Activity of Cefiderocol Against *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* Endemic to Medical Centers in New York City

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Therapeutic options for the treatment of infections owing to multidrug-resistant Gram-negative pathogens are often limited. Cefiderocol is a novel siderophore cephalosporin with activity against Gram-negative pathogens, including many multidrug-resistant strains. The activity of cefiderocol was examined against *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* that included (1) a recent surveillance collection of clinical isolates, (2) a collection of carbapenem-resistant isolates from a previous surveillance study, and (3) a collection of well-characterized isolates. Susceptibility testing for cefiderocol was performed with iron-depleted cation-adjusted Mueller–Hinton broth. Cefiderocol minimum inhibitory concentrations (MICs) were correlated with resistance mechanisms in the well-characterized isolates. For the *Enterobacterales*, including a collection of KPC-possessing *Klebsiella pneumoniae*, cefiderocol MICs were all ≤ 4 mg/L. Cefiderocol MICs were two- to fourfold higher in cephalosporin-resistant isolates. For *K. pneumoniae*, MICs did not correlate with expression of genes encoding porins or efflux systems. For *P. aeruginosa*, $>99\%$ of isolates were inhibited by ≤ 4 mg/L, including the collection of carbapenem-resistant isolates. For *P. aeruginosa*, cefiderocol activity was not affected by expression of *ampC*, *oprD*, or several efflux systems. All the surveillance isolates of *A. baumannii*, and 88% of the collection of carbapenem-resistant isolates, had cefiderocol MICs ≤ 4 mg/L. MICs were twofold higher in *A. baumannii* isolates with proven extended-spectrum beta-lactamases, and cefiderocol activity did not correlate with expression of efflux systems. Cefiderocol demonstrated potent activity against important nosocomial pathogens. Continued development of this agent as a therapeutic option against multidrug-resistant bacteria should be encouraged.

Keywords: *Acinetobacter*, *Pseudomonas*, Enterobacteriaceae

Introduction

THE WORLD HEALTH ORGANIZATION has declared antimicrobial resistance a global emergency and the development of new antimicrobials as a priority.¹ Carbapenem-resistant *Enterobacterales*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* are considered “critical” pathogens.¹ The spread of multidrug-resistant Gram-negative pathogens has spurred the development of novel and potentially therapeutic agents. Next-generation aminoglycosides and β -lactamase inhibitors that have been recently brought into clinical practice are welcomed additions to our therapeutic armamentarium; however, resistance to these agents may limit their utility. For example, the diazabicyclooctanes are a new class of β -lactamase inhibitors that are active against many pathogens carrying serine β -lactamases.² However, the currently available agents are

not therapeutic options for isolates possessing metallo- β -lactamases. Clearly, alternative approaches are needed.

Cefiderocol (previously S-649266) is novel siderophore cephalosporin with a catechol moiety at position 3 of the cephalosporin side chain. This moiety facilitates formation of chelated complexes with iron and crosses the outer membrane of Gram-negative bacilli through active iron transporters.³ Several studies have shown potent *in vitro* activity of cefiderocol against *Enterobacterales*, *P. aeruginosa*, and *A. baumannii*, including isolates resistant to carbapenems.^{4–8} The spectrum of activity of cefiderocol includes isolates harboring a wide range of carbapenemases, including serine (KPC, OXA-type) and metallo (VIM, IMP, NDM) β -lactamases.^{7–13} Finally, in one clinical trial cefiderocol was comparable with imipenem–cilastatin for treatment of complicated urinary tract infections owing to carbapenem-susceptible pathogens.¹⁴

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In this report we examine the *in vitro* activity of cefiderocol against *Enterobacterales*, *P. aeruginosa*, and *A. baumannii* endemic to New York City.

Materials and Methods

Isolates

Clinical isolates of *Enterobacterales*, *P. aeruginosa*, and *A. baumannii* underwent susceptibility testing. Three groups of *Enterobacterales* were analyzed, including (1) 2558 single-patient isolates of *Escherichia coli*, *Enterobacter* spp. (included in this group was *Klebsiella aerogenes*), and *Klebsiella pneumoniae* gathered during a 3-month surveillance study involving seven hospitals in Brooklyn, New York in 2017; (2) 111 carbapenem-resistant (and KPC-possessing) isolates of *K. pneumoniae* gathered from a similar surveillance study performed in 2013–2014; and (3) 34 well-characterized isolates of *K. pneumoniae*.^{15–17} For the last group, the presence of β -lactamases and genetic expression of *bla*_{KPC}, *ompK35*, *ompK36*, and *acrB* were previously determined.¹⁷ Multi-locus sequence typing was performed on select isolates of *K. pneumoniae* according to established protocols.¹⁸

For *P. aeruginosa* and *A. baumannii*, a similar three groups of isolates were analyzed. These groups included (1) 269 single-patient isolates of *P. aeruginosa* and 46 isolates of *A. baumannii* collected during the 2017 surveillance study, (2) carbapenem-resistant isolates of *P. aeruginosa* ($n=130$) and *A. baumannii* ($n=78$) gathered during a 2013–2014 surveillance study, and (3) 33 isolates of *P. aeruginosa* and 34 isolates of *A. baumannii* that were previously characterized for mechanisms of antimicrobial resistance.^{19–21} For *P. aeruginosa*, the presence of β -lactamases and genetic expression of *ampC*, *oprD*, *mexA*, *mexC*, *mexE*, and *mexX* were analyzed.²⁰ For the *A. baumannii* isolates, the presence of β -lactamases and genetic expression of *ampC*, *oxa51*, *adeB*, and *abeM* were determined, as previously described.²¹

Susceptibility testing

Cefiderocol minimum inhibitory concentrations (MICs) were performed in iron-depleted cation-adjusted Mueller–Hinton broth.²² MICs for the remaining antibiotics were performed by the agar dilution method with Mueller–Hinton agar according to established CLSI methods.²³ Susceptibility rates were determined using CLSI criteria; for cefiderocol, the provisional breakpoint of 4 mg/L was used.²⁴ Control strains included *E. coli* ATCC 25922 and 35218 and *P. aeruginosa* ATCC 27853.

Statistical analysis using the two-tailed Student's *t*-test and multiple linear regression were used to compare MICs with characterized mechanisms of resistance. A value of $p<0.05$ was considered significant.

Results

Enterobacterales

Among the surveillance isolates gathered in 2017 (Table 1), all *E. coli* isolates ($n=1869$) had cefiderocol MICs ≤ 2 mg/L. Among the ceftazidime-resistant isolates ($n=141$), the MIC₅₀/MIC₉₀ values were 0.5/2 mg/L, which were fourfold higher compared with the values of the ceftazidime-susceptible isolates (0.12/0.5 mg/L). The mean cefiderocol MIC was higher in the group resistant to ceftazidime vs. the isolates susceptible

to ceftazidime (0.55 ± 0.51 vs. 0.16 ± 0.17 mg/L, $p<0.001$). Similarly, all the *Enterobacter* spp. ($n=172$, including 58 isolates of *K. aerogenes* and 104 isolates of *Enterobacter cloacae*) had cefiderocol MICs ≤ 2 mg/L. For the *Enterobacter* isolates that were resistant to ceftazidime ($n=38$), the MIC₅₀/MIC₉₀ values for cefiderocol were 0.25/1 mg/L, which were twofold higher than those values of the ceftazidime-susceptible isolates (0.12/0.5 mg/L). In addition, the 18 isolates of *Enterobacter* that were nonsusceptible to piperacillin/tazobactam (and presumably AmpC hyperproducers) had MIC₅₀/MIC₉₀ values for cefiderocol that were twofold higher than that of the susceptible isolates (0.25/1 vs. 0.12/0.5 mg/L, respectively).

All the 2017 surveillance isolates of *K. pneumoniae* ($n=517$) had cefiderocol MICs of ≤ 2 mg/L, including 19 isolates with *bla*_{KPC}. Of the 19 *bla*_{KPC}-possessing isolates, 12 belonged to ST258, two belonged to ST340, and one each belonged to ST45, ST327, ST584, ST3359, and ST3369. Compared with the ceftazidime-susceptible isolates, the ceftazidime-resistant isolates (but lacking *bla*_{KPC}) had greater mean cefiderocol MICs (0.43 ± 0.46 vs. 0.21 ± 0.20 mg/L, $p<0.001$) and MIC₅₀/MIC₉₀ values (0.25/1 vs. 0.12/0.5 mg/L). For the 111 KPC-possessing isolates gathered in 2013–2014, the MIC₅₀/MIC₉₀ values for cefiderocol were 1 and 2 mg/L, and all had an MIC of ≤ 4 mg/L.

There were 34 previously characterized isolates of *K. pneumoniae*, including 14 with the carbapenemase KPC (Supplementary Table S1). The mean cefiderocol MIC for isolates ($n=10$) that did not have an extended-spectrum beta-lactamase (ESBL) or KPC β -lactamase was 0.24 ± 0.18 mg/L (range = 0.06–0.5 mg/L). The mean cefiderocol MIC for isolates ($n=10$) that possessed only an ESBL (*bla*_{SHV}) was 1.1 mg/L ± 1.09 mg/L (range = 0.25–4 mg/L; $p=0.04$ compared with isolates lacking an ESBL). The one isolate in this group with an MIC = 4 mg/L also possessed an AmpC-type (ACT-1) enzyme. Four isolates with *bla*_{KPC} but without an ESBL had cefiderocol MICs of 0.5–1 mg/L (mean 0.875 mg/L). The remaining 10 isolates possessed both an ESBL and KPC, with a mean cefiderocol MIC of 1.07 ± 1.19 mg/L ($p=0.07$ compared with isolates lacking an ESBL, range = 0.06–4 mg/L). There was no correlation between cefiderocol MICs and expression of *bla*_{KPC}, the efflux-related genes *marA*, *ramA*, *soxS*, and *acrB*, and the porin-related genes *ompK35* or *ompK36*. Isolates with a frameshift mutation involving *ompK35* had similar MICs as isolates without this mutation.

P. aeruginosa and *A. baumannii*

Pseudomonas aeruginosa. There were 269 isolates of *P. aeruginosa* gathered in the 2017 surveillance study (Table 2), and 99.6% had a cefiderocol MIC ≤ 4 μ g/mL. Compared with the isolates susceptible to ceftazidime, the nonsusceptible isolates had MIC₅₀/MIC₉₀ values for cefiderocol that were twofold higher (0.5/4 vs. 0.25/2 mg/L), but mean values were similar (0.84 ± 1.09 vs. 0.75 ± 1.15 mg/L, $p=NS$). There were 130 carbapenem-nonsusceptible isolates gathered in the 2013–2014 surveillance study, and the MIC₅₀/MIC₉₀ values were 0.5/1 mg/L.

There were 33 characterized isolates of *P. aeruginosa* (Supplementary Table S2). Isolates with increased expression of *ampC* (>10 times control) had similar cefiderocol MICs

TABLE 1. SUSCEPTIBILITY RESULTS INVOLVING ENTEROBACTERIACEAE FROM THE 2017 SURVEILLANCE COLLECTION AND THE 2013–2014 CARBAPENEM-RESISTANT COLLECTION

	<i>MIC</i> ₅₀	<i>MIC</i> ₉₀	<i>Range</i>	
	<i>mg/L</i>			<i>Susceptible, %</i>
2017 surveillance isolates				
<i>Escherichia coli</i> (<i>n</i> = 1869)				
Cefiderocol	0.12	0.5	≤0.03 to 2	100
Piperacillin/tazobactam	2/4	4/4	≤0.25/4 to >128/4	99
Ceftriaxone	≤0.06	16	≤0.06 to >32	88
Ceftazidime	0.25	2	≤0.12 to >32	92
Meropenem	≤0.12	≤0.12	≤0.12 to 4	99.9
Gentamicin	1	>16	≤0.25 to >16	86
TMP/SMX	≤0.25/4.75	>4/76	≤0.25/4.75 to >4/76	64
Ciprofloxacin	≤0.12	>4	≤0.12 to >4	67
<i>Enterobacter</i> spp. (<i>n</i> = 172)				
Cefiderocol	0.12	0.5	≤0.03 to 1	100
Piperacillin/tazobactam	4/4	32/4	≤0.25/4 to >128/4	90
Ceftriaxone	0.25	32	≤0.06 to >32	81
Ceftazidime	0.5	32	≤0.12 to >32	83
Meropenem	≤0.12	≤0.12	≤0.12 to >8	98
Gentamicin	1	1	≤0.25 to >16	94
TMP/SMX	≤0.25/4.75	>4/76	≤0.25/4.75 to >4/76	84
Ciprofloxacin	≤0.12	1	≤0.12 to >4	91
<i>Klebsiella pneumoniae</i> (<i>n</i> = 517)				
Cefiderocol	0.12	0.5	≤0.03 to 2	100
Piperacillin/tazobactam	4/4	8/4	≤0.25/4 to >128/4	96
Ceftriaxone	≤0.06	>32	≤0.06 to >32	83
Ceftazidime	0.25	16	≤0.12 to >32	84
Meropenem	≤0.12	≤0.12	≤0.12 to >8	96
Gentamicin	0.5	8	≤0.25 to >16	89
TMP/SMX	≤0.25/4.75	>4/76	≤0.25/4.75 to >4/76	79
Ciprofloxacin	≤0.12	>4	≤0.12 to >4	85
2013–2014 Carbapenem-resistant surveillance isolates				
<i>K. pneumoniae</i> (<i>n</i> = 111)				
Cefiderocol	1	2	≤0.03 to 4	100

TMP/SMX, trimethoprim sulfamethoxazole.

TABLE 2. SUSCEPTIBILITY RESULTS INVOLVING *PSEUDOMONAS AERUGINOSA* AND *ACINETOBACTER BAUMANNII* FROM THE 2017 SURVEILLANCE COLLECTION AND THE 2013–2014 CARBAPENEM-RESISTANT COLLECTION OF ISOLATES

	<i>MIC</i> ₅₀	<i>MIC</i> ₉₀	<i>Range</i>	
	<i>mg/L</i>			<i>Susceptible, %</i>
2017 surveillance isolates				
<i>P. aeruginosa</i> (<i>n</i> =269)				
Cefiderocol	0.25	0.5	≤0.03 to 8	99.6
Piperacillin/tazobactam	8/4	128/4	2/4 to >128/4	75
Ceftazidime	4	32	1 to >32	83
Meropenem	1	8	≤0.12 to >8	76
Gentamicin	2	8	0.5 to >16	79
Ciprofloxacin	0.25	>4	≤0.12 to >4	69
2013–2014 Carbapenem-resistant surveillance isolates				
<i>P. aeruginosa</i> (<i>n</i> =130)				
Cefiderocol	0.5	1	≤0.03 to 4	100
2017 surveillance isolates				
<i>A. baumannii</i> (<i>n</i> =46)				
Cefiderocol	0.25	1	0.06 to 4	100
Piperacillin/tazobactam	32/4	>128/4	≤0.25/4 to >128/4	43
Ceftazidime	8	>32	≤0.12 to >32	54
Meropenem	4	8	≤0.12 to >8	48
Gentamicin	2	>16	0.5 to >16	70
Ciprofloxacin	>4	>4	≤0.12 to >4	46
2013–2014 Carbapenem-resistant surveillance isolates				
<i>A. baumannii</i> (<i>n</i> =78)				
Cefiderocol	0.5	8	0.12 to >32	88

compared with isolates without increased expression of this enzyme (0.67 ± 1.01 vs. 0.27 ± 0.23 mg/L, $p = 0.2$). By regression analysis, there was no correlation between cefiderocol MICs and expression of *ampC*, *mexA*, *mexC*, *mexE*, *mexX*, and *oprD*.

Acinetobacter baumannii. There were 46 isolates of *A. baumannii* gathered in 2017, and all had cefiderocol MICs ≤ 4 mg/L. Compared with the isolates susceptible to ceftazidime, the MIC₅₀ value for cefiderocol was twofold higher in the 18 ceftazidime-nonsusceptible isolates (0.25 vs. 0.12 mg/L). There were 78 carbapenem-resistant isolates gathered in 2013–2014, including 47 with *bla*_{OXA-23}-type β -lactamases. Overall, the MIC₅₀/MIC₉₀ values were 0.5/8 mg/L, which was identical to the subset of isolates with *bla*_{OXA-23}-type β -lactamases.

There were 34 isolates characterized of *A. baumannii* (Supplementary Table S3). Isolates with an SHV ESBL had significantly higher cefiderocol MICs than isolates without ESBLs (8.04 ± 11.58 vs. 0.86 ± 1.08 mg/L, $p = 0.02$). By regression analysis, there was no correlation between cefiderocol MICs and expression of genes encoding *ampC*, *bla*_{OXA-51}, and the efflux systems *adeB* and *abeM*.

Discussion

The progressive and global spread of multidrug-resistant Gram-negative pathogens has led to increasingly difficult-to-treat nosocomial infections. Given the extremely limited treatment options currently available, novel therapeutic agents are urgently needed. Cefiderocol is a novel catechol-substituted siderophore cephalosporin with a broad spectrum of antimicrobial activity. Against *Enterobacterales*, MIC₉₀ values of ~ 0.5 –1 mg/L have been reported, with $>95\%$ being inhibited by ≤ 4 mg/L (the proposed breakpoint for cefiderocol).^{4,6,9,10} Consistent with these reports, the *Enterobacterales* in our study had overall MIC₉₀ values of 0.5 mg/L, and all were inhibited by ≤ 4 mg/L. In a study by Jacobs *et al.*, cefiderocol MICs were higher in *Enterobacterales* possessing an ESBL, carbapenemase, or AmpC-type β -lactamase compared with isolates lacking these enzymes.¹² Our study also documented greater cefiderocol MICs in isolates of *E. coli* and *K. pneumoniae* that were cephalosporin resistant. The activity of cefiderocol has been reported to be maintained in *Enterobacterales* possessing a wide variety of carbapenemases, including KPC, NDM VIM, IMP, and OXA-48.^{5,9,10,12} The activity of cefiderocol was maintained in all our KPC-producing *K. pneumoniae*, with 90% of the isolates being inhibited by ≤ 2 mg/L, consistent with other reports.^{10,12}

Cefiderocol has also been reported to have considerable activity against other Gram-negative pathogens. For *P. aeruginosa*, including carbapenem-resistant isolates, MIC₉₀ values of 0.5–1 mg/L have been reported.^{4–8,10,12} In our study, 99.6% of our surveillance isolates had cefiderocol MICs ≤ 4 mg/L. MICs did not appear to be significantly affected by the development of cephalosporin or carbapenem resistance, consistent with findings reported elsewhere for *P. aeruginosa*.¹² Similarly, for *A. baumannii* overall MIC₉₀ values of 1–2 mg/L, and 8 mg/L for carbapenem-resistant isolates, have been reported.^{4–8,10,12} All our 2017 surveillance isolates, and 88% of our previous collection of carbapenem-resistant *A. baumannii*, were inhibited by ≤ 4 mg/L. For *A. baumannii*, cefiderocol MICs were unaffected by the presence of OXA-23, consistent with

findings reported elsewhere.¹⁰ However, as with the *Enterobacterales*, we noted cefiderocol MICs were significantly higher in ESBL-possessing isolates of *A. baumannii*.

The catechol moiety in cefiderocol chelates free iron, enabling entry into bacteria through their iron transport system.²⁵ As such, cefiderocol may evade porin-related bacterial mechanisms of antimicrobial resistance. Consistent with other reports, when our collection of characterized isolates of *K. pneumoniae* were examined, cefiderocol MICs were not significantly affected by alterations in the porins OmpK35 and OmpK36.^{3,10} In addition, we found no correlation between cefiderocol MICs and expression of several efflux-related genes. For *P. aeruginosa*, overexpression of the MexAB-OprM efflux system had no effect on the activity of cefiderocol.³ Similarly, in our collection of characterized isolates of *P. aeruginosa*, we found no correlation between expression of several efflux systems or in expression of the porin *oprD*. Finally, when tested against our collection of characterized isolates of *A. baumannii*, no correlation was found between cefiderocol MICs and expression of the efflux genes *adeB* and *abeM*.

Our study reaffirms the activity of cefiderocol against a large number of Gram-negative pathogens, including multidrug-resistant isolates. However, our findings may not be generalized to other multidrug-resistant pathogens, because only a limited variety of carbapenemases was identified (*bla*_{KPC} in *Enterobacterales* and *bla*_{OXA}-type in *A. baumannii*). Given the limited options available for many resistant nosocomial pathogens, our findings support the continued development of this agent.

Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3

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