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Activity of Cefiderocol against >1,000 Isolates of *Pseudomonas aeruginosa* with Extensively Drug-Resistant (XDR), Multidrug-Resistant (MDR), β-Lactam-, Ciprofloxacin-, and Colistin-Non-Susceptible Phenotypes collected by the CANWARD Surveillance Study from 2007 to 2019

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Introduction

Pseudomonas aeruginosa is an important nosocomial pathogen. It is frequently implicated as a cause of hospital-acquired urinary tract infections, pneumonia, wound/surgical site infections, and bacteremia, as well as infections among immunocompromised patients and those with burns. Treatment of infections caused by *P. aeruginosa* can be problematic, as this pathogen demonstrates intrinsic resistance to many different antimicrobials. Additionally, *P. aeruginosa* clinical isolates can acquire resistance to the limited number of antimicrobials that do possess antipseudomonal activity, leaving clinicians with few therapeutic options. Acquired beta-lactam resistance among *P. aeruginosa* may be mediated by a variety of mechanisms including derepression of AmpC, acquisition of metallo-beta-lactamases, reduced antimicrobial permeability, and over expression of efflux pumps.

Cefiderocol is a novel parenteral siderophore cephalosporin that utilizes the bacterial iron uptake system for entry into cells (1). It demonstrates *in vitro* activity (MIC_{90} 0.5 µg/ml) against a wide range of Gram-negative bacteria, including *P. aeruginosa* (1). Cefiderocol is resistant to hydrolysis by the chromosomal AmpC found in *P. aeruginosa*, and it has a low propensity for induction of this enzyme (1). It also demonstrates stability versus clinically relevant carbapenemase enzymes, including most metallo-beta-lactamases (1). Additionally, overproduction of the MexAB-OprM efflux pump and loss of OprD in *P. aeruginosa* do not appear to adversely affect the *in vitro* activity of this antimicrobial (1). These properties make cefiderocol an appealing option for the treatment of infections caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) *P. aeruginosa* isolates.

Cefiderocol has demonstrated comparable efficacy to carbapenems in the treatment of complicated urinary tract infections (APEKS-cUTI) and nosocomial pneumonia (APEKS-NP) (2,3). However, in clinical practice this antimicrobial may be reserved for patients with infections caused by difficult-to-treat pathogens including *P. aeruginosa*. The purpose of this study was to evaluate the *in vitro* activity of cefiderocol versus a collection highly antimicrobial-resistant clinical isolates of *P. aeruginosa* obtained from patients admitted to or evaluated at hospitals in Canada between 2007 and 2019.

Materials and Methods

The *P. aeruginosa* clinical isolates included here were collected as part of the CANWARD study (January 2007 to December 2019) (4). CANWARD is an ongoing national Public Health Agency of Canada (PHAC) / Canadian Antimicrobial Resistance Alliance (CARA) partnered surveillance study designed to assess antimicrobial resistance among bacterial pathogens recovered from patients receiving care at hospitals in major population centers across Canada (www.can-r.ca).

Bacterial Isolates: On an annual basis, each participating center was asked to submit clinical isolates (consecutive, one per patient/infection site) from blood, respiratory, urine, and wound infections. Study isolates were shipped to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) where their identities were confirmed by colonial appearance, spot testing (4), and/or matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Billerica, MA, USA). The isolates evaluated in this study are a subset of all *P. aeruginosa* recovered in CANWARD, and were selected if they were XDR (defined as isolates not susceptible to ≥5 of the following six antipseudomonal agents or agent classes: ceftazidime or cefepime, meropenem or imipenem, piperacillin-tazobactam, ciprofloxacin, gentamicin or tobramycin, and colistin (only resistant isolates were included in the definition), MDR (defined as isolates not susceptible to antipseudomonal agents from ≥3 different antimicrobial classes from the following list: ceftazidime or cefepime, meropenem or imipenem, piperacillin-tazobactam, ciprofloxacin, gentamicin or tobramycin, and colistin (only resistant isolates were included in the definition) or isolates non-susceptible to any one antipseudomonal agent from the list above.

Antimicrobial Susceptibilities: Following two subcultures from frozen stock, the *in vitro* activity of cefiderocol and relevant comparators was determined by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) reference method (5). In-house-prepared 96-well broth microdilution panels with cation-adjusted Mueller Hinton II broth (BD BBL; Becton, Dickinson and Company, Sparks, MD) were used for antimicrobial susceptibility testing. Cefiderocol was tested in chelating resin-treated iron-depleted cation-adjusted Mueller-Hinton II broth (5). All antimicrobial agents were acquired as laboratory-grade powders from their respective manufacturers or from a commercial source. MICs were interpreted using 2022 CLSI breakpoints (6). For cefiderocol, the CLSI interpretive criteria for *P. aeruginosa* are susceptible, ≤4 µg/ml; intermediate, 8 µg/ml; resistant, ≥16 µg/ml (6). MDR and XDR isolates were defined as those testing not susceptible to ≥3 (MDR) or ≥5 (XDR) of the following: antipseudomonal cephalosporins (ceftazidime or cefepime), antipseudomonal carbapenems (meropenem or imipenem), antipseudomonal penicillins (piperacillin-tazobactam), fluoroquinolones (ciprofloxacin), aminoglycosides (gentamicin or tobramycin), and colistin (only resistant isolates included in the MDR and XDR definition) (7).

Results

Table 1. *In vitro* activity of cefiderocol and selected comparators against *P. aeruginosa* isolates with antimicrobial-resistant phenotypes

P. aeruginosa phenotype (no. of isolates)	Cefiderocol		Ceftolozane-tazobactam		Ceftazidime-avibactam[a]		Imipenem-relebactam	
	MIC_{50} / MIC_{90} µg/ml	%S / %I / %R[b]	MIC_{50} / MIC_{90} µg/ml	%S / %I / %R	MIC_{50} / MIC_{90} µg/ml	%S / %I / %R	MIC_{50} / MIC_{90} µg/ml	%S / %I / %R
All (1,050)	0.5 / 2	98.3 / 1.1 / 0.6	2 / 8	86.9 / 6.1 / 7.0	8 / 16	73.0 / NA / 27.0	1 / 4	77.7 / 12.8 / 9.5
XDR[c] (235)	0.5 / 4	97.4 / 2.6 / 0	4 / 32	66.8 / 11.9 / 21.3	8 / >16	57.0 / NA / 43.0	4 / 16	49.8 / 24.7 / 25.5
MDR[d] (771)	0.5 / 2	97.9 / 1.4 / 0.6	2 / 8	82.5 / 8.3 / 9.2	8 / 16	64.6 / NA / 35.4	2 / 8	71.2 / 15.8 / 13.0
Ceftolozane-tazobactam-NS[e] (138)	1 / 4	95.7 / 3.6 / 0.7	16 / >64	0 / 47.1 / 52.9	16 / >16	34.8 / NA / 65.2	2 / 32	53.6 / 14.5 / 31.9
Ceftazidime-avibactam-R (283)	1 / 4	96.5 / 2.1 / 1.4	2 / 64	68.2 / 12.7 / 19.1	16 / >16	0 / NA / 100	2 / 8	61.5 / 20.1 / 18.4
Imipenem-relebactam-NS (234)	0.5 / 4	98.7 / 1.3 / 0	2 / 16	72.6 / 10.7 / 16.7	8 / >16	53.4 / NA / 46.6	4 / 16	0 / 57.3 / 42.7
Piperacillin-tazobactam-NS (739)	0.5 / 2	97.8 / 1.5 / 0.7	2 / 8	82.1 / 8.7 / 9.2	8 / 16	62.4 / NA / 37.6	2 / 8	72.0 / 15.6 / 12.4
Meropenem-NS (745)	0.5 / 2	97.7 / 1.6 / 0.7	2 / 8	83.8 / 7.3 / 8.9	8 / 16	67.5 / NA / 32.5	2 / 8	68.6 / 18 / 13.1
Imipenem-NS (726)	0.5 / 2	98.1 / 1.4 / 0.6	2 / 8	84.2 / 7.1 / 8.7	8 / 16	70.8 / NA / 29.2	2 / 8	67.8 / 18.4 / 13.8
Cefepime-NS (673)	0.5 / 2	97.6 / 1.5 / 0.9	2 / 16	80.4 / 9.3 / 10.3	8 / 16	60.0 / NA / 40.0	2 / 8	69.5 / 16.7 / 13.8
Ceftazidime-NS (666)	0.5 / 4	97.6 / 1.5 / 0.9	2 / 16	79.4 / 9.8 / 10.8	8 / 16	58.3 / NA / 41.7	2 / 8	70.6 / 16.3 / 13.1
Ciprofloxacin-NS (750)	0.5 / 2	98.1 / 1.1 / 0.8	2 / 8	83.6 / 7.5 / 8.9	8 / 16	69.3 / NA / 30.7	2 / 8	72.7 / 15.0 / 12.3
Gentamicin-NS (368)	0.5 / 2	98.4 / 1.6 / 0	2 / 16	76.1 / 9.5 / 14.4	8 / 16	70.4 / NA / 29.6	2 / 8	61.4 / 19.9 / 18.7
Tobramycin-NS (197)	0.5 / 2	97.5 / 2.5 / 0	2 / 64	66.5 / 12.2 / 21.3	8 / 16	67.0 / NA / 33.0	2 / 16	52.8 / 23.3 / 23.9
Colistin-NS (43)	1 / 4	97.7 / 2.3 / 0	2 / 64	69.8 / 6.9 / 23.3	8 / >16	58.1 / NA / 41.9	2 / 8	72.1 / 13.9 / 14.0

[a] NA, an MIC intermediate breakpoint is not defined for ceftazidime-avibactam.
[b] S, susceptible; I, intermediate; R, resistant.
[c] XDR, extensively drug-resistant. XDR isolates were defined as isolates not susceptible to ≥5 of the following six antipseudomonal agents or agent classes: ceftazidime or cefepime, meropenem or imipenem, piperacillin-tazobactam, ciprofloxacin, gentamicin or tobramycin, and colistin (only resistant isolates were included in the definition).
[d] MDR, multidrug-resistant. MDR isolates were defined as isolates not susceptible to antipseudomonal agents from ≥3 different antimicrobial classes from the following list: ceftazidime or cefepime, meropenem or imipenem, piperacillin-tazobactam, ciprofloxacin, gentamicin or tobramycin, and colistin (only resistant isolates were included in the definition).
[e] NS, not susceptible.

Table 2. Cefiderocol MIC distributions for *P. aeruginosa* isolates with antimicrobial-resistant phenotypes

P. aeruginosa phenotype (no. of isolates)	Cefiderocol MIC, µg/ml No. of isolates (% of isolates tested with antimicrobial-resistant phenotype)										
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
All (1,050)	50 (4.8%)	68 (6.5%)	233 (22.2%)	298 (28.4%)	156 (14.9%)	161 (15.3%)	66 (6.3%)	12 (1.1%)	4 (0.4%)	2 (0.2%)		
XDR[a] (235)	15 (6.4%)	12 (5.1%)	41 (17.4%)	52 (22.1%)	38 (16.2%)	51 (21.7%)	20 (8.5%)	6 (2.6%)				
MDR[b] (771)	37 (4.8%)	47 (6.1%)	168 (21.8%)	199 (25.8%)	120 (15.6%)	129 (16.7%)	55 (7.1%)	11 (1.4%)	4 (0.5%)	1 (0.1%)		
Ceftolozane-tazobactam-NS[c] (138)	5 (3.6%)	5 (3.6%)	14 (10.1%)	24 (17.4%)	37 (26.8%)	28 (20.3%)	19 (13.8%)	5 (3.6%)		1 (0.7%)		
Ceftazidime-avibactam-R (283)	1 (0.4%)	8 (2.8%)	51 (18.0%)	79 (27.9%)	55 (19.4%)	48 (17.0%)	31 (11.0%)	6 (2.1%)	3 (1.1%)	1 (0.4%)		
Imipenem-relebactam-NS (234)	11 (4.7%)	13 (5.6%)	54 (23.1%)	57 (24.4%)	30 (12.8%)	39 (16.7%)	27 (11.5%)	3 (1.3%)				
Piperacillin-tazobactam-NS (739)	34 (4.6%)	47 (6.4%)	152 (20.6%)	187 (25.3%)	120 (16.2%)	125 (16.9%)	58 (7.8%)	11 (1.5%)	4 (0.5%)	1 (0.1%)		
Meropenem-NS (745)	35 (4.7%)	37 (5.0%)	173 (23.2%)	202 (27.1%)	112 (15.0%)	117 (15.7%)	52 (7.0%)	12 (1.6%)	4 (0.5%)	1 (0.1%)		
Imipenem-NS (726)	40 (5.5%)	38 (5.2%)	171 (23.6%)	184 (25.3%)	109 (15.0%)	121 (16.7%)	49 (6.7%)	10 (1.4%)	3 (0.4%)	1 (0.1%)		
Cefepime-NS (673)	32 (4.8%)	43 (6.4%)	141 (21.0%)	168 (25.0%)	111 (16.5%)	111 (16.5%)	51 (7.6%)	10 (1.5%)	4 (0.6%)	2 (0.3%)		
Ceftazidime-NS (666)	29 (4.4%)	37 (5.6%)	139 (20.9%)	166 (24.9%)	107 (16.1%)	118 (17.7%)	54 (8.1%)	10 (1.5%)	4 (0.6%)	2 (0.3%)		
Ciprofloxacin-NS (750)	42 (5.6%)	44 (5.9%)	165 (22.0%)	207 (27.6%)	111 (14.8%)	118 (15.7%)	49 (6.5%)	8 (1.1%)	4 (0.5%)	2 (0.3%)		
Gentamicin-NS (368)	25 (6.8%)	21 (5.7%)	73 (19.8%)	97 (26.4%)	53 (14.4%)	68 (18.5%)	25 (6.8%)	6 (1.6%)				
Tobramycin-NS (197)	10 (5.1%)	10 (5.1%)	42 (21.3%)	56 (28.4%)	26 (13.2%)	35 (17.8%)	13 (6.6%)	5 (2.5%)				
Colistin-NS (43)	2 (4.7%)	3 (7.0%)	6 (14.0%)	10 (23.3%)	10 (23.3%)	7 (16.3%)	4 (9.3%)	1 (2.3%)				

[a] XDR, extensively drug-resistant. XDR isolates were defined as isolates not susceptible to ≥5 of the following six antipseudomonal agents or agent classes: ceftazidime or cefepime, meropenem or imipenem, piperacillin-tazobactam, ciprofloxacin, gentamicin or tobramycin, and colistin (only resistant isolates were included in the definition).
[b] MDR, multidrug-resistant. MDR isolates were defined as isolates not susceptible to antipseudomonal agents from ≥3 different antimicrobial classes from the following list: ceftazidime or cefepime, meropenem or imipenem, piperacillin-tazobactam, ciprofloxacin, gentamicin or tobramycin, and colistin (only resistant isolates were included in the definition).
[c] NS, not susceptible.

Conclusions

1. Cefiderocol was highly active *in vitro* (98.3% susceptible) against a selected collection of *P. aeruginosa* clinical isolates with beta-lactam and non-beta-lactam not susceptible phenotypes.
2. Cefiderocol retained *in vitro* activity against the vast majority of MDR (97.9% susceptible) isolates.
3. Cefiderocol retained *in vitro* activity against the vast majority of XDR (97.4% susceptible) isolates.
4. Cefiderocol retained *in vitro* activity against the vast majority of isolates testing not susceptible to antimicrobials often reserved for the management of infections caused by antimicrobial-resistant pathogens (e.g., ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-relebactam).
5. These *in vitro* data suggest that cefiderocol may be a treatment option for infections caused by highly-antimicrobial-resistant *P. aeruginosa.*

Table 3. *In vitro* activity of cefiderocol and comparator antimicrobial agents against selected antimicrobial-resistant *P. aeruginosa* isolates cultured from specimens of Canadian patients from 2007 to 2019; CANWARD surveillance study

P. aeruginosa (no. of isolates)	MIC, µg/ml			MIC Interpretation (%)		
Antimicrobial agent	MIC_{50}	MIC_{90}	MIC range	Susceptible	Intermediate	Resistant
All isolates (1,050)						
Cefiderocol	0.5	2	≤0.06-32	98.3	1.1	0.6
Ceftolozane-tazobactam	2	8	0.25->64	86.9	6.1	7
Ceftazidime-avibactam	8	16	0.5->16	73	NA[a]	27
Imipenem-relebactam	1	4	≤0.03->32	77.7	12.8	9.5
Piperacillin-tazobactam	32	256	≤1->512	29.6	36.5	33.9
Meropenem	8	32	0.25->32	29	15.8	55.2
Imipenem	8	32	0.12->32	30.9	11.1	58
Cefepime	16	32	1->64	35.9	39	25.1
Ceftazidime	16	>32	2->32	36.6	19.7	43.7
Ciprofloxacin	2	16	≤0.06->16	28.6	18.3	53.1
Gentamicin	4	>32	≤0.5->32	65	13.9	21.1
Tobramycin	1	64	≤0.5->64	81.2	2.3	16.5
Colistin	1	2	0.12->16	NA[b]	95.9	4.1

[a] NA, an MIC intermediate breakpoint is not defined for ceftazidime-avibactam.
[b] NA, an MIC susceptible breakpoint is not defined for colistin.

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