Susceptibility of cefiderocol and other antibiotics against carbapenem-resistant, Gram-negative bacteria

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Background: Cefiderocol is a promising antimicrobial agent against carbapenem-resistant, Gram-negative bacteria, but susceptibility data from the Chinese mainland are lacking. The aim of the present study was to test the susceptibility of cefiderocol against carbapenem-resistant, Gram-negative bacteria collected from Beijing, China.

Methods: Carbapenem-resistant Klebsiella pneumoniae (CR-KP; n=105), carbapenem-resistant Acinetobacter baumannii (CR-AB; n=126), carbapenem-resistant Pseudomonas aeruginosa (CR-PA; n=74), and Stenotrophomonas maltophilia (SM; n=72) isolates were collected from inpatients at 4 tertiary hospitals in Beijing, China. Minimum inhibitory concentrations (MICs) for cefiderocol were determined using iron-depleted cation-adjusted Mueller Hinton broth (CAMHB), and for comparators using CAMHB, according to the recommended Clinical and Laboratory Standards Institute (CLSI) methodology. Carbapenemase and other β-lactamase gene profiles were determined using polymerase chain reaction (PCR).

Results: Cefiderocol inhibited 100% of CR-KP and CR-PA, and 98.6% of the SM isolates at the susceptibility breakpoint concentration of 4 mg/L. However, the susceptibility rate for cefiderocol against CR-AB was only 62.7%, with MIC90 values as high as 128 mg/L. Nearly all the cefiderocol-susceptible CR-AB isolates were found to be positive for blaOXA-23 and blaTEM, whereas all the cefiderocol-resistant CR-AB isolates were found to be positive for the blaPER genes, in addition to blaOXA-23 and blaTEM.

Conclusions: Cefiderocol showed potent in vitro activity against CR-KP, CR-PA, and SM isolates collected from Beijing, China. However, the resistance rate for cefiderocol against CR-AB was higher than that reported by other research centers, and the presence of blaPER might contribute to resistance in non-susceptible CR-AB isolates.

Keywords: Cefiderocol; carbapenem-resistant; multidrug-resistant (MDR); Gram-negative bacteria

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Introduction

With the extensive use of carbapenems, the emergence of carbapenem-resistant, Gram-negative bacteria has become a threat to public health worldwide. These pathogens are usually multidrug-resistant (MDR), show multiple mechanisms of resistance, and are highly resistant to commonly prescribed antimicrobial agents. Owing to the very limited therapeutic options, polymyxins and...
tigecycline are often prescribed as last-resort therapies. However, there are limitations to these therapies, such as the high nephrotoxicity of polymyxins and unsatisfactory pharmacokinetics of tigecycline (1,2). Furthermore, there is resistance to these therapies following their increased clinical application (3,4). Infections caused by carbapenem-resistant, Gram-negative bacteria are still associated with high morbidity and mortality rates, considerably increasing clinical and economic burdens.

In recent years, several new antibiotics have been developed for the treatment of carbapenem-resistant, Gram-negative bacteria. Among them, a novel synthetic siderophore-conjugated antibiotic, cefiderocol, has shown promise as an antimicrobial agent (5). The addition of a catechol siderophore moiety on the C-3 side-chain allows cefiderocol to hijack bacterial iron transport systems, facilitating entry into cells, and therefore achieving high periplasmic concentrations (6). In addition, cefiderocol has high affinity for penicillin-binding protein 3 and is less susceptible to β-lactamases, including Klebsiella pneumoniae carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), and oxacillinases (OXA) carbapenemases (7). Cefiderocol has been approved in the Food and Drug Administration for the treatment of nosocomial pneumonia and complicated urinary tract infections in 2019. Europe approved its use for the treatment of refractory MDR, Gram-negative infections with limited treatment options in 2020.

In the previous study, the in vitro activity of cefiderocol was evaluated against Gram-negative bacteria isolated from Europe, North America, Latin America, and Japan, showing good activity against MDR pathogens, including extended spectrum β-lactamase (ESBL)- and carbapenemase-producing isolates (8). However, susceptibility data on pathogens from mainland China have not been reported. Therefore, in the present study, we analyzed the antimicrobial susceptibility of cefiderocol against clinical isolates of several carbapenem-resistant, Gram-negative bacteria collected from Beijing, China. We present the following article in accordance with the MDAR reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-889/rtc).

Methods

Four species of non-duplicate carbapenem-resistant, Gram-negative bacteria were isolated from inpatients at 4 tertiary A-level hospitals (Peking University People's Hospital, The Sixth Medical Center of PLA General Hospital, Air Force Medical Center and Peking University First Hospital) in 2012–2018. These bacteria were carbapenem-resistant Klebsiella pneumoniae (CR-KP; n=105), carbapenem-resistant Pseudomonas aeruginosa (CR-PA; n=74), MDR Stenotrophomonas maltophilia (SM; n=72), and carbapenem-resistant Acinetobacter baumannii (CR-AB; n=126). Most isolates were isolated from sputum and blood samples. The isolates were stored at −80°C before testing. They were recovered from Mueller-Hinton agar plates for 3 successive generations. All the isolates were identified using the VITEK automated platform (bioMérieux, Marcy-l’Étoile, France). Escherichia coli American Type Culture Collection 25922 was used as the quality control strain. As all in vitro samples were anonymized, the ethics committees waived the requirement for ethical approval of our study or informed consent from patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The minimum inhibitory concentrations (MICs) of various antimicrobial agents (ceftazidime, meropenem, imipenem, amikacin, ceftazidime, cefepime, ceftazidime/avibactam, piperacillin/tazobactam, ticarcillin/clavulanate, ceferozone/sulbactam, tigecycline, minocycline, colistin, levofloxacin, ciprofloxacin, moxifloxacin, fosfomycin, rifampicin, trimethoprim-sulfamethoxazole, and chloramphenicol) were determined by standard broth microdilution methods with cation-adjusted Mueller Hinton broth (CAMHB) according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) (9). The MICs of cefiderocol were determined in iron-depleted CAMHB according to the CLSI (9). The MICs of cefiderocol were defined as the lowest concentration to completely inhibit organism growth or the lowest concentration at which growth was significantly reduced compared to that of the control well (trailing end-points were disregarded) (9). Isolates were tested in duplicate. If the results were not consistent, a third test was performed. The breakpoints for cefiderocol and other comparator agents were determined using the criteria established by the CLSI guidelines (9). The breakpoints for tigecycline against CR-KP were determined using the criteria established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (10). For cefiderocol, MIC ≤4 mg/L was considered susceptible, 8 mg/L as intermediate, and ≥16 mg/L as resistant.

All CR-KP isolates were screened for the presence of carbapenemases genes (blaKPC, blaNDM, blaIMP, blaJ236, blaSIM and
and all CR-AB isolates were screened for various β-lactamase genes (\textit{bla}_{SHV}, \textit{bla}_{PER}, \textit{bla}_{TEM}, \textit{bla}_{CTX-M-1}, \textit{bla}_{CTX-M-2}, \textit{bla}_{CTX-M-9}, \textit{bla}_{CTX-M-24}, \textit{bla}_{GES}, \textit{bla}_{IMP}, \textit{bla}_{VIM}, \textit{bla}_{OXA-23}, \textit{bla}_{OXA-24}, \textit{bla}_{OXA-58}) by polymerase chain reaction (PCR) assays, as previously described (11).

**Statistical analysis**

Statistical analyses were performed with GraphPad Prism 8.0 software (GraphPad Software Inc., La Jolla, CA, USA). Experimental data were expressed as mean ± standard deviation. P values were calculated using the Student’s \( t \)-test if calculation was needed, and P values <0.05 were considered statistically significant.

**Results**

**Susceptibility of cefiderocol against CR-KP**

MIC values of cefiderocol against the CR-KP isolates ranged from <0.03 to 2 mg/L, with MIC\(_{50}\) and MIC\(_{90}\) values of 0.125 and 1 mg/L, respectively (Table 1). Cefiderocol inhibited 100% of the tested isolates at the susceptibility breakpoint concentration of 4 mg/L. Susceptibility rates for colistin and ceftazidime/avibactam were 97.1% and 94.3%, respectively. MIC values of tigecycline ranged from 0.25 to 4 mg/L, and the susceptibility rate was 58.1%, with a breakpoint of 0.5 mg/L, according to the EUCAST. The curves of the cumulative percentage of CR-KP isolates inhibited at various concentrations of cefiderocol, colistin, tigecycline, minocycline, and ceftazidime/avibactam showed that cefiderocol was the most potent antimicrobial (Figure 1A). All isolates were screened for carbapenemase genes (\textit{bla}_{KPC}, \textit{bla}_{NDM}, \textit{bla}_{IMP}, \textit{bla}_{VIM}, \textit{bla}_{SIM}, and \textit{bla}_{OXA-4}) using PCR assay. Eight isolates harbored \textit{bla}_{NDM-1}, whereas other isolates harbored \textit{bla}_{KPC-2}. MICs of cefiderocol for most isolates harboring \textit{bla}_{KPC-2} were <0.5 mg/L. All isolates harboring \textit{bla}_{NDM-1} were resistant to ceftazidime/avibactam, with the MICs of cefiderocol ranging from 1 to 2 mg/L, which were relatively higher than those of isolates with \textit{bla}_{KPC-2}.

**Susceptibility of cefiderocol against CR-PA**

As shown in Table 1, the MIC values of cefiderocol ranged from <0.03 to 4 mg/L, with MIC\(_{50}\) and MIC\(_{90}\) values of 0.5 and 4 mg/L, respectively. Other active agents against CR-PA were colistin, with 97.3% of isolates found to be susceptible, and amikacin, with 80% of isolates found to be susceptible. Figure 1B shows the cumulative percentage of CR-PA isolates inhibited at various concentrations of cefiderocol and comparator agents. A further analysis showed that the MIC\(_{50}\) and MIC\(_{90}\) values for cefiderocol tested against CR-PA with concurrent cephepine resistance (\( n=23 \)) were 2 and 4 mg/L, respectively, whereas those for cephepine non-resistant isolates (\( n=51 \)) were 0.25 and 2 mg/L, respectively (Table 2).

**Susceptibility of cefiderocol against MDR SM**

All the SM isolates tested in this study were MDR, with a resistance rate to trimethoprim-sulfamethoxazole of 77.8%. As shown in Table 1, the MIC values of cefiderocol ranged from <0.03 to 128 mg/L, with MIC\(_{50}\) and MIC\(_{90}\) values of 0.125 and 0.5 mg/L, respectively. One isolate was resistant to cefiderocol. Figure 1C shows the cumulative percentage of MDR SM isolates inhibited at various concentrations of cefiderocol and comparator agents. Cefiderocol was the most active agent, followed by minocycline, with a susceptibility rate of 93%. MICs of tigecycline and moxifloxacin ranged from 0.5–32 mg/L and 0.25–16 mg/L, respectively, with MIC\(_{50}\) values of 2 and 1 mg/L, respectively.

**Susceptibility of cefiderocol against CR-AB**

MIC values of cefiderocol against the various CR-AB isolates ranged from 0.06 to >128 mg/L, with MIC\(_{50}\) and MIC\(_{90}\) values of 0.5 and 128 mg/L, respectively (Table 1). The susceptibility rate for cefiderocol was only 62.7%, with a resistance rate of 35%. Susceptibility rates for colistin and amikacin was 97.6% and 40.5%, respectively. MIC values of tigecycline ranged from 0.125 to 8 mg/L, with MIC\(_{50}\) and MIC\(_{90}\) values of 1 and 2 mg/L, respectively. Figure 1D shows the cumulative percentage of isolates inhibited at various MICs of cefiderocol and comparator agents against CR-AB isolates, indicating that colistin was the most active comparator agent.

We further screened all the CR-AB isolates for various β-lactamase genes (\textit{bla}_{SHV}, \textit{bla}_{PER}, \textit{bla}_{TEM}, \textit{bla}_{CTX-M-1}, \textit{bla}_{CTX-M-2}, \textit{bla}_{CTX-M-9}, \textit{bla}_{CTX-M-24}, \textit{bla}_{GES}, \textit{bla}_{IMP}, \textit{bla}_{VIM}, \textit{bla}_{OXA-23}, \textit{bla}_{OXA-24}, \textit{bla}_{OXA-58}) by PCR assay. Most cefiderocol-susceptible CR-AB isolates were found to be positive for \textit{bla}_{OXA-23} and \textit{bla}_{TEM}, whereas all the cefiderocol non-susceptible CR-AB isolates were found to be positive for the \textit{bla}_{PER} genes, in addition to \textit{bla}_{OXA-23} and \textit{bla}_{TEM}. The MIC distributions of cefiderocol against \textit{bla}_{PER}-positive and \textit{bla}_{PER}-
### Table 1: In vitro activities of cefiderocol and comparative agents against clinical isolates of CR-KP, SM, CR-PA, and CR-AB

| Species/antibiotic | Antimicrobial agent                  | MIC (mg/L) | Resistance (%) | Resistance (%) |
|-------------------|--------------------------------------|------------|----------------|----------------|
|                   |                                      | Range      | MIC₉₀ | MIC₉₀ | Susceptible | Intermediate | Resistant |
| CR-KP (n=105)     | Cefiderocol                          | <0.03–2    | 0.125 | 1     | 100         | 0            | 0         |
|                   | Imipenem                             | 8–>128     | 128   | >128  | 0           | 0            | 100       |
|                   | Meropenem                            | 8–>128     | >128  | >128  | 0           | 0            | 100       |
|                   | Amikacin                             | 1–>512     | 256   | >512  | 39.0        | 1.9          | 59.0      |
|                   | Ceftazidime/avibactam                | 0.25–32    | 8     | 8     | 94.3        | –            | 5.7       |
|                   | Cefoperazone/sublactam               | 16–>512    | 256   | 512   | 58.1        | –            | 41.9      |
|                   | Minocycline                          | 1–128      | 8     | 16    | 43.8        | 24.8         | 31.4      |
|                   | Tigecycline                          | 0.25–4     | 0.5   | 2     | –           | –            | –         |
|                   | Colistin                             | 0.125–64   | 0.5   | 1     | 97.1        | –            | 2.9       |
|                   | Levofloxacin                         | 0.5–>128   | 32    | 128   | 0.9         | 0            | 99.1      |
|                   | Fosfomycin                           | 8–>256     | >256  | >256  | 3.8         | 8.6          | 87.6      |
|                   | Rifampicin                           | 16–>512    | 32    | 512   | –           | –            | –         |
| CR-PA (n=74)      | Cefiderocol                          | <0.03–4    | 0.5   | 4     | 100         | 0            | 0         |
|                   | Imipenem                             | 4–>128     | >128  | >128  | 0           | 2.7          | 97.3      |
|                   | Meropenem                            | 8–>128     | >128  | >128  | 0           | 0            | 100       |
|                   | Amikacin                             | 0.125–>64  | 4     | >64   | 80.0        | 4.0          | 16.0      |
|                   | Piperacillin/tazobactam              | 8–>128     | >128  | >128  | 16.2        | 24.3         | 59.5      |
|                   | Cefoperazone/sublactam               | 0.5–>128   | 32    | >128  | –           | –            | –         |
|                   | Cefepime                             | 2–>128     | 16    | >128  | 44.6        | 24.3         | 31.1      |
|                   | Ceftazidime                          | 0.25–>128  | 8     | >128  | 45.9        | 12.2         | 41.9      |
|                   | Colistin                             | 0.125–8    | 0.5   | 1     | 97.3        | –            | 2.7       |
|                   | Ciprofloxacin                        | 0.06–128   | 8     | 32    | 23.0        | 6.8          | 70.3      |
|                   | Levofloxacin                         | 0.25–>128  | 32    | 128   | 12.2        | 6.8          | 81.1      |

Table 1 (continued)
negative CR-AB was shown in Figure 2.

**Discussion**

MDR, Gram-negative bacteria, including carbapenem-resistant *Enterobacteriaceae*, CR-AB, and CR-PA, and MDR SM, are considered superbugs in healthcare settings. They are associated with resistance to nearly all classes of antibiotics commonly used in clinical settings. Current available treatment options for systemic infections caused by these organisms are limited. Cefiderocol, the novel siderophore cephalosporin, has showed potent *in vitro*
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**Figure 1** Cumulative MIC distribution (percentage of isolates) of cefiderocol and comparator agents for CR-KP, CR-PA, SM and CR-AB. MIC, minimum inhibitory concentration; CR-KP, carbapenem-resistant *Klebsiella pneumoniae*; CR-PA, carbapenem-resistant *Pseudomonas aeruginosa*; SM, *Stenotrophomonas maltophilia*; CR-AB, carbapenem-resistant *Acinetobacter baumannii*.

**Table 2** *In vitro* activity of cefiderocol and comparative agents against CR-PA with concurrent non-resistance or resistance cefepime

| Antimicrobial susceptibility phenotype | Antimicrobial agent | MIC (mg/L) | Resistance (%) |
|---------------------------------------|--------------------|------------|----------------|
| Cefepime non-resistant
(n=51)                                 | Cefiderocol        | <0.03–4    | 2              | 100 0 0 |
|                                       | Cefazidime         | 1–>128     | >128           | 56.9 17.6 25.5 |
|                                       | Colistin           | 0.125–8    | 1              | 98.0 – 2.0 |
|                                       | Amikacin           | 0.125–64   | 32             | 84.3 3.9 11.8 |
|                                       | Ciprofloxacin      | 0.06–128   | 32             | 31.4 9.8 58.8 |
| Cefepime resistant
(n=23)                               | Cefiderocol        | 0.125–4    | 4              | 100 0 0 |
|                                       | Cefazidime         | 0.25–>128  | 128            | 21.7 0 78.3 |
|                                       | Colistin           | 0.125–4    | 1              | 95.7 – 4.3 |
|                                       | Amikacin           | 0.5–>64    | >64            | 69.6 4.3 26.1 |
|                                       | Ciprofloxacin      | 0.125–128  | 32             | 4.3 0 95.7 |

CR-PA, carbapenem-resistant *Pseudomonas aeruginosa*; MIC, minimum inhibitory concentration.
activity against carbapenem-resistant, Gram-negative bacteria, giving hope for combating these superbugs. However, resistance to a novel antibiotic could already exist. Therefore, antimicrobial resistance surveillance from both a global and local scale can provide useful information for guidance on the empirical use of antibiotics and the development of rational antimicrobial stewardship policies.

In the current study, all CR-KP isolates were susceptible to cefiderocol. Cefiderocol showed more potent in vitro antimicrobial activity than colistin, tigecycline, and ceftazidime/avibactam. In China, the main carbapenemases in CR-KP are KPC, followed by NDM (12). We further found that the MICs of cefiderocol for CR-KP with \( \text{bla}_{\text{NDM,1}} \) ranged from 1 to 2 mg/L, which were relatively higher than those of isolates with \( \text{bla}_{\text{KPC,2}} \). These findings were in accordance with those reported in the SIDERO-CR study, which showed that cefiderocol had less potent activity against NDM-producing isolates compared with other isolates (13). It has been reported that the use of ceftazidime/avibactam to treat KPC-producing CR-KP could lead to a shift in the carbapenemase landscape, from the KPC to MBLs (14). The wide of use cefiderocol in future may also lead to the selection of NDM-producing isolates.

Previous susceptibility has demonstrated the potency of cefiderocol against the CR-AB. The ARGONAULT-I study tested the MIC values of cefiderocol against 101 CR-AB isolates, with MICs ranging from \( \leq 0.03 \) to >64 mg/L, and MIC\(_{50}\) and MIC\(_{90}\) values of 0.25 and 1 mg/L, respectively (15). In their study, Falagas et al. included 107 CR-AB isolates collected from 18 Greek hospitals, with MIC\(_{50}\) and MIC\(_{90}\) values of cefiderocol of 0.06 and 0.5 mg/L, respectively (16). Hackel et al.’s study included 368 MDR AB isolates collected from laboratories from 52 countries in 2014 to 2016. They found that the MIC\(_{50}\) and MIC\(_{90}\) values of cefiderocol were 0.25 and 8 mg/L, respectively (17). Surprisingly, the susceptibility rate for cefiderocol against CR-AB in our study was much lower than those reported in the above studies. It has been reported that PER \( \beta\)-lactamase is associated with cefiderocol resistance in CR-AB (18). We found that all cefiderocol non-susceptible CR-AB isolates were positive for the \( \text{bla}_{\text{PER}} \) gene, in addition to \( \text{bla}_{\text{OXA-23}} \) and \( \text{bla}_{\text{TEM}} \), suggesting that PER \( \beta\)-lactamase contributes to decreased cefiderocol susceptibility and a possible high prevalence of \( \text{bla}_{\text{PER}} \) in CR-AB isolates in Beijing, China.

Cefiderocol at a concentration of 4 mg/L inhibited 100% of all CR-PA isolates and 98.6% of all MDR SM isolates, indicating that cefiderocol had potent in vitro activity against these 2 non-fermentative bacteria in the present study. The MIC distribution for SM was similar to that reported in other studies (19-21). Nevertheless, the MIC values for CR-PA (MIC\(_{90}\) = 4 mg/L) were generally higher than those reported by other centers. The ARGONAULT-I study tested the MIC values of cefiderocol against 27 CR-PA isolates, with the MICs ranging from 0.03 to 1 mg/L and MIC\(_{50}\) and MIC\(_{90}\) values of 0.25 and 0.5 mg/L, respectively (15). A study by Kazmierczak et al., which included 353 meropenem non-susceptible PA isolates collected from Europe and North America in the SIDERO-WT-2014 surveillance project, showed that the MIC\(_{50}\) and MIC\(_{90}\) values of cefiderocol were 0.12 and 1 mg/L, respectively (11). Liu et al.’s study, which included 150 CR-PA isolates collected from Taiwan, China, showed MIC\(_{50}\) and MIC\(_{90}\) values of cefiderocol of 0.25 and 1 mg/L, respectively (22). Our further analysis showed the MICs for cefiderocol tested against CR-PA isolates with concurrent cefepime resistance were generally higher than those for cefepime non-resistant isolates. The concrete mechanisms of cefepime resistance and the relationship between cefepime resistance and decreased cefiderocol susceptibility should be further investigated.

Our study has several limitations. First, a relatively small number of isolates collected from a single region were tested. Second, we did not perform an in-depth investigation of the molecular epidemiology of the isolates. Therefore, the generalizability of our findings to other centers and regions where the genotypes and the frequency of different \( \beta\)-lactamase genes might differ requires further confirmation.

Overall, the first susceptibility surveillance on cefiderocol...
from mainland China found that cefiderocol had potent *in vitro* activity against CR-KP, CR-PA, and MDR SA isolates collected from Beijing, China. However, the resistance rate for cefiderocol against CR-AB was higher than that reported by other research centers (8), and the presence of *bla*<sub>PER</sub> might be related to cefiderocol resistance in those non-susceptible CR-AB.

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**Footnote**

**Reporting Checklist:** The authors have completed the MDAR reporting checklist. Available at [https://atm.amegroups.com/article/view/10.21037/atm-22-889/rc](https://atm.amegroups.com/article/view/10.21037/atm-22-889/rc)

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**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at [https://atm.amegroups.com/article/view/10.21037/atm-22-889/coil](https://atm.amegroups.com/article/view/10.21037/atm-22-889/coil)). WN reports that this research was funded by Peking University People’s Hospital Research and Development Funds (Grant No. RS2020-04). The other authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. As all *in vitro* samples were anonymized, the ethics committees waived the requirement for ethical approval of our study or informed consent from patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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