In vitro activity of aztreonam-avibactam against metallo-β-lactamase-producing Enterobacteriaceae isolates collected during a global surveillance program, 2012–2015

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Background: A series of questionnaire surveys was conducted in a global surveillance program to collect Enterobacteriaceae isolates producing metallo-β-lactamases (MBLs) from 40 participating countries to assess in vitro activity of aztreonam-avibactam against MBL-positive isolates. Enterobacteriaceae isolates were collected during 2012–2015 from four categories: urinary tract, respiratory tract, skin and soft tissue, and bloodstream. Enterobacteriaceae isolates with meropenem, doripenem, or imipenem MIC >1 mg/L or ertapenem MIC >0.5 mg/L were tested against aztreonam-avibactam at a fixed concentration of 4 mg/L.

Materials & Methods

- 31,300 non-repetitive Enterobacteriaceae isolates from intravascular, urinary tract, respiratory tract, skin and soft tissues, and bloodstream (2012–2015) were collected from 40 participating countries.
- Susceptibility testing was performed by Clinical and Laboratory Standards Institute (CLSI) broth microdilution guidelines [2]. Aztreonam-avibactam was tested at a fixed concentration of 4 mg/L.
- PCR and sequencing of β-lactamase genes (blaIMP, blablaVIM, blablaNDM, blablaKPC, blablaCMY, blablaGES, blablaSER, blablaHER, blablaSHV, blablaCTX-M, blablaTEM, and blablaOXA-48-like) were performed on 3,350 isolates with amoxicillin-clavulanic acid or imipenem MIC >1 mg/L or oxacillin MIC >4 mg/L as described previously [3].

Results

- 2% of 2,932,932 Enterobacteriaceae isolates were MBL-positive and 22% of these were collected in 2014–2015.
- No isolates were obtained from patients in China in 2014–2015.
- Of the 51,352 Enterobacteriaceae collection from 2012–2015, 267 isolates of 11 species produced MBLs, with a significant number (44%) of MBLs being aztreonam-refractory to hydrolysis by MBLs but is inactivated by Class A (KPC, extended-spectrum β-lactamases) or Class C serine carbapenemases (KPC, extended-spectrum β-lactamases) enzymes.
- The proportion of MBL-positive Enterobacteriaceae isolates with meropenem, doripenem, or imipenem MIC >1 mg/L or ertapenem MIC >0.5 mg/L was performed on isolates with meropenem, doripenem, or imipenem MIC >1 mg/L or ertapenem MIC >0.5 mg/L. Aztreonam-avibactam was tested at a fixed concentration of 4 mg/L.


does not include species with endogenous AmpC or ESBL enzymes.

Table 1 - In vitro activity of aztreonam-avibactam and comparator agents tested against MBL-positive isolates producing MBLs

<table>
<thead>
<tr>
<th>Organism (n)a / Drug Group (n)a</th>
<th>MIC Range (mg/L)</th>
<th>MIC50 (mg/L)</th>
<th>MIC90 (mg/L)</th>
<th>% Susceptiblec</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBL + ESBL + AmpC</td>
<td>≤0.015 to 8</td>
<td>≤0.015</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>MBL + ESBL</td>
<td>≤0.015 to 8</td>
<td>≤0.015</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>MBL + MIR</td>
<td>≤0.015 to 2</td>
<td>≤0.015</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>MBL + VIM</td>
<td>≤0.015 to 2</td>
<td>≤0.015</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>MBL + KPC + ESBL</td>
<td>≤0.015 to 2</td>
<td>≤0.015</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>MBL + OXA-48-like + AmpC</td>
<td>≤0.015 to &gt;128</td>
<td>≥1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>MBL + KPC + AmpC</td>
<td>≤0.015 to &gt;128</td>
<td>≥1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>MBL + OXA-48-like + MIR</td>
<td>≤0.015 to &gt;128</td>
<td>≥1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>MBL + OXA-48-like + VIM</td>
<td>≤0.015 to &gt;128</td>
<td>≥1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Conclusion

- Aztreonam-avibactam was highly active in vitro against all class III metallo-β-lactams (MBLs), including ESBLs, AmpCs, and ESBLs. Aztreonam-avibactam was highly active against all class III metallo-β-lactams (MBLs), including ESBLs, AmpCs, and ESBLs. Aztreonam-avibactam was strongly active against all class III metallo-β-lactams (MBLs), including ESBLs, AmpCs, and ESBLs. Aztreonam-avibactam was strongly active against all class III metallo-β-lactams (MBLs), including ESBLs, AmpCs, and ESBLs.

References & Acknowledgments

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Figure 1A. Aztreonam-avibactam MIC distributions against Enterobacteriaceae isolates producing MBLs (n=96).

Figure 1B. Aztreonam and aztreonam-avibactam MIC distributions against Enterobacteriaceae isolates producing NDM-type MBLs (n=142).

Figure 1C. Aztreonam and aztreonam-avibactam MIC distributions against Enterobacteriaceae isolates producing IMP-type MBLs (n=29).

Figure 2A. Geographic distribution of MBL-producing isolates collected in 2012–2015, by region.

Figure 3A. Percentage of isolates (%) inhibited at each MIC (mg/L) by aztreonam-avibactam.

Figure 3B. Aztreonam and aztreonam-avibactam MIC distributions against Enterobacteriaceae isolates producing VIM-type MBLs (n=96).