Activity of Cefiderocol and Comparators against US isolates of Pseudomonas aeruginosa, Acinetobacter baumannii-calcoaceticus species complex, and Stenotrophomonas maltophilia, including Carbapenem-Resistant Isolates

Dee Shortridge, Jennifer M. Streit, Rodrigo Mendes, Mariana Castanheira

JMI Laboratories 345 Beaver Kreek Centre, Suite A
Wayne, PA 19087 Phone: (215) 653-3370
www.jmilabs.com/data/posters

Conclusions

Cefiderocol had potent activity against P. aeruginosa, including XDR isolates and isolates resistant to other BL/BLI combination therapies. Cefiderocol also had excellent activity against A. baumannii-calcoaceticus species complex, including XDR and meropenem-resistant isolates. All S. maltophilia were inhibited by cefiderocol at an MIC of ≤4 mg/L. These in vitro data suggest that cefiderocol is an important treatment option for infections caused by non-fermenting species, including resistant pathogens for which there are limited therapeutic choices.

Acknowledgements

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References


Cefiderocol is a novel siderophore-conjugated cephalosporin with broad activity against aerobic Gram-negative bacteria, including multidrug-resistant (MDR) organisms.

Acinetobacter baumannii-calcoaceticus species complex, Pseudomonas aeruginosa and Stenotrophomonas maltophilia can be extensively-drug resistant (XDR) and present serious treatment challenges. Cefiderocol was approved by the EMA for the treatment of infections caused by Gram-negative bacteria in adult patients with limited treatment options and the FDA for complicated urinary tract infection (UTI); hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia.

The susceptibility of cefiderocol and comparators was investigated against US Gram-negative non-fermentative isolates collected in 2020 as part of the SENTRY Antimicrobial Surveillance Program.

Introduction

Cefiderocol was defined as susceptible to ≤2 drug classes.
– Other agents tested included the beta-lactam/ beta-lactamase inhibitor (BL/BLI) combinations cefotaxime-avibactam, cefepime-relebactam, imipenem-relebactam, meropenem/vaborbactam, and meropenem.

Results

The most common non-fermenting Gram-negative organism was Pseudomonas aeruginosa (n=230) followed by A. baumannii-calcoaceticus species complex (n=229) and S. maltophilia (n=186) (Figure 1).
– The most common infection type was pneumonia (n=79%), followed by skin/skin structure infection (n=29%).
– The cumulative MIC distributions of cefiderocol and comparators were shown for P. aeruginosa (Figure 2) and A. baumannii-calcoaceticus species complex (Figure 3).

Cefiderocol and comparator BL/BLI susceptibilities against P. aeruginosa were ≥96.0%, except for meropenem/vaborbactam (85.2%, Table 1).
– Cefiderocol was the most active drug tested against XDR P. aeruginosa isolates (97.3/96.7/96.3% susceptibility according to CLSI, FDA, EUCAST respectively). The susceptibilities of BL/BLI comparators ranged from 40.5/45.8/48.3% (Table 1).
– Cefiderocol was also active against meropenem-resistant P. aeruginosa (96.7%).
– Cefiderocol remained active against 8 resistant isolates to all BL/BLI tested showing 87.5% susceptibility according to breakpoints provided by CLSI, FDA, and EUCAST respectively.
– Against all A. baumannii-calcoaceticus species complex, cefiderocol was very active (97.0/95.2/96.5%). CLSI, FDA, EUCAST (Table 2).
– Cefiderocol susceptibility rates against the XDR and meropenem-resistant A. calcoaceticus-baumannii species complex subsets were 94.2/81.2/92.8% and 93.2/81.2/92.0%, respectively (CLSI, FDA, EUCAST).
– Cefiderocol was highly active against S. maltophilia with 100.0/98.9% susceptibility at MIC values ≤4 mg/L and ≤2 mg/L according to breakpoints provided by CLSI and EUCAST, respectively (Table 2).
– CLSI S. maltophilia breakpoints will be updated in 2022 to ≤1 mg/L; cefiderocol was active against 97.3% of isolates at MIC values of ≤1 mg/L.

Materials and Methods

A total of 1,358 isolates were consecutively collected from multiple specimen types in 29 US hospitals during 2020.

Susceptibility testing was performed using the broth microdilution method.
– Cefiderocol was tested in iron-depleted Mueller-Hinton broth, FDA, CLSI, and/or EUCAST (2021) breakpoints were used as available.
For cefiderocol, the following breakpoints were used for the organism groups in this study:
– For P. aeruginosa: cefiderocol CLSI breakpoints are ≤4/8/≤16 mg/L, (susceptible, intermediate, and resistant, respectively), FDA breakpoints are ≤1/2/≤4 mg/L, and EUCAST breakpoints are ≤2/≤4/≤2 mg/L.
– For A. baumannii-calcoaceticus species complex: cefiderocol CLSI breakpoints are ≤4/8/≤16 mg/L (susceptible/intermediate/resistant), FDA breakpoints are ≤1/2/≤4 mg/L, EUCAST non-species-specific PK/PD breakpoints are ≤2/≤4 mg/L.
– For S. maltophilia: cefiderocol CLSI breakpoints are ≤4/8/≤16 mg/L and will be updated in 2022 to ≤1/≤4 mg/L and EUCAST non-species-specific PK/PD breakpoints are ≤2/≤4 mg/L.

Table 1. Susceptibilities of P. aeruginosa and resistant subgroups tested against cefiderocol and comparators

<table>
<thead>
<tr>
<th>Drug/Species Complex</th>
<th>MIC (mg/L)</th>
<th>%S</th>
<th>%S</th>
<th>%S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem-vaborbactam</td>
<td>1/8/16</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Imipenem-relebactam</td>
<td>0.12/0.5</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Cefiderocol</td>
<td>0.12/0.25</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2. Susceptibilities of Acinetobacter baumannii-calcoaceticus species complex and resistant groups as well as Stenotrophomonas maltophilia tested against cefiderocol and comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC (mg/L)</th>
<th>%S</th>
<th>%S</th>
<th>%S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem-relebactam</td>
<td>0.25/1</td>
<td>97.3</td>
<td>97.3</td>
<td>97.3</td>
</tr>
</tbody>
</table>

Table 3. Susceptibilities of cefiderocol and comparators for 228 US isolates of A. baumannii-calcoaceticus species complex (n=228)

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC (mg/L)</th>
<th>%S</th>
<th>%S</th>
<th>%S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem-vaborbactam</td>
<td>0.25/1</td>
<td>97.0</td>
<td>92.2</td>
<td>96.5</td>
</tr>
<tr>
<td>Imipenem-relebactam</td>
<td>0.03/0.015</td>
<td>77.6</td>
<td>77.6</td>
<td>77.6</td>
</tr>
<tr>
<td>Cefiderocol</td>
<td>0.12/0.5</td>
<td>98.7</td>
<td>96.7</td>
<td>97.4</td>
</tr>
</tbody>
</table>

Figure 1. Frequency of the most commonly isolated non-fermentative organisms

Figure 2. Cumulative percent MIC distribution of cefiderocol and comparators for 999 US isolates of P. aeruginosa (n=999)

Figure 3. Cumulative percent MIC distribution of cefiderocol and comparators for 228 US isolates of A. baumannii-calcoaceticus species complex (n=228)