully eradicated *S. maltophilia* bacteraemia in an immunocompromised patient.[16] In the literature, 80% of *Burkholderia* strains are inhibited by ceftazidime/avibactam at an MIC ≤8 mg/L,[17] and ceftazidime/avibactam as salvage therapy had cured an infant with persistent BCC bacteraemia.[18] On the basis of limited data, ceftazidime/avibactam, aztreonam/avibactam, imipenem/relebactam, meropenem/vaborbactam and cefepime/zidebactam were ineffective against *Elizabethkingia* spp.[19,20] Few studies investigating the cefiderocol MICs for *Elizabethkingia* showed low MICs (≤4 mg/L), but the resistance levels of tested *Elizabethkingia* isolates were either undescribed or ciprofloxacin-susceptible, which were different from our isolates.[14,21]

Our results support the recommendation of IDSA guidance to consider cefiderocol as an alternative or adjunctive treatment option for CRAB, DTRPA and *S. maltophilia*.[8] However, as emphasized in the European guideline, clinical evidence of cefiderocol was still insufficient for these pathogens.[22] This study has several limitations. First, this was a single-centre study and the sample size was modest for some NFGNB spp. Second, only bacteraemic isolates were included, and their susceptibility pattern may differ from isolates from other types of infection. Third, the initial selection of drug-resistant NFGNB isolates was based on susceptibilities reported by VITEK-2, which may not be consistent with results of broth microdilution methods. Nonetheless, in clinical practice, antimicrobial regimens have often been determined based on MIC results from the VITEK-2 system.

In conclusion, cefiderocol showed potent *in vitro* activity against multidrug-resistant *A. baumannii*, *P. aeruginosa*, BCC

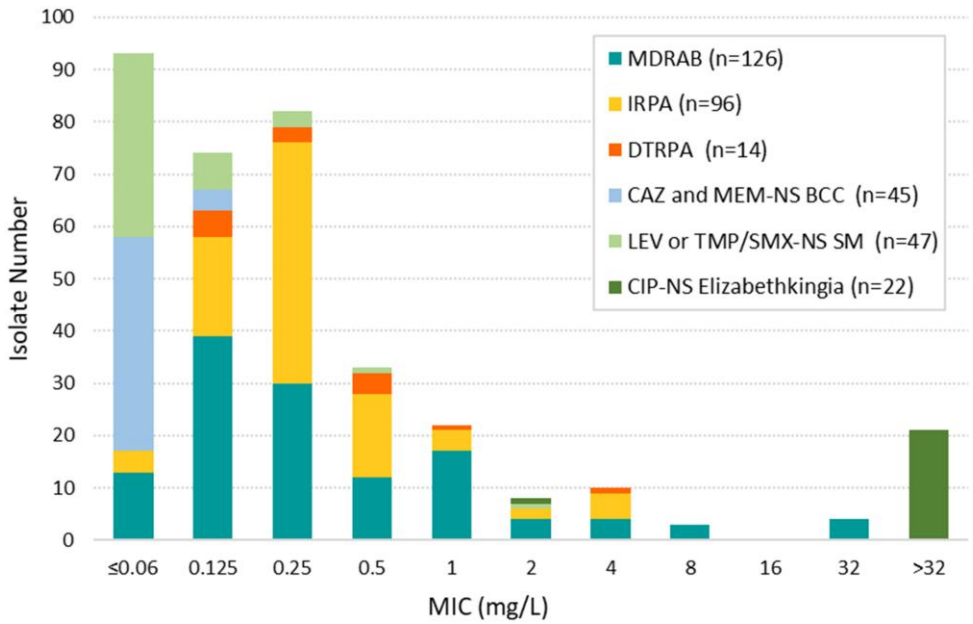

Figure 1. Distribution of cefiderocol MIC for five species of multidrug-resistant NFGNB. BCC, *Burkholderia cepacia* complex; CAZ, ceftazidime; CIP, ciprofloxacin; DTRPA, difficult-to-treat resistance *P. aeruginosa*; IRPA, imipenem-resistant *P. aeruginosa*; LEV, levofloxacin; MDRAB, multidrug-resistant *A. baumannii*; MEM, meropenem; NS, non-susceptible; TMP/SMX, trimethoprim-sulfamethoxazole; SM, *S. maltophilia*.

and *S. maltophilia*, which suggests its potential application as an alternative treatment when other antibiotics are ineffective or intolerable. More studies are needed to determine the activity of cefiderocol against drug-resistant *Elizabethkingia* spp.

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Transparency declarations

The authors have no conflict of interest.

Ethical approval statement

The study was approved by the NTUH Research Ethics Committee (registration number 202301184W).

Supplementary data

Figures S1 to S3 and Table S1 are available as Supplementary data at *JAC-AMR* Online.

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