Antimicrobial Activity of Ceftazidime-Avibactam and Comparator Agents against Pseudomonas aeruginosa and Enterobacteriales Causing Pneumonia in Cystic Fibrosis Patients

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INTRODUCTION
• More than 50% of cystic fibrosis (CF) individuals aged 18 years and older in the USA are infected with Pseudomonas aeruginosa, of which approximately one-third is multidrug-resistant (MDR).
• Very few agents remain active against MDR P. aeruginosa and rapidly introducing antimicrobial therapy is crucial to reduce morbidity and mortality of patients with infections caused by these organisms.
• Ceftazidime-avibactam is approved by the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) to treat hospital-acquired bacterial infections caused by P. aeruginosa.

MATERIALS AND METHODS
• Bacterial isolates determined to be significant by local criteria as the reported probable cause of respiratory infection were consecutively collected from CF patients (17 years and older).
• Isolates were collected from 43 medical centers worldwide (10 nations) in 2018-2019.
• The organism collection included 273 P. aeruginosa and 62 Enterobacterales isolates.
• Susceptibility testing was performed by reference broth microdilution methods at a central laboratory (JMI Laboratories, North Liberty, Iowa).
• Antimicrobial agents tested included ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (C-T), piperacillin-tazobactam (PIP-TAZ), meropenem (MEM), ceftazidime (CAZ), ceftriaxone (CRO), tobramycin (TOB), imipenem (IMI), and gentamicin (GEN).
• MDR was defined as nonsusceptibility (CLS) breakpoints to at least 1 drug in 3 classes.

RESULTS
• Ceftazidime-avibactam (MIC50/90, 2/8 mg/L; 96.0% susceptible [S]) was the most active agent against P. aeruginosa, followed by ceftazidime-tazobactam (MIC50/90, 14 mg/L; 95.3%), ceftazidime (MIC50/90, 2/42 mg/L; 90.6%), piperacillin-tazobactam (MIC50/90, 4/128 mg/L; 80.2%), and tobramycin (MIC50/90, 2/16 mg/L; 96.8%); Figure 1).
• Ceftazidime-avibactam retained activity against P. aeruginosa isolates nonsusceptible to meropenem (90.5% to ceftazidime-avibactam; tobramycin, piperacillin-tazobactam, and ceftriaxone [75.6% to ceftazidime-avibactam or tobramycin]; and ceftazidime-avibactam [73.6% to ceftazidime-avibactam; Table 1 and Figure 2]).
• Moreover, 65.4% of ceftazidime-tazobactam-nonsusceptible isolates remained susceptible to ceftazidime-avibactam (Table 1).
• Among P. aeruginosa, 30.2% were multidrug-resistant (MDR, resistant to ≥3 classes), and 69.9% and 73.2% of MDR P. aeruginosa were susceptible to ceftazidime-avibactam and ceftolozane-tazobactam, respectively (Figure 2).
• Among P. aeruginosa isolates nonsusceptible to piperacillin-tazobactam, meropenem, and ceftazidime (75.3% of total), susceptibility to ceftazidime-avibactam and ceftolozane-tazobactam was 78.9% and 47.4%, respectively (Figure 2).
• The most active agents against Enterobacterales were ceftazidime-avibactam (MIC50/90, 0.125/0.5 mg/L; 100.0%), and meropenem (MIC50/90, 0.03/0.12 mg/L; 98.6%, Figure 1); Table 2).
• Enterobacterales isolates (MIC50/90, ≤0.125/4 mg/L) were active against 88.9% of MDR isolates.
• Among Enterobacterales isolates, 17.7% were MDR.

Table 1. Cross-resistance among β-lactams and β-lactamase inhibitor combinations when tested against P. aeruginosa isolates from CF patients (2018–2019)

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MEM</th>
<th>PIP-TAZ</th>
<th>CAZ</th>
<th>CRO</th>
<th>LEV</th>
<th>GEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAZ-AVI</td>
<td>86.5</td>
<td>85.2</td>
<td>79.2</td>
<td>63.6</td>
<td>65.2</td>
<td>63.2</td>
</tr>
<tr>
<td>C-T</td>
<td>90.6</td>
<td>63.0</td>
<td>52.8</td>
<td>63.3</td>
<td>63.3</td>
<td>58.3</td>
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<tr>
<td>PIP-TAZ</td>
<td>96.0</td>
<td>0.0</td>
<td>7.9</td>
<td>96.5</td>
<td>96.5</td>
<td>96.5</td>
</tr>
<tr>
<td>MEM</td>
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<td>20.4</td>
<td>17.0</td>
<td>20.4</td>
<td>20.4</td>
<td>20.4</td>
</tr>
<tr>
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<td>0.0</td>
<td>0.0</td>
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</tr>
</tbody>
</table>

CONCLUSIONS
• Ceftazidime-avibactam retained potent and broad-spectrum activity against P. aeruginosa (99.6%) and Enterobacterales (99.6%) isolated from CF patients worldwide and retained potent activity against isolates resistant to other agents (Table 1).
• Ceftazidime-avibactam and ceftolozane-tazobactam exhibited similar P. aeruginosa and Enterobacterales activity with more active than ceftazidime-tazobactam against P. aeruginosa-resistant subsets.
• Ceftolozane-tazobactam represents a valuable option to treat CF patients with respiratory tract infections.

ACKNOWLEDGMENTS
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REFERENCES

Figure 1. Antimicrobial susceptibility of P. aeruginosa (n=273) collected from cystic fibrosis patients worldwide (2018–2019)

Figure 2. Antimicrobial activity of ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (C-T), and tobramycin (TOB) tested against P. aeruginosa resistant subsets from cystic fibrosis patients (2018-2019)

Figure 3. Antimicrobial susceptibility of Enterobacteriales (n=62) collected from cystic fibrosis patients worldwide (2018–2019)

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