The Susceptibility of Sulbactam/ETX2514 and Comparators to Global Isolates of Acinetobacter baumannii

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Background: The diazabicyclooctenone ETX2514 is a novel broad-spectrum serine β-lactamase inhibitor that restores sulbactam (SUL) activity against resistant Acinetobacter baumannii. The combination subactam-ETX2514 (ETX2514SUL) is promising in vitro and in vivo activity against this organism. The purpose of this study was to evaluate the activity of ETX2514SUL and comparators against global, non-duplicate isolates of carbapenem-resistant A. baumannii (CRAB).

Materials and methods: Clinical isolates (n=246) were obtained from various body sites in patients and were collected in 37 countries and from six world regions between 2012-2016. Antimicrobial susceptibility testing was performed by broth microdilution in cation-adjusted Mueller-Hinton broth according to CLSI guidelines. The concentration ranges tested in 2-fold dilutions were: ETX2514SUL (fixed 4µg/mL), 0.06-128/8/256 µg/mL; imipenem/sulbactam/ETX2514 (1:1:2), 0.06/0.06/0.12-128/128/256 µg/mL; amikacin, 0.25-256 µg/mL; colistin (COL), 0.06-128 µg/mL; imipenem, 0.06-128 µg/mL; meropenem, 0.06-128 µg/mL; minocycline, 0.03-64 µg/mL; and sulbactam, 0.06-128 µg/mL. Susceptibility was determined using CLSI 2018 breakpoints where applicable. Based on core genome MLST results, isolates represented the 9 worldwide clonal lineages and included 184 isolates with blaOXA-23-like, 47 isolates with blaOXA-40-like, 3 isolates with blaOXA-58-like, 1 isolate with blaOXA-235-like, 3 isolates with NDM, one isolate with IMP, and 7 isolates with overexpression of intrinsic blaOXA-51.

Results: The ETX2514SUL MIC50/90 values for all isolates were 1/4 and 2/4 µg/mL, respectively. Comparatively, SUL, COL, minocycline, and amikacin MIC50/90 values were 16/64, 0.5/1, 0/1, and 2/256 µg/mL, respectively. Ten isolates were resistant to COL (4.1%), all of which had low ETX2514SUL MICs of ≤2/4 µg/mL.

Conclusions: ETX2514SUL had excellent in vitro potency, including against isolates that were pan-resistant to SUL, imipenem/meropenem, and COL, and amikacin, compared to other compounds. ETX2514SUL may be a therapeutic option for treatment of infections due to multidrug-resistant A. baumannii.

Methods cont.

- The isolates represented the nine previously described international clonal lineages (1) and included 184 isolates with blaOXA-23-like, 47 isolates with blaOXA-40-like, 3 isolates with blaOXA-58-like, 1 isolate with blaOXA-235-like, 3 isolates with NDM, one isolate with IMP, and 7 isolates with overexpression of intrinsic blaOXA-51.
- The majority of A. baumannii isolates apart from being resistant to carbapenems were also resistant to amikacin and had high subcactam MICs. The resistance rate to colistin was 4.1%.
- The ETX2514SUL MIC50/90 values for all isolates were 1/4 and 2/4 µg/mL, respectively. Comparatively, SUL, COL, minocycline, and amikacin MIC50/90 values were 16/64, 0.5/1, 0/1, and ≥128/256 µg/mL, respectively.
- Only nine isolates (3.6%) had ETX2514SUL MICs of ≥2/4 µg/mL.

Table 1. MIC distribution, MIC50 and MIC90 values of the 246 carbapenem-resistant A. baumannii isolates

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC50 µg/mL</th>
<th>MIC90 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUL</td>
<td>0.06</td>
<td>128</td>
</tr>
<tr>
<td>ETX2514SUL</td>
<td>128</td>
<td>128</td>
</tr>
<tr>
<td>Imipenem</td>
<td>128</td>
<td>128</td>
</tr>
<tr>
<td>Meropenem</td>
<td>128</td>
<td>128</td>
</tr>
<tr>
<td>Minocycline</td>
<td>128</td>
<td>128</td>
</tr>
<tr>
<td>Sulbactam</td>
<td>128</td>
<td>128</td>
</tr>
</tbody>
</table>

References andAcknowledgements


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Conclusions

- ETX2514SUL had excellent in vitro potency against A. baumannii isolates including those that were resistant to sulbactam, imipenem/meropenem, colistin, and amikacin, compared to other compounds.
- ETX2514SUL has the potential to become a useful addition to the limited armamentarium of drugs that can be used to treat this problem pathogen.