Introduction

The emergence of carbapenem resistance is a significant burden to healthcare systems due to poor outcomes and severe infection control implications. Carbapenem-producing organisms (CPO) are associated with increased morbidity and mortality due to extensive antibiotic resistance and multi-drug resistance. Evidence behind CPO treatment strategies is limited and handicapped by use of antibiotics associated with severe toxicities, as well as an overall lack in development of new, effective antibiotics. The relationship between carbapenem non-susceptibility (CARB-NS) and carbapenem production is controversial.

We describe the underlying mechanisms of CARB-NS clinical isolates found in our institution through molecular testing, and outcomes of patients infected with confirmed CPO.

Methods

Study Design

This was an IRB approved cross-sectional study conducted at a large urban healthcare system located in metropolitan Detroit, Michigan.

Study Population

The study population included patients with clinically evaluable CARB-NS isolates from respiratory, blood, urine or other infection sites from January 2014 to December 2015. CARB-NS was defined per CLSI breakpoints (Enterobacteriaceae: carbapenem MIC > 0.5 g/mL or meropenem MIC > 1 g/mL. Pseudomonas spp., carbapenem MIC > 2 g/mL).

Isolates Characteristic

<table>
<thead>
<tr>
<th>Organisms</th>
<th>P. aeruginosa</th>
<th>K. pneumoniae</th>
<th>E. coli</th>
<th>S. marcescens</th>
<th>P. mirabilis</th>
<th>Other*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolation Site</td>
<td>48%</td>
<td>29%</td>
<td>19%</td>
<td>0%</td>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

Data Collection and Analysis

Microbiologic data was collected from clinical support software and using a standardized case report form. Data included: culture type, minimum inhibitory concentrations, select infection characteristics, and clinically infected patient outcomes. Susceptibility classification was performed locally according to standard practice via VITEK-2 (bioMérieux) and E-test (bioMérieux) per CLSI standards and breakpoints. Descriptive statistics were used to evaluate the prevalence of molecular confirmed CPO as well as CPO treatment outcomes. Bivariate and multivariate analyses were used to identify variables associated with molecularly confirmed carbapenem resistances.

Results

Isolates Characteristic

- P. aeruginosa: 48%
- K. pneumoniae: 29%
- E. coli: 19%
- S. marcescens: 0%
- P. mirabilis: 0%

Carbapenem-producing Organisms*

<table>
<thead>
<tr>
<th>Organisms</th>
<th>bta-KPC positive</th>
<th>bla-CTX-M positive</th>
<th>bla-KPC/CTX-M negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood (n = 47)</td>
<td>52%</td>
<td>6%</td>
<td>42%</td>
</tr>
<tr>
<td>Respiratory (n = 74)</td>
<td>14%</td>
<td>1%</td>
<td>85%</td>
</tr>
<tr>
<td>Urine (n = 47)</td>
<td>63%</td>
<td>3%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Variables Associated with blaCARB*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>blaCARB negative (n = 64)</th>
<th>blaCARB positive (n = 65)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous ESBL/CPE, isolated, 5 years</td>
<td>13 (65%)</td>
<td>18 (64%)</td>
<td>1.0 (0.31-3.4)</td>
<td>0.88 (0.28-3.4)</td>
</tr>
<tr>
<td>Indwelling device</td>
<td>21 (48%)</td>
<td>23 (35%)</td>
<td>1.7 (0.73-3.3)</td>
<td>2.1 (0.88-5.0)</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>16 (36%)</td>
<td>13 (20%)</td>
<td>2.3 (0.96-5.4)</td>
<td>2.6 (1.16-6.5)</td>
</tr>
<tr>
<td>Surgical procedure, 30 days</td>
<td>15 (34%)</td>
<td>10 (15%)</td>
<td>2.0 (0.68-6.5)</td>
<td>3.5 (1.3-9.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (41%)</td>
<td>33 (57%)</td>
<td>0.67 (0.3-1.5)</td>
<td>Not tested</td>
</tr>
</tbody>
</table>

Characteristics of blaCARB Producing Organisms

- Variables n (%) or median (IQR)
- Demographics Age, years: 65 (55-70) 62 (55-69)
- Patient History Prior 30-day abx use: 23 (52%) 15 (34%)
- Previous 30-day surgery: 15 (34%) 9 (23%)
- Prior indwelling device: 21 (44%) 11 (29%)
- Previous ESBL/CPE, 5 years: 13/20 (65%) 8/13 (62%)

Comorbidities Charlson Comorbidity Index 6 (4-8) 6 (3-9)

Hospital Course

- Intensive care unit (ICU) stay: 29/39 (74%) 21/72 (78%)
- CARB prior to index culture: 10/28 (26%) 8/27 (30%)

Definitive Treatment Regimens, non-urine

- Definitive Beta-lactam usage* CEPH: 10/28 (26%) CARB: 8/27 (30%)

Definitive Beta-lactam usage* CEPH: 43% CARB: 43% BLIC: 33%

Patient Outcomes, Treated Population

- In-hospital death: 13% 4%
- 30-day readmission: All-cause, 6 mos: 33% 26%
- Infection-related mortality: All-cause, 6 mos: 19% 9%
- All-cause mortality, 6 mos: 57%

Summary

- For the overall patient population, the mechanisms of CARB-NS in Detroit were not commonly related to carbapenemases
- When limited to Enterobacteriaceae, about half harbored blaCARB
- Definitive treatment strategies varied widely and in-hospital and 6-month mortality was high
- An understanding of the regional genomic sequence of CARB-NS is beneficial for clinicians to target appropriate antibiotic therapy and to improve infection control procedures

Footnotes:

1. All carbapenem resistances were confirmed by in vitro susceptibility. The most common carbapenemase tested was IMPu. All other carbapenemase tested had confirmed positive, multiple (56%), and other (9%). The most common carbapenemase tested was IMPu, KPC, and other (9%).
2. Of all unique patients with confirmed bta-KPC (n = 18) were treated with cefepime antibiotics. The most common carbapenemase tested was IMPu (29%), multiple (56%), and other (9%).

4.67% of beta-lactams had confirmed positive, multiple (56%), and other (9%). The most common carbapenemase tested was IMPu, KPC, and other (9%).