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Comparison of Cefiderocol and Cefepime-Taniborbactam Activities against Resistant Subgroups of Enterobacterales and *Pseudomonas aeruginosa*, and Cefiderocol and Sulbactam-Durlobactam Against Carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex

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Introduction

- Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against Gram-negative bacteria.
- Cefiderocol was approved by the EMA for the treatment of infections caused by Gram-negative bacteria in adult patients with limited treatment options and by the US FDA for complicated urinary tract infection, hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia.
- We compared the susceptibility of cefiderocol (CFDC) and 2 Phase III combination agents, cefepime/taniborbactam (FTB) and sulbactam/durlobactam (SUD).
- FTB was tested against 101 Enterobacterales producing metallo-β-lactamases (MBLs), and 104 *Pseudomonas aeruginosa* resistant to ceftolozane-tazobactam (CT) or ceftazidime-avibactam (CZA), of which 52 produced MBLs.
- SUD was tested against 159 carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex.

Materials and Methods

- Isolates were collected in 2019–2021 as part of the SENTRY Antimicrobial Surveillance Program from 25 countries.
- Susceptibility testing was performed using the CLSI method with cation-adjusted Mueller-Hinton broth (CAMHB).
- CFDC was tested in iron-depleted CAMHB.
- CLSI, EUCAST, and US FDA (2022) breakpoints were applied for CFDC.
  - No breakpoints were available for SUD and FTB. Cefepime breakpoints were applied for FTB for comparative purposes.
- Isolates producing MBLs were identified using whole genome sequencing.
  - Genomes were analysed for MBL genes, including $bla_{NDM, VIM, FIM}$, and $_{IMP}$.

Results

- Susceptibility of 101 MBL-producing Enterobacterales to CFDC ($MIC_{50/90}$, 2/8 mg/L) was 88.1/66.3% (CLSI and FDA/EUCAST; Table 1). FTB inhibited 62.4% at ≤1 mg/L and 72.3% at ≤2 mg/L ($MIC_{50/90}$, 1/16 mg/L; Table 2, Figure 1), the EUCAST, and CLSI susceptible breakpoints for cefepime.
- Susceptibility of 104 CT or CZA-R *P. aeruginosa* to CFDC was 92.3/82.7/70.2% (CLSI/EUCAST/FDA; $MIC_{50/90}$ 0.5/4 mg/L) and FTB inhibited 51.9% at ≤8 mg/L ($MIC_{50/90}$, 8/>32 mg/L), the EUCAST susceptible-increased exposure breakpoint, and CLSI susceptible-dose dependent breakpoint for cefepime.
- CFDC showed potent activity against 52 MBL-producing *P. aeruginosa* with 94.2/92.3/80.8% susceptible (CLSI/EUCAST/FDA; $MIC_{50/90}$ 0.25/2 mg/L). FTB inhibited 63.5% at ≤8 mg/L ($MIC_{50/90}$, 8/>32 mg/L; Table 2).
- Carbapenem-resistant *A. baumannii-calcoacetius* complex susceptibility to CFDC was 96.9/95.6/90.6% (CLSI/EUCAST/FDA; $MIC_{50/90}$, 0.25/1 mg/L). SUD inhibited 95.6% at ≤4 mg/L ($MIC_{50/90}$, 2/4 mg/L).

Conclusions

- CFDC was the most potent β-lactam against challenging sets of resistant isolates, including Enterobacterales producing MBLs, *P. aeruginosa* resistant to CT or CZA, and *A. baumannii-calcoacetius* complex.
- FTB activity against Enterobacterales was similar to CFDC based on MIC_{90} values, and less active than CFDC against *P. aeruginosa*.
- SUD was less active against *A. baumannii-calcoacetius* complex than CFDC based on MIC_{90} values.
- These *in vitro* data support the use of CFDC as a treatment option for infections caused by highly resistant Gram-negative isolates, including MBL-producing organisms.

Table 1. Susceptibilities of cefiderocol, cefepime-taniborbactam or sulbactam-durlobactam, and comparator agents tested against different organism groups

Organism Antimicrobial agent	No. of isolates	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S CLSI [a]	%S EUCAST [a]	%S US FDA [a]
Enterobacterales (MBL–producing)						
Cefiderocol	101	2	8	88.1	66.3	88.1
Cefepime-taniborbactam	101	1	16	72.3 [b]	62.4 [b]	
Meropenem-vaborbactam	101	32	>32	27.7	33.7	27.7
Ceftazidime-avibactam	101	>32	>32	6.9	6.9	6.9
Cefepime	101	>32	>32	1.0 [c]	1.0	1.0
Piperacillin-tazobactam	101	>128	>128	3.0	3.0	3.0
Meropenem	101	32	>32	11.9	14.9	11.9
Pseudomonas aeruginosa (ceftazidime-avibactam and/or ceftolozane-tazobactam–resistant)						
Cefiderocol	104	0.5	4	92.3	82.7	70.2
Cefepime-taniborbactam	104	8	>32	51.9 [d]	51.9 [d]	
Ceftazidime-avibactam	104	32	>32	1.9	1.9	1.9
Ceftolozane-tazobactam	104	>16	>16	0.0	0.0	0.0
Cefepime	104	>32	>32	3.8 [c]	(3.8) [c]	3.8
Piperacillin-tazobactam	104	64	>128	5.8	(5.8) [c]	5.8
Meropenem	104	32	>32	4.8	4.8	4.8
Acinetobacter baumannii-calcoaceticus complex (carbapenem-resistant)						
Cefiderocol	159	0.25	1	96.9	95.6	90.6
Sulbactam-durlobactam	159	2	4			
Cefepime	159	>32	>32	1.9 [c]		
Piperacillin-tazobactam	159	>128	>128	0.0		0.0
Meropenem	159	>32	>32	0.0	0.0	0.0
Ampicillin-sulbactam	159	64	>64	2.5		2.5

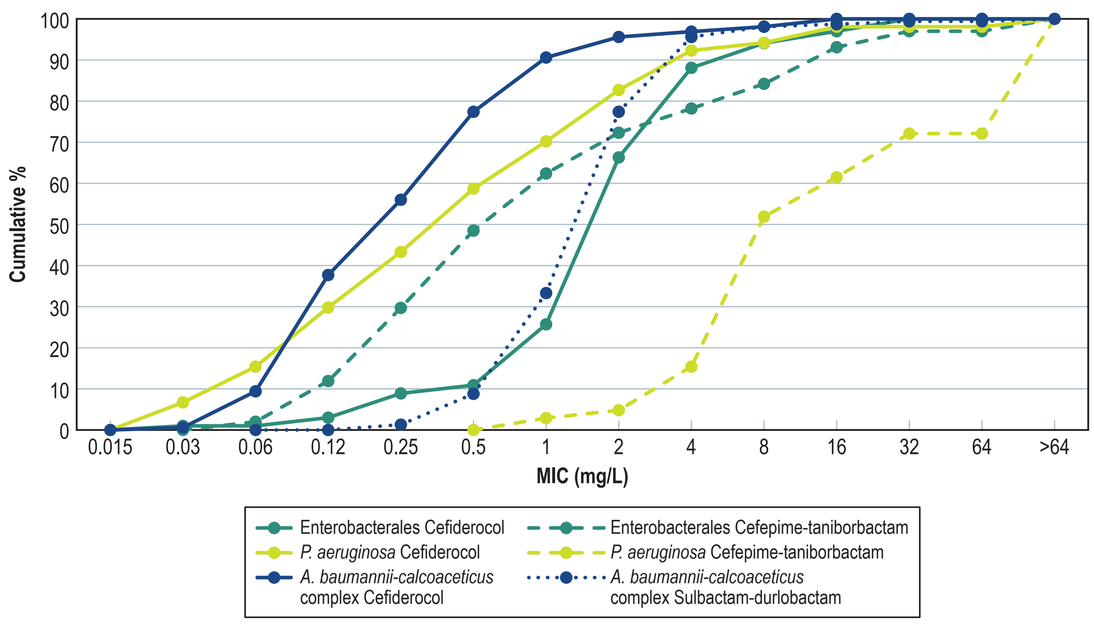
[a] Susceptibility (%S) criteria as published by CLSI (2022), EUCAST (2022), and US FDA (2022).
[b] Cefepime-taniborbactam % based on Enterobacterales cefepime susceptible breakpoints of ≤2 mg/L (CLSI, 2022) or ≤1 mg/L (EUCAST, 2022).
[c] CLSI susceptible-dose dependent (SDD) is shown as susceptible; EUCAST susceptible increased exposure (SIE) shown in parentheses.
[d] Cefepime-taniborbactam % based on *P. aeruginosa* cefepime SDD or SIE breakpoints of ≤8 mg/L (CLSI and EUCAST).

Table 2. Cefiderocol, cefepime-taniborbactam, and sulbactam-durlobactam MIC distributions against different organism groups

Organism/organism group Antimicrobial agent	Number of isolates and cumulative % inhibited at MIC (mg/L)												MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> [a]		
MBL-producing Enterobacterales [b, c] (n=101)														
Cefiderocol	1 1.0%	0 1.0%	2 3.0%	6 8.9%	2 10.9%	15 25.7%	41 66.3%	**22** **88.1%**	6 94.1%	3 97.0%	3 100.0%		2	8
Cefepime-taniborbactam	0 0.0%	2 2.0%	10 11.9%	18 29.7%	19 48.5%	14 62.4%	10 72.3%	6 78.2%	6 84.2%	9 93.1%	4 97.0%	3 100.0%	1	16
CT and/or CAZ-AVI-resistant *Pseudomonas aeruginosa* (n=104)														
Cefiderocol	7 6.7%	9 15.4%	15 29.8%	14 43.3%	16 58.7%	12 70.2%	13 82.7%	**10** **92.3%**	2 94.2%	4 98.1%	0 98.1%	2 100.0%	0.5	4
Cefepime-taniborbactam					0 0.0%	3 2.9%	2 4.8%	11 15.4%	38 51.9%	10 61.5%	11 72.1%	29 100.0%	8	>32
MBL-producing *P. aeruginosa* (n=52) [d]														
Cefiderocol	5 9.6%	5 19.2%	11 40.4%	8 55.8%	8 71.2%	5 80.8%	6 92.3%	**1** **94.2%**	2 98.1%	1 100.0%	0 100.0%	0 100.0%	0.25	2
Cefepime-taniborbactam					0 0.0%	3 5.8%	2 9.6%	9 26.9%	19 63.5%	2 67.3%	3 73.1%	14 100.0%	8	>32
CR *Acinetobacter baumannii-calcoaceticus* complex (n=159)														
Cefiderocol	1 0.6%	14 9.4%	45 37.7%	29 56.0%	34 77.4%	21 90.6%	8 95.6%	**2** **96.9%**	2 98.1%	3 100.0%			0.25	1
Sulbactam-durlobactam			0 0.0%	2 1.3%	12 8.8%	39 33.3%	70 77.4%	29 95.6%	4 98.1%	1 98.7%	1 99.4%	1 100.0%	2	4

[a] Greater than highest concentration tested.
[b] Organisms include *Citrobacter amalonaticus / farmeri* (1), *C. freundii species* complex (2), *Enterobacter cloacae* species complex (16), *Escherichia coli* (15), *Klebsiella oxytoca* (4), *K. pneumoniae* (56), *Proteus mirabilis* (5), and *Providencia rettgeri* (2).
[c] MBLs produced included NDM-1 (40), NDM-4 (5), NDM-5 (26), NDM-7 (6), IMP-8 (2), VIM-1 (16), VIM-4 + VIM-75 (5), and NDM-1 + VIM-1 (1).
[d] MBLs produced included FIM-1 (1), IMP-1 (1), IMP-7 (3), IMP-13 (3), NDM-1 (4), VIM-1 (5), VIM-2 (28), VIM-4 (3), VIM-20 (1), VIM-43 (1), GES-5+VIM-2 (1), and HMB-1 + VIM-1 (1).
CLSI susceptible breakpoint for cefiderocol shown in bold. MIC_{90} shaded in green.

Figure 1. Cumulative MIC distributions of cefiderocol and cefepime-taniborbactam against MBL producing Enterobacterales and ceftolozane-tazobactam resistant *P. aeruginosa*, and cefiderocol and sulbactam-durlobactam against CR-*A. baumannii-calcoaceticus* complex.



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