### INTRODUCTION

- Carbenem-resistant *Klebsiella pneumoniae* (CR-Kp) have emerged worldwide as important nosocomial pathogens, capable of causing infections with high rates of morbidity and mortality.
- Aminoglycosides retain potent bactericidal activity against some, but not all carbenem-resistant *K. pneumoniae* strains.
- Aminoglycoside resistance is mediated by multiple mechanisms, including impaired membrane permeability, efflux mechanisms, ribosomal alterations or expression of aminoglycoside modifying enzymes (AMEs).
- AMEs are the most important determinant of aminoglycoside resistance among *K. pneumoniae*.
- Plazomicin is a next-generation aminoglycoside that has side chain substituents that shield it from the action of most AMEs.
- The only mechanism resistance demonstrated among carbenem-resistant *K. pneumoniae* to date is expression of acquired 16S ribosomal RNA (rRNA) methyltransferase.

### METHODS

- Standard broth microdilution method according to the Clinical and Laboratory Standards Institute was used to determine minimum inhibitory concentrations (MICs) of the carbapenems.
- Time-kill assays (TKAs) were performed to evaluate the bactericidal activity.
- Polymerase chain reaction (PCR) and DNA sequencing were used to detect presence of AMEs.
- Presence of efflux pump was determined using an efflux pump inhibitor carbonyl cyanide m-chlorophenyl hydrazone (CCCP).

### RESULTS

#### A. Strain characterization

- 47 ST258
- 40 KPC-2
- 5 KPC-3
- 5 non KPC-producers

### E. Association between AMEs and aminoglycoside MICs

<table>
<thead>
<tr>
<th>Pattern of AME</th>
<th>Gentamicin MIC</th>
<th>Tobramycin MIC</th>
<th>Amikacin MIC</th>
<th>Plazomicin MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not present</td>
<td>0.5 0.5 0.5</td>
<td>0.5 0.5 0.5</td>
<td>0.5 0.5 0.5</td>
<td>0.5 0.5 0.5</td>
</tr>
<tr>
<td>Present</td>
<td>1.5 1.5 1.5</td>
<td>1.5 1.5 1.5</td>
<td>1.5 1.5 1.5</td>
<td>1.5 1.5 1.5</td>
</tr>
</tbody>
</table>

### CONCLUSIONS

- CR-Kp strains, including ST258 strains considered clonal by conventional criteria, exhibit remarkable diversity of AME enzymes.
- Patterns of AMEs identified CR-Kp strains that were likely to be aminoglycoside-resistant, and may serve as rapid markers for guiding treatment decision-making.
- In particular, detection of AAC(6')-Ib combined with another AME (especially AAC(3')-IV) was highly sensitive for identifying gentamicin-resistant strains.
- AAC(6')-Ib can confer decreased susceptibility to amikacin, which may not be captured by MIC breakpoints.
- Plazomicin appears to be an important addition to the antimicrobial armamentarium at a time of rapidly emerging antibiotic resistance among *Enterobacteriaceae*. 

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**B. Susceptibility to aminoglycosides**

<table>
<thead>
<tr>
<th>AG</th>
<th>MIC range</th>
<th>Resistance *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>0.25–&gt;64 µg/mL (40%)</td>
<td>20/50</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1–64 µg/mL (16%)</td>
<td>8/50</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>0.25–&gt;64 µg/mL (98%)</td>
<td>49/50</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>0.125–1 µg/mL</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Including isolates with intermediate susceptibility NA no CLSI breakpoint*

**B2. Correlation between different aminoglycosides**

<table>
<thead>
<tr>
<th>Gentamicin-susceptible (AG)</th>
<th>Gentamicin-resistant (AG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin MIC</td>
<td>Tobramycin MIC</td>
</tr>
<tr>
<td>Gentamicin MIC Range</td>
<td>AGC</td>
</tr>
<tr>
<td>Gentamicin MIC (µg/mL)</td>
<td>Tobramycin MIC (µg/mL)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>16</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>16</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*Values denote the difference in median MIC of respective aminoglycosides between the gentamicin-susceptible and -resistant isolates.*

**Note:**

- There was a correlation between gentamicin MIC and tobramycin MIC and plazomicin MICs.
- There was no correlation between gentamicin MIC and amikacin MIC.

### C. Time-kill assays (TKAs)

- Dose-dependent killing against all strains.
- 1xMIC: 17% bactericidal.
- 4xMIC: 94% bactericidal, but regrowth evident in 29%.
- 16xMIC or 64xMIC: 100% bactericidal, no regrowth.

### D. Aminoglycoside modifying enzymes

- AAC(6')-I, 98% (49)
- AAC(3')-I, 38% (19)
- AAC(3)-IIa, 12% (6)
- AAC(6')-Ib, 56% (28)