Emergence of diverse Carbapenem-resistant Enterobacteriaceae (CRE) in the Dominican Republic

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ABSTRACT

Background: Despite the global threat of CRE, data from resource-limited regions such as the Dominican Republic (DR) are limited. A lack of novel antibiotics and molecular diagnostic tools for outbreak detection, coupled with the role of travel in circulating CRE to and from the DR represent significant challenges to limiting their spread. We report the first molecular characterization of DR CRE isolates and compared them to geographically diverse CRE.

Methods: Isolates from DR (1 Citrobacter freundii, 3 Klebsiella pneumoniae), obtained from patients with bacteremia (1) and pneumonia (3) were compared to CRE from a New York City hospital in a Dominican neighborhood, including isolates (2 Enterobacter cloacae, 1 K. pneumoniae) from a patient transferred from another DR institution. Whole genome sequencing was used to determine multi-locus sequence type (MLST) and resistance gene profiles. Phylogenetic analyses of isolates with same ST were performed.

Results: Isolates from the DR and the Dominican patient were of unique genomic backgrounds, and harbored blaKPC and blaOXA (Table 1). Replicon typing suggested that these were located on plasmids. Phylogenetic analyses using the NYU collection of ~400 sequenced CRE isolates, indicated that DR and NYC K. pneumoniae ST307 isolates were related (33 SNPs). Further review showed that both patients had recent admissions in Puerto Rico (PR), highlighting the role of regional spread.

Conclusion: Genotyping of DR CRE isolates revealed a high genomic diversity, suggesting multiple introductions. Phylogenetics of K. pneumoniae ST307 place these within a global context, demonstrating links across the Caribbean and North America. International surveillance systems integrating genomics are needed to track and limit the spread of CRE in resource-limited settings such as DR.

BACKGROUND

• Carbapenem-resistant Enterobacteriaceae (CRE) represent an urgent threat to healthcare according to CDC1.
• The Klebsiella pneumoniae carbapenemase (KPC) is the dominant mechanism of carbapenem resistance in the US2.
• Burden of CRE in resource limited settings incompletely described
• Potential challenges include difficulties in diagnostics, lack of appropriate antibiotics and lack of molecular tools for outbreak detections
• Travel as a potential source of CRE introduction and spread into the Caribbean

OBJECTIVES

1. Molecular characterization of CRE isolated in large teaching hospital in the Dominican Republic
2. Comparison to CRE collection from Northern Manhattan, largest Dominican population outside of the DR

METHODS

• Retrospective review of first four CRE infections identified at HGPS, Santo Domingo, DR
• Cases were identified by VITEK 2 compact (bioMérieux) and carbapenemase screening was done performing a Modified Hodge Test
• Comprehensive collection of CRE isolate collection at NYC teaching hospital reviewed, including 3 isolates from patient airlifted to NYC from the DR
• illumina whole genome sequencing of all available isolates
• SRST2 to extract and assign resistance gene profiles (ARGANNOT database) and plasmid replications
• Phylogenetic analyses of isolates from the same MLST present in DR and NYC (ST307)
• For ST307, included additional publicly available genomes from diverse countries

RESULTS

• Four cases occurred between 2015 and 2017
• Treated with colistin plus carbapenem, +/- tigecycline
• Treatment complicated by lack of molecular diagnostic tools and limited treatment options; AC2, FIBK, CoRNA
• ST307 only susceptible to polymyxin high rate of mortality (3/4 patients)
• Sequencing: Isolate from DR and NYC identified as ST307; same plasmid replicon types
• Pairwise SNP distance between these isolates only 33
• Both patients with healthcare contact in Puerto Rico

Table 1: Isolate Characteristics

<table>
<thead>
<tr>
<th>Organism</th>
<th>MLST</th>
<th>KPC-gene</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>K. pneumoniae</td>
<td>ST11</td>
<td>blaKPC-2</td>
<td>DR</td>
</tr>
<tr>
<td>ST1040</td>
<td>blaKPC-3</td>
<td>NYC, DR patient</td>
<td></td>
</tr>
<tr>
<td>ST307</td>
<td>blaKPC-2</td>
<td>DR, travel to Puerto Rico</td>
<td></td>
</tr>
<tr>
<td>Novel ST</td>
<td>blaKPC-3</td>
<td>DR</td>
<td></td>
</tr>
<tr>
<td>C. freundii</td>
<td>ST95</td>
<td>blaKPC-2</td>
<td>DR</td>
</tr>
<tr>
<td>E. cloacae</td>
<td>ST456</td>
<td>blaKPC-3</td>
<td>NYC, DR patient</td>
</tr>
</tbody>
</table>

REFERENCES


CONCLUSIONS

• CRE have emerged in diverse species and clonal backgrounds in the Dominican Republic
• Limited treatment options against KPC in DR with poor outcomes
• Diagnostic tools should be affordable and easier to perform in resource limited settings
• ST307 described from diverse locations, a new clone with epidemic potential and resistance to many other antibiotic classes?
• Molecular characterization its necessary to understand the problem of antimicrobial resistance as well to institute active surveillance trying to find colonization and avoid passive transmission.
• Potential for KPC transmission across the Caribbean and via healthcare tourism

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Figure 1: Phylogenetic comparison of ST307 isolates from DR, NYC and US

Location isolated:
- Boston
- Dominican Republic
- Houston
- New York City

Initial origin of isolates:
- Same as infection Puerto Rico

Resistance genes (DR, NYC):
- blaCTX-M-15, blaOXA-100, blaOXA-1v
- blaKPC-2, sulI
- aadB, aac6, gyrA Y83I, parC S801, fosA3, dfrA14, sulI, tetD, catB4