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INTRODUCTION

- Cefiderocol, a siderophore cephalosporin, combats Gram-negative pathogens by hijacking the iron transport system to accumulate in the periplasmic space, where it binds to penicillin-binding proteins (PBP), in particular to PBP3, to inhibit cell wall synthesis.
- Cefiderocol is approved in the USA for the treatment of complicated urinary tract infections, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia. In Europe, it is approved for the treatment of infections caused by susceptible Gram-negative bacteria in adult patients with limited treatment options. In China, clinical trials with cefiderocol treatment are ongoing.
- In this study, we evaluated the *in vitro* activity of cefiderocol against Gram-negative bacilli isolated from clinical settings in China in 2023, with a focus on meropenem-resistant isolates.

METHODS

- A total of 2,049 clinical strains were collected from 63 hospitals across China in 2023, including Enterobacterales (n=993), *Pseudomonas aeruginosa* (n=377), *Acinetobacter baumannii* (n=368), *Stenotrophomonas maltophilia* (n=188), and *Burkholderia cepacia* (n=123).
- Antimicrobial susceptibility testing was performed using the broth microdilution method according to Clinical and Laboratory Standards Institute (CLSI) M100 (2024) standards, with iron-depleted cation-adjusted Mueller–Hinton broth for cefiderocol. Minimum inhibitory concentrations (MICs) were interpreted according to CLSI breakpoints (2024) for most antibiotics, and for tigecycline and colistin, breakpoints by the U.S. Food and Drug Administration (FDA) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) of 2024 were applied, respectively.

Table 1. Cumulative percentage of Enterobacterales isolates inhibited by cefiderocol

Organism (n)	Cumulative susceptibilities (%)												
	MIC (mg/L)												
	≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
<i>Escherichia coli</i> (299)	35.8	51.5	61.5	73.9	84.6	90.6	95.7	98.7	99.3				100.0
Meropenem-resistant <i>E. coli</i> (22)				4.5	9.1	27.3	63.6	86.4	90.9				100.0
<i>Klebsiella pneumoniae</i> (358)	30.4	43.3	52.8	60.9	70.9	76.8	88.3	95.8	98.3	98.9	99.7		100.0
Meropenem-resistant <i>K. pneumoniae</i> (122)	0.8	1.6	4.9	13.1	28.7	37.7	68.9	91.0	98.4		100.0		
<i>Enterobacter cloacae</i> (124)	10.5	23.4	37.9	50.0	63.7	75.0	86.3	93.5	97.6	99.2			100.0
Meropenem-resistant <i>E. cloacae</i> (11)					9.1	18.2	27.3	36.4	72.7	90.9			100.0
<i>Klebsiella oxytoca</i> (41)	48.8	53.7	63.4	75.6	92.7	97.6	100.0						
<i>Klebsiella aerogenes</i> (41)	41.5	61.0	73.2	82.9	90.2	95.1	100.0						
<i>Citrobacter freundii</i> (36)	52.8	63.9	69.4	80.6	86.1	94.4	100.0						
<i>Providencia</i> spp. (11)	27.3	54.5		63.6	72.7	90.9	100.0						
<i>Proteus</i> spp. (83)	57.8	73.5	85.5	91.6	92.8	95.2	97.6			98.8			100.0

MIC, minimum inhibitory concentration. Green, blue and pink color represents the CLSI susceptibility breakpoint, MIC₅₀ and MIC₉₀ values, respectively.

Table 2. Cucumulative percentage of non-fermenter isolates inhibited by cefiderocol

Organism (n)	Cumulative susceptibilities (%)												
	MIC (mg/L)												
	≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
<i>Pseudomonas aeruginosa</i> (377)	15.6	21.5	35.5	59.2	85.9	97.1	99.5	99.7		100.0			
Meropenem-resistant <i>P. aeruginosa</i> (71)	23.9	31.0	49.3	66.2	84.5	94.4	97.2	98.6		100.0			
<i>Acinetobacter baumannii</i> (368)	8.4	24.2	35.9	67.4	87.8	93.5	95.9	99.5		100.0			
Meropenem-resistant <i>A. baumannii</i> (228)		1.8	9.6	53.5	82.5	91.2	94.3	99.1		100.0			
<i>Stenotrophomonas maltophilia</i> (188)	7.4	25.0	50.5	76.6	93.1	98.4	100.0						
<i>Burkholderia cepacia</i> (123)	22.0	56.9	80.5	91.9	98.4		100.0						

MIC, minimum inhibitory concentration. Green, blue and pink color represents the CLSI susceptibility breakpoint, MIC₅₀ and MIC₉₀ values, respectively.

RESULTS

- Among all isolates, 50.8% (1,040/2,049), 15.8% (323/2,049), and 9.3% (190/2,049) were obtained from the respiratory tract, urinary tract, and blood, respectively. Among them, 478 (23.3%, 478/2049) meropenem-resistant strains were detected.
- The MIC_{50/90} values of cefiderocol for Enterobacterales species ranged from ≤0.03 mg/L to 0.25 mg/L and from 0.25 mg/L to 4 mg/L, respectively, and susceptibility rates ranged from 93.5% to 100% (**Tables 1** and **3**). For meropenem-resistant Enterobacterales, the MIC_{50/90} values were 2 mg/L and 8 mg/L, with an overall susceptibility rate of 87.6%.
- Cefiderocol showed high antibacterial activity against non-fermenter species, with MIC_{50/90} values ranging between 0.06 mg/L and 0.25 mg/L, and between 0.25 mg/L and 1 mg/L, respectively. The susceptibility rates ranged from 98.4% to 99.7%. For meropenem-resistant *P. aeruginosa* and *A. baumannii*, the MIC_{50/90} values of cefiderocol were 0.25 mg/L and 1 mg/L, respectively, for both species, with susceptibility rates of 98.6% and 99.1%, respectively (**Tables 2** and **4**).
- Cefiderocol showed similar antibacterial activity to polymyxin E and tigecycline against most bacteria, outperforming carbapenems and β-lactam/β-lactamase inhibitor combinations. In particular, against meropenem-resistant strains, cefiderocol was one of the most active agents, except for tigecycline or colistin.

Table 3. Susceptibility and resistant rates of *Enterobacterales* to cefiderocol and other antibiotics

Organism (n)	Cefiderocol		Cefepime		Cefoperazone-sulbactam		Ceftazidime-avibactam		Imipenem-relebactam		Ampicillin-sulbactam		Meropenem		Colistin		Tigecycline		Amikacin		Levofloxacin	
	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%
<i>Escherichia coli</i> (299)	98.7	0.7	45.8	45.2	78.3	12.7	92.6	7.4	92.6	6.7	21.1	55.2	92.6	7.4	96.7	3.3	99.3	0	85.3	7.7	38.1	58.9
Meropenem-resistant <i>E. coli</i> (22)	86.4	9.1	0	100.0	4.5	90.9	0	100.0	9.1	90.9	4.5	90.9	0	100.0	81.8	18.2	95.5	0	72.7	22.7	4.5	90.9
<i>Klebsiella pneumoniae</i> (358)	95.8	1.7	47.2	46.9	55.6	40.8	91.3	8.7	90.2	7.3	36.0	54.7	64.2	34.1	95.0	5.0	94.1	1.4	73.2	24.6	46.4	48.9
Meropenem-resistant <i>K. pneumoniae</i> (122)	91.0	1.6	0	98.4	0.8	98.4	78.7	21.3	72.1	20.5	1.6	98.4	0	100.0	92.6	7.4	91.8	0.8	30.3	65.6	4.1	94.3
<i>Enterobacter cloacae</i> (124)	93.5	2.4	68.5	22.6	70.2	21.8	90.3	9.7	90.3	8.1	8.9	76.6	90.3	8.9	87.1	12.9	95.2	1.6	92.7	4.8	69.4	25.0
Meropenem-resistant <i>E. cloacae</i> (11)	36.4	27.3	0	90.9	0	100.0	0	100.0	0	90.9	9.1	90.9	0	100.0	100.0	0	81.8	0	54.5	18.2	36.4	63.6
<i>Klebsiella oxytoca</i> (41)	100.0	0	82.9	4.9	90.2	7.3	97.6	2.4	95.1	2.4	41.5	29.3	97.6	2.4	95.1	4.9	92.7	2.4	97.6	2.4	73.2	24.4
<i>Klebsiella aerogenes</i> (41)	100.0	0	82.9	14.6	85.4	9.8	97.6	2.4	95.1	2.4	2.4	82.9	92.7	7.3	90.2	9.8	90.2	4.9	92.7	2.4	73.2	19.5
<i>Citrobacter freundii</i> (36)	100.0	0	72.2	22.2	72.2	19.4	86.1	13.9	86.1	13.9	16.7	66.7	80.6	19.4	94.4	5.6	97.2	2.8	91.7	8.3	55.6	38.9
<i>Providencia</i> spp. (11)	100.0	0	27.3	54.5	54.5	27.3	63.6	36.4	27.3	45.5	9.1	81.8	63.6	36.4	0	100.0	63.6	0	54.5	45.5	9.1	81.8
<i>Proteus</i> spp. (83)	97.6	2.4	72.3	18.1	97.6	1.2	97.6	2.4	4.8	73.5	43.4	44.6	98.8	0	1.2	98.8	27.7	10.8	85.5	3.6	53.0	39.8

R, resistant; S, susceptible. Other Enterobacterales species with fewer than 10 CR isolates are not shown in the table.

Table 4. Susceptibility and resistant rates of non-fermenter species to cefiderocol and other antibiotics

Organism (n)	Cefiderocol		Cefepime		Cefoperazone-sulbactam		Ceftazidime-avibactam		Imipenem-relebactam		Ampicillin-sulbactam		Meropenem		Colistin		Tigecycline		Amikacin		Levofloxacin	
	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%	S%	R%
<i>Pseudomonas aeruginosa</i> (377)	99.7	0.3	81.7	8.5	75.1	16.4	92.0	8.0	91.2	3.7	–	–	75.3	18.8	99.7	0.3	–	–	98.4	0.8	74.3	15.4
Meropenem-resistant <i>P. aeruginosa</i> (71)	98.6	1.4	39.4	28.2	26.8	57.7	70.4	29.6	56.3	18.3	–	–	0	100.0	100.0	0	–	–	93.0	4.2	33.8	45.1
<i>Acinetobacter baumannii</i> (368)	99.5	0.5	36.4	61.4	38.3	57.9	–	–	–	–	32.3	65.5	37.8	62.0	97.3	2.7	–	–	48.1	51.6	37.2	50.5
Meropenem-resistant <i>A. baumannii</i> (228)	99.1	0.9	0.4	97.4	1.8	92.5	–	–	–	–	0.4	99.1	0	100.0	95.6	4.4	–	–	17.1	82.5	1.8	78.9
<i>Stenotrophomonas maltophilia</i> (188)	98.4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	86.2	10.1
<i>Burkholderia cepacia</i> (123)	–	–	–	–	–	–	–	–	–	–	–	–	86.2	6.5	–	–	–	–	–	–	75.6	11.4

R, resistant; S, susceptible; –, breakpoint is not available. *Burkholderia cepacia* with fewer than 10 CR isolates are not shown in the table.

CONCLUSIONS

Cefiderocol showed good *in vitro* activity against Gram-negative isolates collected in China, including meropenem-resistant isolates, and exhibits potential as a critical therapeutic option for infections caused by Gram-negative bacteria in patients from China.