Widespread Dissemination of CTX-M 15 Genotype Extended Spectrum Beta-Lactamase Producing Enterobacteriaceae among Patients Presenting to Community Hospitals in southeastern United States

Author: Luke F. Chen, MBBS, MPH, CIC, FRACP,1,2,3 Joshua T. Freeman, MBChB FRCPA5, Brad Nicholson, PhD, Anna Keiger, Sarah Lancaster, Maria Joyce, Christopher Woods, MD, MPH,1,3,4, Evelyn Cook, RN, Linda Adcock, RN, BSN, CIC, Susan Louis, RN, CIC, Andrea L. Cromer, RN, CIC, Daniel J. Sexton, MD, FIDSA1,2,3 and Deverick J. Anderson, MD, MPH,1,2,3

Affiliations: (1)Duke University Medical Center, Durham, NC, (2)Duke Infection Control Outreach Network, Durham, NC, (3) Duke University CDC Prevention Epicenter Program, Durham, NC, (4) Durham VA Medical Center, Durham, NC, (5) Department of Clinical Microbiology, Auckland City Hospital, Auckland, New Zealand

Corresponding author:

Luke F. Chen
Duke University Medical Center, Durham, NC, 27705

Telephone: 919-681-5447

Email: Luke.chen@duke.edu
Abstract

ESBL-producing organisms are increasingly prevalent. We determined the characteristics of 66 consecutive ESBL-producing isolates from six community hospitals in North Carolina and Virginia from 2010-2012. Fifth-three (80%) ESBL-producing isolates contained CTX-M enzymes; CTX-M-15 was found in 68% of E. coli and 73% of Klebsiella isolates. ST131 was the commonest type of E. coli, accounting for 48% of CTX-M-15-producing and 66% of CTX-M-14-producing isolates. In conclusion, CTX-M genotype and ST131 E. coli were common among ESBL isolates from US community hospitals.
Infections associated with extended-spectrum beta-lactamase (ESBL) producing organisms are increasing worldwide (1, 2). The emergence of ESBL-producing organisms in the United States has been partially driven by the dissemination of the CTX-M family of ESBL enzymes, which are commonly associated with additional virulence factors and resistance determinants that confer selection advantages. We previously reported an increase in ESBL producing *E. coli* infections among sixteen community hospitals in the southeastern region of United States from 2006 to 2008 (3). We hypothesized that CTX-M producing organisms were widely-disseminated and represented the majority of organisms with ESBL phenotype in the community setting. Therefore, we conducted the current study to determine the clinical and molecular epidemiology of infections due to ESBL-producing organisms among community hospitals.

Six community hospitals affiliated with the Duke Infection Control Outreach Network (DICON) in North Carolina and Virginia provided 66 consecutive phenotypically-confirmed ESBL isolates for analysis from 7/2010-2/2012 (4, 5). *E. coli* was the most common isolates (67%), followed by *K. pneumoniae* (29%), *K. oxytoca* (3%), and *E. cloacae* (2%). Demographic and clinical characteristics are summarized on Table 1. Thirty-seven (56%) of these ESBL-producing isolates were detected from a urinary source; 63% of these urinary tract infections occurred in the absence of a urinary catheter.

Using standard epidemiological definitions, 35 (65%) of these ESBL infections were categorized as community-onset, healthcare-associated, 10 (19%) were categorized as community-acquired, and only 9 (17%) were categorized as hospital-onset ESBL infections (6, 7).

Molecular epidemiology studies showed that 53 (80%) of these ESBL-producing isolates carried a CTX-M β-lactamase; including 37 (84%) isolates of *E. coli*, 15 (71%) *Klebsiella* isolates, and the single isolate of *E. cloacae*. Overall, 25 (68%) *E. coli* ESBL isolates had CTX-M-15 and 6 (16%) had CTX-M-14. One *E. coli* isolates (3%) had CTX-M 107. Of the 15 *Klebsiella* isolates that had CTX-M β-lactamase, 11 (73%) isolates were found to have CTX-M-15.

Multi-locus sequence typing (MLST) of *E. coli* isolates showed that ST131 was the predominant sequence type (8). Clonal analysis with pulsed-field gel electrophoresis of XbaI-digested genomic DNA showed there were three main clones of ST 131 *E. coli* (9). One clone was responsible for the majority of ESBL-producing *E. coli* isolates detected at a community hospital. Two other clones of ST 131 were found in patients hospitalized in separate and geographically distant hospitals.
Sequence type 131 was associated with 12 (48%) CTX-M-15 producing E. coli and 4 (66%) of the CTX-M-14 isolates. ST405 was the second most common sequence type for ESBL producing E. coli isolates. ST405 was also closely-associated with CTX-M-15 genotype of ESBL.

ESBL-producing organisms have disseminated widely throughout the world over the last decade and they gained a foothold in the United States in the last 5 years. We identified three important findings in this multi-center cohort study in community hospitals. First, ESBL-producing organisms were already readily detectable in community hospitals in United States in 2010-2012. Second, CTX-M β lactamases were common and accounted for detectable in four out of five ESBL producing organisms. Finally, we found that CTX-M-15 and ST131 were the most prominent genotypic correlates of resistance among ESBL producing E. coli isolates from community hospitals.

The most surprising finding in the current study is that most ESBL infections in community hospitals were present on admission and such infections are brought into the hospital setting from the community. Moreover, approximately half of patients with ESBL infections were admitted directly from home, rather than from other hospitals, nursing homes or other extended care facilities as described by prior investigators (10-12). The high number of ESBL infections from patients admitted directly from home may be explained by the fact that almost 65% of patients in this cohort had hospitalization within 1 year of study enrollment.

Recent data have documented the importance of CTX-M enzymes in the ESBL epidemic around the world (13). In the current study, CTX-M accounted for 80% of ESBL producers and CTX-M-15 was the predominant ESBL observed. The results of these molecular analyses were comparable with data reported from other parts of the world where ESBL producers (and CTX-M) were already considered endemic (14). Additionally, the fact that CTX-M producers and ST131 E. coli were found in patients without common epidemiological links directly from the community suggested that ESBL-producing organisms are widely disseminated in the community. These observations confirm that there is a CTX-M epidemic in our midst and communities around United States already have endemicity of these highly drug-resistant organisms.

Our study is among the first to show that CTX-M and ST131 ESBL-producing organisms are frequently detected in community hospitals. Our data complemented the study by Doi et al, which reported high number of community-onset ESBL infections being detected at tertiary care medical centers around the US (15). Our community hospital specific information is important because the
The widespread dissemination of CTX-M-15-producing ESBL organisms and ST131 *E. coli* in the community setting has tremendous implications for management and patient outcomes. ESBL-producing organisms, especially those carrying CTX-M-15, are commonly resistant to first line drugs such as cephalosporins. Furthermore, these ESBL-producing organisms frequently concurrently carry genetic determinants that confer resistance to fluoroquinolones and aminoglycosides (16). Thus, carbapenems, along with other drugs such as beta-lactam/beta-lactamase inhibitor combinations, may likely have an increasing role as empirical therapy for patients suspected to be infected with ESBL-producing organisms in community hospitals (17, 18).

In conclusion, our study demonstrated that CTX-M producing ESBL-producing organisms and ST131 *E. coli* are prevalent in the community setting in the United States. The vast majority of ESBL infections were imported into the hospital, though most occurred in patients with previous healthcare exposure. Thus, when deciding upon empiric antibiotic therapy and infection control precautions, the importance of elucidating prior healthcare contact as a risk factor cannot be overstated.
Disclosures:

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Table 1. Clinical Epidemiology of 66 Patients with ESBL Infection and comparison of ESBL-producing *E. coli* and *Klebsiella* spp.

<table>
<thead>
<tr>
<th></th>
<th>All Patients with ESBL Infections N=66</th>
<th>ESBL-producing <em>E. coli</em> n=44</th>
<th>ESBL-producing <em>Klebsiella</em> spp. n=21</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, IQR)</td>
<td>74 (62-83)</td>
<td>74 (64-85)</td>
<td>71 (56-79)</td>
<td></td>
</tr>
<tr>
<td>Discharged from hospital within 1 year*, n (%)</td>
<td>35 (65)</td>
<td>23 (64)</td>
<td>12 (71)</td>
<td>0.71</td>
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<tr>
<td>Type of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection (UTI), n (%)</td>
<td>37 (56)</td>
<td>24 (55)</td>
<td>13 (62)</td>
<td>0.58</td>
</tr>
<tr>
<td>Bloodstream infection (BSI), n (%)</td>
<td>11 (17)</td>
<td>9 (20)</td>
<td>2 (10)</td>
<td>0.28</td>
</tr>
<tr>
<td>Pneumonia, n (%)</td>
<td>5 (8)</td>
<td>1 (2)</td>
<td>3 (14)</td>
<td>0.06</td>
</tr>
<tr>
<td>Other**, n (%)</td>
<td>13 (19)</td>
<td>10 (23)</td>
<td>3 (14)</td>
<td>0.43</td>
</tr>
<tr>
<td>Location of infection onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community-acquired, n (%)</td>
<td>10 (19)</td>
<td>9 (25)</td>
<td>1 (6)</td>
<td>0.10</td>
</tr>
<tr>
<td>Community-onset, healthcare-associated, n (%)</td>
<td>35 (65)</td>
<td>23 (64)</td>
<td>12 (71)</td>
<td>0.71</td>
</tr>
<tr>
<td>Hospital-onset, healthcare-associated, n (%)</td>
<td>9 (17)</td>
<td>4 (11)</td>
<td>4 (24)</td>
<td>0.26</td>
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<tr>
<td>Admission source</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Home, n (%)</td>
<td>25 (46)</td>
<td>17 (47)</td>
<td>7 (41)</td>
<td>0.68</td>
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<tr>
<td>Nursing Home, n (%)</td>
<td>16 (30)</td>
<td>12 (33)</td>
<td>4 (24)</td>
<td>0.48</td>
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<td>Transfer from hospital, n (%)</td>
<td>7 (13)</td>
<td>3 (8)</td>
<td>4 (24)</td>
<td>0.14</td>
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<tr>
<td>Other extended care facility, n (%)</td>
<td>5 (9)</td>
<td>4 (11)</td>
<td>1 (6)</td>
<td>0.54</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Missing data (gender in 12, race in 20 patients, location of infection onset in 12, infection type in 12)


