1711

In Vitro Activity of Cefiderocol Against US *Achromobacter* spp. and *Burkholderia* spp. Clinical Isolates from the SENTRY Surveillance Program 2020-2021

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INTRODUCTION

- *Achromobacter* spp. and *Burkholderia* spp. are non-fermentative Gram-negative bacteria. Infections caused by *Achromobacter* spp. and *Burkholderia* spp. have limited clinical treatment options due to the intrinsic resistance of these non-fermenters to several antimicrobial agents [1, 2].
- *Achromobacter* spp. is routinely isolated from the respiratory tract of patients with cystic fibrosis (CF). It can also cause widespread infection in patients with underlying disease [1]. *Achromobacter* spp. is intrinsically resistant to several antibiotics (eg, most cephalosporins, aztreonam, and aminoglycosides), and some strains exhibit resistance to carbapenems. Carbapenem resistance is mainly caused by multidrug efflux pumps and metallo-β-lactamases and it is considered difficult to overcome it even with the new β-lactam/β-lactamase inhibitors that have been launched in recent years [1].
- The *Burkholderia* genus consists of more than 80 different species, some of which are pathogens of humans, animals and plants. Human pathogens include *Burkholderia mallei* and *Burkholderia pseudomallei*, which are the causative pathogens of glanders and melioidosis, respectively. Also known are *Burkholderia cepacia* complex and *Burkholderia gladioli*, which cause infections in CF and immunocompromised patients [3]. *B. cepacia* complex shows intrinsic resistance to many antibiotics including β-lactam due to production of β-lactamase and expression of multidrug efflux pumps. In addition, the unique lipopolysaccharides (LPS) structure inhibits polymyxin binding to the outer membrane, which causes polymyxin resistance, and the *gyrA* modification causes quinolone resistance [4].
- Cefiderocol (CFDC) is a siderophore cephalosporin antibiotic approved in the US and Europe, with potent activity against Gram-negative bacteria including carbapenem-resistant strains [5,6].
- We evaluated the *in vitro* activity of CFDC and comparator agents against *Achromobacter* spp. and *Burkholderia* spp. clinical isolates, collected from hospitalized patients in the US medical centers as part of the SENTRY Antimicrobial Surveillance Program.

MATERIALS AND METHODS

Isolates

- A total of 78 strains of *Achromobacter* spp. and a total of 99 strains of *Burkholderia* spp. (consisting of 87 strains of *B. cepacia* and 8 strains of *B. gladioli*, and 4 isolates of *B. multivorans*) isolated in the US between 2020 to 2021 were identified.
- Isolate identification was provided by the submitting site and confirmed at JMI Laboratories using MALDI-TOF.
- The breakdowns of infection types of *Achromobacter* spp. and *Burkholderia* spp. are shown in Figure 1 and Figure 2, respectively. For both bacterial species, pneumonia in hospitalized patients was the most common source of isolates, followed by bloodstream infection and urinary tract infection.

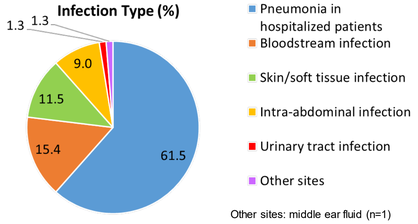
Susceptibility testing

- Minimum inhibitory concentration (MIC) measurements for CFDC and comparator agents were performed by broth microdilution according to the CLSI guidance. CFDC was tested in iron-depleted cation-adjusted Mueller Hinton broth.

Susceptibility analysis

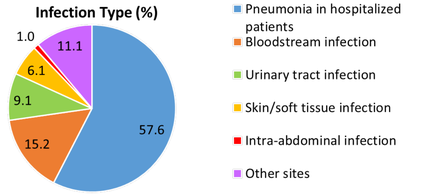
- Susceptibility analysis was performed against all strains and meropenem (MEM)-non-susceptible (NS) strains in each bacterial species. In both bacterial species, MEM-NS strains were defined as strains with MEM MIC >4 μg/mL.
- MIC_{50}, MIC_{90}, and MIC range of CFDC and comparator agents were calculated. Susceptibility rate was determined by using CLSI and EUCAST breakpoints [7].

Figure 1 Infection type (%) of 78 *Achromobacter* spp. isolates collected from medical centers in the US during 2020 and 2021 in the SENTRY surveillance program



Other sites: middle ear fluid (n=1)

Figure 2 Infection type (%) of 99 *Burkholderia* spp. isolates collected from medical centers in the US during 2020 and 2021 in the SENTRY surveillance program



Other sites: sinus (n=3); aspirate (n=1); intravenous/IV Line (n=1); unknown (n=6)

RESULTS

Table 1 Activity of cefiderocol and comparator agents tested against all 78 *Achromobacter* spp. isolates collected from medical centers in the US during 2020 and 2021 in the SENTRY surveillance program

Antimicrobial agent	μg/mL			Susceptibility (%) based on CLSI [a]	Susceptibility (%) based on EUCAST
	MIC_{50}	MIC_{90}	MIC range		
Cefiderocol	0.03	0.5	0.008 to 4	-	98.7[b]
Imipenem-relebactam	1	2	0.5 to >8	-	92.3[b]
Meropenem-vaborbactam	0.12	4	0.06 to >8	-	96.2[b]
Ceftazidime-avibactam	4	16	2 to >32	-	85.9[b]
Ceftolozane-tazobactam	>16	>16	4 to >16	-	0.0[b]
Aztreonam	>16	>16	>16 to >16	0.0	0.0[b]
Ceftazidime	4	16	2 to >32	75.6	65.4[b]
Cefepime	32	>32	4 to >32	6.4	2.6[b]
Piperacillin-tazobactam	0.5	32	0.25 to >128	88.5	80.8[c]
Meropenem	0.12	8	0.06 to >32	87.2	74.4[c]
Imipenem	1	>8	0.5 to >8	83.3	69.2[b]
Ciprofloxacin	4	>4	1 to >4	7.7	0.0 [b]
Levofloxacin	4	16	1 to >32	44.9	0.0 [b]
Amikacin	>32	>32	4 to >32	6.4	0.0 [b]
Gentamicin	>16	>16	2 to >16	5.1	0.0 [b]
Trimethoprim-sulfamethoxazole	≤0.12	2	≤0.12 to >4	91.0	69.2[c]
Minocycline	1	4	0.12 to 16	98.7	-
Colistin	2	4	0.12 to >8	-	-

[a] Criteria as published by CLSI (2022). Since breakpoints for *Achromobacter* spp. have not been established for any antibacterial agents in CLSI, for antimicrobial agents with breakpoints for "other non-Enterobacterales", their breakpoints were used.
[b] Criteria as published by EUCAST (2022). PK-PD (non-species related) breakpoints were used.
[c] Criteria as published by EUCAST (2022). *Achromobacter xylosoxidans* breakpoints were used.
-, Clinical breakpoints were not available;
MIC_{50}, MIC at which 50% of tested strains were inhibited; MIC_{90}, MIC at which 90% of tested strains were inhibited.

Table 2 Activity of cefiderocol and comparator agents tested against 10 MEM-NS *Achromobacter* spp. isolates collected from medical centers in the US during 2020 and 2021 in the SENTRY surveillance program

Antimicrobial agent	μg/mL			Susceptibility (%) based on CLSI [a]	Susceptibility (%) based on EUCAST
	MIC_{50}	MIC_{90}	MIC range		
Cefiderocol	0.12	1	0.03 to 2	-	100.0[b]
Imipenem-relebactam	4	8	1 to >8	-	40.0[b]
Meropenem-vaborbactam	8	>8	0.12 to >8	-	70.0[b]
Ceftazidime-avibactam	8	16	4 to >32	-	70.0[b]
Ceftolozane-tazobactam	>16	>16	>16 to >16	-	0.0[b]
Aztreonam	>16	>16	>16 to >16	0.0	0.0[b]
Ceftazidime	16	32	8 to >32	10.0	0.0[b]
Cefepime	>32	>32	>32 to >32	0.0	0.0[b]
Piperacillin-tazobactam	32	64	8 to >128	40.0	0.0[c]
Meropenem	32	>32	8 to >32	0.0	0.0[c]
Imipenem	>8	>8	4 to >8	10.0	0.0[b]
Ciprofloxacin	>4	>4	1 to >4	20.0	0.0[b]
Levofloxacin	8	16	1 to 32	30.0	0.0[b]
Amikacin	>32	>32	32 to >32	0.0	0.0[b]
Gentamicin	>16	>16	>16 to >16	0.0	0.0[b]
Trimethoprim-sulfamethoxazole	0.5	>4	≤0.12 to >4	70.0	30.0[c]
Minocycline	2	4	0.5 to 4	100.0	-
Colistin	1	2	0.5 to 4	90.0	-

[a] Criteria as published by CLSI (2022). Since breakpoints for *Achromobacter* spp. have not been established for any antibacterial agents in CLSI, for antimicrobial agents with breakpoints for "other non-Enterobacterales", their breakpoints were used.
[b] Criteria as published by EUCAST (2022). PK-PD (non-species related) breakpoints were used.
[c] Criteria as published by EUCAST (2022). *Achromobacter xylosoxidans* breakpoints were used.
-, Clinical breakpoints were not available;
MIC_{50}, MIC at which 50% of tested strains were inhibited; MIC_{90}, MIC at which 90% of tested strains were inhibited.

Table 3 Activity of cefiderocol and comparator agents tested against all 99 *Burkholderia* spp. isolates collected from medical centers in the US during 2020 and 2021

Antimicrobial agent	μg/mL			Susceptibility (%) based on CLSI [a]	Susceptibility (%) based on EUCAST [b]
	MIC_{50}	MIC_{90}	MIC range		
Cefiderocol	0.06	1	≤0.004 to >64	-	94.9
Imipenem-relebactam	0.5	2	0.06 to >8	-	92.9
Meropenem-vaborbactam	1	2	0.25 to >8	-	98.0
Ceftazidime-avibactam	2	8	1 to >32	-	97.0
Ceftolozane-tazobactam	2	16	0.5 to >16	-	80.8
Ceftazidime	4	16	0.5 to >32	85.7	64.6
Meropenem	4	8	0.25 to 32	78.0	43.4
Levofloxacin	2	16	0.25 to >32	48.4	9.1
Trimethoprim-sulfamethoxazole	0.5	4	≤0.12 to >4	88.9	-
Minocycline	2	8	0.25 to >32	83.5	-

[a] Criteria as published by CLSI (2022). Breakpoints for *B. cepacia* complex were used.
[b] Criteria as published by EUCAST (2022). PK-PD (non-species related) breakpoints were used.
-, Clinical breakpoints were not available;
MIC_{50}, MIC at which 50% of tested strains were inhibited; MIC_{90}, MIC at which 90% of tested strains were inhibited.
Burkholderia spp. consists of 87 strains of *B. cepacia*, 8 strains of *B. gladioli*, and 4 strains of *B. multivorans*.

Table 4 Activity of cefiderocol and comparator agents tested against MEM-NS 20 *Burkholderia* spp. isolates collected from medical centers in the US during 2020 and 2021

Antimicrobial agent	μg/mL			Susceptibility (%) based on CLSI [a]	Susceptibility (%) based on EUCAST [b]
	MIC_{50}	MIC_{90}	MIC range		
Cefiderocol	0.12	0.5	≤0.004 to 32	-	95.0
Imipenem-relebactam	1	8	0.5 to >8	-	75.0
Meropenem-vaborbactam	2	8	1 to >8	-	90.0
Ceftazidime-avibactam	4	8	1 to >32	-	90.0
Ceftolozane-tazobactam	4	>16	0.5 to >16	-	65.0
Ceftazidime	8	>32	2 to >32	60.0	25.0
Meropenem	8	16	8 to 32	0.0	0.0
Levofloxacin	8	>32	1 to >32	30.0	0.0
Trimethoprim-sulfamethoxazole	1	4	0.5 to >4	75.0	-
Minocycline	2	8	0.25 to 32	75.0	-

[a] Criteria as published by CLSI (2022). Breakpoints for *B. cepacia* complex were used.
[b] Criteria as published by EUCAST (2022). PK-PD (non-species related) breakpoints were used.
-, Clinical breakpoints were not available;
MIC_{50}, MIC at which 50% of tested strains were inhibited; MIC_{90}, MIC at which 90% of tested strains were inhibited.
Burkholderia spp. consists of 18 strains of *B. cepacia* and 2 strains of *B. multivorans*.

in vitro activity of CFDC against *Achromobacter* spp.

- Of the 78 strains of *Achromobacter* spp., 10 strains (12.8%) were MEM-NS.
- MIC_{50}, MIC_{90}, MIC range, and susceptibility rate for CFDC and comparator agents for all *Achromobacter* spp. (n=78) and its MEM-NS subset (n=10) are shown in the Table 1 and 2, respectively.
  - CFDC inhibited the growth of all 78 *Achromobacter* spp. isolates tested at ≤4 μg/mL and showed MIC_{90} of 0.5 μg/mL. Based on the EUCAST CFDC PK-PD susceptible breakpoint of ≤2 μg/mL, the CFDC susceptibility rate was 98.7%. CFDC had the lowest $MIC_{50/90}$ values compared with 17 comparator agents consisting of various classes of antibiotics including novel β-lactam/β-lactamase inhibitors.
  - CFDC also showed potent *in vitro* activity against 10 MEM-NS strains, with an MIC_{90} of 1 μg/mL. Based on the EUCAST CFDC PK-PD susceptible breakpoint of ≤2 μg/mL, the CFDC susceptibility rate was 100.0%.

in vitro activity of CFDC against *Burkholderia* spp.

- Of the 99 strains of *Burkholderia* spp., 20 strains (20.2%) were MEM-NS.
- MIC_{50}, MIC_{90}, MIC range, and susceptibility rate for CFDC and comparator agents for all *Burkholderia* spp. (n=99) and its MEM-NS subset (n=20) are shown in the Table 3 and 4, respectively.
  - CFDC inhibited the growth of 96% (95/99) of *Burkholderia* spp. isolates tested at ≤4 μg/mL and showed MIC_{90} of 1 μg/mL. Based on the EUCAST CFDC PK-PD susceptible breakpoint of ≤2 μg/mL, the CFDC susceptibility rate was 94.9%. There were 4 strains with high CFDC MIC (≥16 μg/mL), 3 of which were *B. gladioli* and 1 was *B. multivorans*. CFDC had the lowest $MIC_{50/90}$ values compared with 9 comparator agents consisting of various classes of antibiotics including novel β-lactam/β-lactamase inhibitors.
  - CFDC also showed potent *in vitro* activity against 10 MEM-NS strains, with an MIC_{90} of 0.5 μg/mL. Based on the EUCAST CFDC PK-PD susceptible breakpoint of ≤2 μg/mL, the CFDC susceptibility rate was 95.0%.

CONCLUSIONS

- CFDC demonstrated potent *in vitro* activity against *Achromobacter* spp. and *Burkholderia* spp. collected in the US between 2020 and 2021 and their MEM-NS strains.
- These results suggest that CFDC has a high potential for treating infections caused by *Achromobacter* spp. and *Burkholderia* spp., which are difficult to treat due to their intrinsic resistance to various antimicrobial agents.

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