Carbapenems (CARBs) are the primary treatment for infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* strains. Production of a serine carbapenemase, KPC, is increasing alarmingly in the United States and is probably contributing to CARB resistance rates. We describe the clinical and molecular characteristics of four infections caused by KPC-3 *K. pneumoniae* strains.

Carbapenems (CARBs) are the primary treatment strategy for serious infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae*. In a report by the National Healthcare Safety Network, 5% of *K. pneumoniae* isolates collected in the United States between January 2006 and October 2007 were resistant to CARBs (4). First detected in North Carolina in 1996, production of the KPC β-lactamase, a serine carbapenemase, in *K. pneumoniae* has disseminated in many states across the United States and is no longer confined to the northeast regions (5). Furthermore, KPC-producing strains are now emerging worldwide, affecting Israel, Asia, Europe, Canada, and Central and South America (3, 8, 9). The genes encoding KPC enzymes are usually located on plasmids and embedded on transposon Tn*4401*, providing impetus for its rapid dissemination (7). In this report, we describe the clinical and molecular characteristics of four infections caused by KPC-3-producing *K. pneumoniae* strains.

We collected potential ESBL-producing isolates at 12 hospitals located throughout southern California between 1 August 2007 and 31 March 2009. Initial ESBL screening was performed using each institution’s standard of practice. Isolates were included in the study according to initial carbapenem susceptibility results as determined by the Etest (AB bioMérieux, Marcy l’Etoile, France), and those displaying carbapenem MICs that were ≥8 μg/ml were selected for further testing at an independent laboratory. KPC-producing strains were obtained at one study site, Long Beach Memorial Medical Center, which is a nonprofit, community-based, teaching hospital with 462 beds for adult patients. Institutional review board approval was obtained to collect patient data.

ESBL and carbapenemase production confirmatory tests (using a modified Hodge test [MHT]) were performed according to CLSI guidelines. Genes encoding ESBL, plasmidic AmpC, and carbapenemase (including serine- and metallo-β-lactamases) were detected using multiplex PCRs (1, 2, 6, 10). TEM- and SHV-encoding genes were amplified in separate reactions. All amplicons were sequenced, and nucleotide and deduced amino acid sequences were analyzed using the Lasergene software (DNASTar, Madison, WI) and compared with available sequences through BLAST (http://www.ncbi.nlm.nih.gov/blast/). Isolates were typed by pulsed-field gel electrophoresis. Genomic DNA was prepared in agarose blocks and digested with SpeI (New England Biolabs, Beverly, MA). Electrophoresis was performed on a CHEF-DR III apparatus (Bio-Rad, Richmond, CA) under the following conditions: 0.5 × Tris-borate-EDTA (TBE), 1% agarose, 13°C, and 200 V for 24 h, with the switch time ramped from 5 to 90 s.

Of 232 *Enterobacteriaceae* isolates collected, 6 (2.5%) expressed the ESBL enzyme. Among those strains, four (1.7%) *K. pneumoniae* isolates, which also displayed MICs of >8 μg/ml for imipenem and meropenem, were positive for carbapenemase production by MHT and *bla*KPC by PCR. The remaining strains, one *E. coli* and one *K. pneumoniae* strain, were negative for carbapenemases in phenotypic and genotypic tests.

All four strains carried *bla*KPC-3, and further PCRs showed that all strains carried genes encoding TEM-1 and SHV-11/SHV-36. Isolates were negative for all other beta-lactamase-encoding genes tested. These strains were resistant to CARBs, amikacin, aztreonam, piperacillin-tazobactam, cefepime, levofloxacin, and trimethoprim-sulfamethoxazole but susceptible to gentamicin (4 μg/ml), the polymyxins (≤0.5 μg/ml), and tigecycline (0.5 to 1.0 μg/ml). Molecular typing demonstrated that all strains were genetically related.

The clinical characteristics of patients infected with these isolates are described in Table 1. All patients (females with a mean age of 73.3 ± 16.5 years) presented with sepsis and transferred from two different long-term care facilities (LTCFs).
TABLE 1. Characteristics of patients with infections caused by KPC-producing *Klebsiella pneumoniae* strains

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Race</th>
<th>Prior antibiotic exposure (length of administration, mo/day/yr)</th>
<th>Prior infection</th>
<th>Onset of symptoms of infection to antibiotic treatment (days)</th>
<th>Site(s), date(s) of infection</th>
<th>Concurrent infection</th>
<th>Antibiotic treatment (no. of days)</th>
<th>Treatment antibiotics</th>
<th>Concurrent MRSA (no. of days)</th>
<th>Treatment failure</th>
<th>Mean length of stay in hospital unit (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79</td>
<td>AA</td>
<td>Candiduria, MRSA (5)</td>
<td>0</td>
<td>None</td>
<td>0, 12/06/09</td>
<td>20</td>
<td>ATM (2) IPM (4)</td>
<td>FEP (2) TZP (5)</td>
<td>0</td>
<td>False</td>
<td>13.5</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>H</td>
<td>Enterococcus</td>
<td>20</td>
<td>None</td>
<td>0, 02/16/09</td>
<td>0</td>
<td>None</td>
<td>TZP (2) ATM (1)</td>
<td>8</td>
<td>False</td>
<td>4.3</td>
</tr>
<tr>
<td>3</td>
<td>79</td>
<td>AA</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>0, 03/02/09</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>8</td>
<td>True</td>
<td>13.5</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>H</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>0, 03/02/09</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>0</td>
<td>True</td>
<td>4.3</td>
</tr>
</tbody>
</table>

*Abbreviations: AA, African American; ATM, aztreonam; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRO, ceftriaxone; DM, diabetes mellitus; ET, endotracheal; FEP, cefepime; GMS, gentamicin; H, Hispanic; HTN, hypertension; IPM, imipenem; LVX, levofloxacin; MRSA, methicillin-resistant *Staphylococcus aureus*; MV, mechanical ventilator; RBX, rifampin; TGC, ticarcillin-clavulanate; TMD, trimethoprim-sulfamethoxazole.*

Infections were separated by a mean of 26.7 ± 13.6 days. Most infections occurred at hospital admission, except with one patient, who developed infection on day 20 of hospitalization. Three patients had diabetes mellitus and had been hospitalized within the previous 9 months. Interestingly, although all KPC-producing strains were genetically related, it appears that patient 3 developed infection independently since her infection occurred at hospital admission, she was transferred from a different LTCF, and her prior hospitalization preceded our first case of infection with a KPC-producing strain. All other patients were related by medical care in a similar LTCF or hospital unit.

All patients experienced treatment failure at 72 h after initiation of empirical antibiotics, which were subsequently changed when culture and susceptibility results became available. Treatment failure was defined as an absence of clinical improvement, persistent positive cultures, a change in initial antibiotic treatment, or death within 14 days of the first positive culture. Microbiologic and clinical success was documented for all patients by the end of hospitalization. The mean duration of appropriate antibiotic therapy while patients were hospitalized was 8.8 ± 2.2 days. Three patients continued intravenous antibiotics after hospital discharge. The mean lengths of stay in the hospital and intensive care unit were 13.5 ± 9.3 and 4.3 ± 5.3 days, respectively. All patients survived their infections.

KPC-3-producing isolates have been previously documented in California (5); however, here we identified the clonal dissemination of KPC-3 producers in a southern California hospital recovered during a study evaluating clinical outcomes. The clinical information, although generated from a limited number of strains, supports our understanding of infections caused by KPC-producing isolates. With our limited therapeutic options, coupled with the escalating dissemination of Carb-resistent *K. pneumoniae*, vigilant surveillance, prompt detection, and implementation of effective infection control measures in hospitals and LTCFs are imperative.

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