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 \( \leq 4 \) 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 \( \leq 4 \) 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 \( \leq 4 \) 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 \( \beta \)-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 \( \beta \)-lactamase inhibitors that are active against many pathogens carrying serine \( \beta \)-lactamases.2 However, the currently available agents are not therapeutic options for isolates possessing metallo-\( \beta \)-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) \( \beta \)-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
In this report we examine the in vitro activity of cefiderocol against Enterobacteriales, P. aeruginosa, and A. baumannii endemic to New York City.

Materials and Methods

Isolates

Clinical isolates of Enterobacteriales, P. aeruginosa, and A. baumannii underwent susceptibility testing. Three groups of Enterobacteriales were included: (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 P. aeruginosa (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 the last group, the presence of β-lactamases and genetic expression of blaKPC, ompK35, and acrB were previously determined.17 Multilocus 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

Enterobacteriales

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/mL, 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).

Among the ceftazidime-resistant isolates (n = 130), 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 ≤2 mg/L, including 19 isolates with blaKPC. Of the 19 blaKPC-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 blaKPC) had greater mean cefiderocol MICs (0.43±0.46 vs. 0.21±0.20 mg/mL, 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 (blaSHV) was 1.1 mg/L±0.09 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 blaKPC 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/mL (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 blaKPC, 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 μg/mL. Compared with the isolates susceptible to ceftazidime, the nonsusceptible isolates had MIC50/MIC90 values for cefiderocol that were twofold higher (0.54 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...
| MIC<sub>50</sub> | MIC<sub>90</sub> | Range | Susceptible, % |
|-----------------|-----------------|-------|----------------|
| **2017 surveillance isolates** | | | |
| *Escherichia coli* (*n* = 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 |
| *Enterobacter* spp. (*n* = 172) | | | |
| Cefiderocol | 0.12 | 0.5 | ≤0.03 to 2 | 100 |
| Piperacillin/tazobactam | 4/4 | 32/4 | ≤0.25/4 to >128/4 | 90 |
| Ceftriaxone | ≤0.06 | 32 | ≤0.06 to >32 | 81 |
| Ceftazidime | 0.25 | 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 |
| *Klebsiella pneumoniae* (*n* = 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** | | | |
| *K. pneumoniae* (*n* = 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

| MIC<sub>50</sub> | MIC<sub>90</sub> | Range | Susceptible, % |
|-----------------|-----------------|-------|----------------|
| **2017 surveillance isolates** | | | |
| *P. aeruginosa* (*n* = 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** | | | |
| *P. aeruginosa* (*n* = 130) | | | |
| Cefiderocol | 0.5 | 1 | ≤0.03 to 4 | 100 |
| **2017 surveillance isolates** | | | |
| *A. baumannii* (*n* = 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** | | | |
| *A. baumannii* (*n* = 78) | | | |
| Cefiderocol | 0.5 | 8 | 0.12 to >32 | 88 |
isolates lacking these enzymes.12 Our study also documented carbapenemase, or AmpC-type β-lactamases. Overall, the MICs of Enterobacterales were higher in ESBL-possessing isolates of K. pneumoniae when our collection of characterized isolates of A. baumannii, no correlation was found between ceferodrocol MICs and expression of the efflux genes adeB and adeM.

Our study reaffirms the activity of ceferodrocol against a large number of Gram-negative pathogens, including multiresistant isolates. However, our findings may not be generalized to other multiresistant pathogens, because only a limited variety of carbapenemases was identified (blaKPC in Enterobacterales and blaOXA-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.

Funding Information
Shionogi & Co., Ltd, Osaka, Japan provided financial support for these studies.

Supplementary Material
Supplementary Table S1
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Supplementary Table S3

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