Changing Epidemiology of Extended Spectrum Beta-Lactamases Pathogen of Urinary Tract

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This review covers the recent findings on extended spectrum beta-lactamases (ESBL) pathogens, focusing on the epidemiology of infection due to this pathogen. Use of ESBL is growing rapidly and widely.CTX-M-15 producing ESBL Escherichia coli is the most commonly encountered in clinical practice. In general, ESBL infections are represented by urinary tract infections, but they can also cause fatal infections involving the vascular system and central nervous system. Because E. coli is a common colonizer of normal intestine, increasing prevalence of ESBL-producing pathogens is particularly troublesome. In a situation where ESBLs are disseminated in the community, the ideal control of this multidrug-resistant pathogen will be challenging. Precise data on the prevalence and risk factors of ESBL-producing microorganism are still undetermined. More epidemiological studies are needed for the question to be answered. In order to maximize efficiency of treatment, information on the trend of increasing numbers of ESBLs is also needed on persistence of ESBLs in carriers as well as better understanding of how antibiotic treatment and other risk factors affect their persistence and further dissemination. The global emergence of multidrug-resistant ESBL pathogen has recently led to critical treatment problems. Early detection, adequate antibiotic therapy, and effective prevention are necessary for achievement of a safe community.

Keywords: Beta-lactamases; Epidemiology; Pathogen; Uropathogenic Escherichia coli

INTRODUCTION

Extended spectrum beta-lactamases (ESBLs) are the enzymes that have been produced by microorganisms, which weaken the effect of beta-lactam antibiotics with broad-spectrum [1]. Beta-Lactams are one of common regimen for the management of infections including urinary tract infections (UTI) and pneumonia, as well as for fatal state such as bacteremia. Beta-Lactams are also frequently used to prevent infections perioperatively. The ESBL-producing organism was historically first reported in 1983. The characteristics of beta-lactamase in strains of Klebsiella pneumoniae were described as being capable of hydrolyzing extended-spectrum cephalosporins in Germany [2]. Recently, ESBL-producing organisms are considered as important cause of nosocomial and community acquired infections [3]. The outbreak of ESBLs happens from TEM-1, TEM-2, or SHV-1 genes by mutation, which are commonly found in Enterobacteriaece family [4]. The enzymes are found in Klebsiella species and Escherichia coli mostly; however,
they have also been reported in other Enterobacteriaceae family including *Citrobacter*, *Serratia*, *Proteus*, *Providencia*, *Shigella*, *Salmonella*, and *Enterobacter* [5]. The prevalence of isolates expressing ESBLs varies by region with low rates of 3-8% in Sweden, Japan, and Singapore compared to much higher rates of 30-60% in Portugal, Italy, New York, Latin American countries, and Turkey [1]. In the Arabian Peninsula, ESBL detection rates range from 8.5-38.5% in Saudi Arabia and 31.7% in Kuwait [6,7]. This diversity may be due to the fact that the studies focused on biased study group or specific sites of infection.

The major types of beta-lactamases are below: TEM, SHV, CTX-M, and OXA beta-lactamases. CTX-M ESBLs have appeared as the most common and significant type of ESBL worldwide, whose incidence markedly exceeding those of TEM, SHV, and OXA ESBLs. According to recent studies, the most widely distributed CTX-M enzyme is CTX-M-15, which was first reported in *E. coli* from India in 2001 [8]. CTX-M-15 producing *E. coli* with multidrug-resistant is emerging globally as a virulent pathogen causing hospital and community acquired infections since 2003 [9,10].

ESBL-producing members of the family Enterobacteriaceae are clinically important due to the fact that they play a role of inflammation and infections in urinary tract, central nervous system, lower respiratory tract and bloodstream, but are also familiar colonizers of digestive system. These microorganisms form a heterogeneous group that enables hydrolytic reaction against the beta-lactams while remaining sensitive to inhibition by beta-lactamase inhibitors. This is critical because ESBLs are resistant to common antibiotics including penicillins, broad-spectrum cephalosporins, and aztreonam [11], ESBL-producing organisms are also resistant to quinolones, aminoglycosides, and trimethoprim-sulfamethoxazole [1].

Previous large-scale studies demonstrate that ESBL-producing *E. coli* and *K. pneumonia* isolates are susceptible to carbapenems generally [12]. Nevertheless, antibiotic resistance in gram-negative bacilli (GNB) is spreading worldwide with variety of regional resistance. So, we need to monitor susceptibility trends in every corner of the world over time to understand those trends so that effective treatments can be accomplished to meet national social needs. We have reviewed the recent findings on epidemiology of ESBL-producing organisms, based on the comparison with prior surveys.

**METHODS**

A systemic literature review was performed on PubMed and Google Scholar. Keywords included “epidemiology”, “ESBL” and “ST131 *E. coli*”. Original articles, related articles and their references were considered, and a summary of each data was reorganized based on clinical basis.

**THE CHARACTERISTICS OF *ESCHERICHIA COLI* ST131 CLONE**

*E. coli* sequence type 131 (ST131) is a multidrug-resistant and highly virulent clone that was first reported in 2008 and has been reported in various regions globally [13]. It is associated with numerous community and hospital acquired infections particularly UTIs [14]. The prevalence of ST131 isolates varies from region to region and host population, ranging from 12.5-40% [15,16]. Generally, ST131 is resistant to fluoroquinolone, and CTX-M-15 enzyme [10], whereas other beta-lactamases including TEM, SHV are less likely to be [13]. Both ESBL and non-ESBL-producing *E. coli* ST131 isolates are resistant to fluoroquinolones, which may play a role as marker for ST131-positive *E. coli* [17]. The ways to manage *E. coli* ST131 infections are similar to those of other types of *E. coli* [13]. Carbapenem alone or combination therapy with amikacin has been used to eradicate infections associated with CTX-M-producing *E. coli* isolates. And the trial has become a huge success [18].

The diagnosis of ESBLs in the laboratory is not simple. Since the ESBL has emerged as important pathogen, specific guidelines for ESBL detection were proposed in 1999 by the National Committee for Clinical Laboratory Standards (NCCLS). We can suspect the existence of ESBL in case that bacterial growth is present despite 1 μg/ml of broad-spectrum cephalosporins (cefazidime, ceftriaxone, or cefotaxime), or aztreonam, or growth occurs despite the use of 4 μg/ml of cepodoxime. Multiple antibiotics for screening improve the sensitivity of ESBLs detection. Confirmatory tests include the supplement of clavulanic acid to both cefazidime and cefotaxime, Double disk approximation test, three-dimensional test, E-test and Vitek automated susceptibility system (bioMérieux, Marcy l’Etoile, France) has been applied to detect ESBLs in clinical isolates. The superiority of one test over the other is not clear in respect of sensitivity and technically challenging.
A few recent studies using multilocus sequencing typing identified a single clone of ST131 from several countries in Europe (Spain, France, Portugal, and Switzerland), North America (Canada), and Asia (Lebanon, India, Kuwait, and Korea) [9,10]. Serogroup O25 is associated with it. Clone ST131 belongs to phylogenetic group B2 which is highly virulent, and harbors multidrug-resistant incompatibility group FII plasmids. These previous studies proved that CTX-M-15 producing ST131 have also been emerged in various countries. ST131 isolates have also been associated with other types of beta-lactamases, as well as ciprofloxacin resistant *E. coli* isolates that do not have ESBLs [19-21].

It is not obvious what has facilitated ST131 to spread so widely and rapidly. ST131 is clearly more extensively antibiotic-resistant than other types of *E. coli* and contains a plenty of virulence factors. It may have a tendency to be transmitted from host to colonize the intestine followed by UTI [22,23]. The risk factors for intestinal colonization with ST131 in different populations, possible differences between colonizing and clinical ST131 isolates, and the reservoirs and transmission courses have not been closely surveyed [16]. The possible reservoirs of ST131 have been evaluated for decades, which included food or water sources, travel history from nations with a high prevalence of the clone, long-term care facilities, and commercial animals [24,25].

### THE EMERGENCE AND DISTRIBUTION OF ESBLs BY REGIONAL GROUPS

Until 1990s, enterobacteria, mainly *K. pneumoniae*, producing SHV and TEM types of ESBLs have traditionally been causative of serious nosocomial infections. This trend has changed significantly, and *E. coli* producing CTX-M beta-lactamases has emerged and cause of community-onset infections, mostly UTIs. Most infections caused by ESBL-producing *E. coli* or *K. pneumoniae* had mostly been described as nosocomially acquired or nursing home related. These

<table>
<thead>
<tr>
<th>Location</th>
<th>First author, year</th>
<th>ESBL (+)/total clinical samples in strains</th>
<th>Total number (%) of ESBL (+) pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia [26]</td>
<td>Hawser, 2009</td>
<td>A (1/13), B (0/3), C (0/0)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Benin [27]</td>
<td>Ahoyo, 2007</td>
<td>A (31/143)</td>
<td>31 (21.7)</td>
</tr>
<tr>
<td>Central African Republic [28]</td>
<td>Bercion, 2009</td>
<td>A (29/357), B (17/57), F (3/3), G (1/1)</td>
<td>50 (12.0)</td>
</tr>
<tr>
<td>China [29]</td>
<td>Hawkey, 2008</td>
<td>A (158/287), B (25/91), C (1/4)</td>
<td>184 (48.2)</td>
</tr>
<tr>
<td>Egypt [30,31]</td>
<td>Fam, 2011</td>
<td>A (55/291), B (23/165)</td>
<td>78 (17.1)</td>
</tr>
<tr>
<td></td>
<td>Saied, 2011</td>
<td>A (9/23), B (130/162)</td>
<td>139 (75.1)</td>
</tr>
<tr>
<td>Hong Kong [29]</td>
<td>Hawkey, 2008</td>
<td>A (8/45), B (0/0), C (0/0)</td>
<td>8 (17.8)</td>
</tr>
<tr>
<td>India [32]</td>
<td>Varaiya, 2008</td>
<td>A (264/334), B (77/111), C (15/15)</td>
<td>356 (77.4)</td>
</tr>
<tr>
<td>Morocco [34,35]</td>
<td>Barguiga, 2013</td>
<td>B (34/453)</td>
<td>34 (7.5)</td>
</tr>
<tr>
<td>New Zealand [26]</td>
<td>Hawser, 2009</td>
<td>A (3/94), B (1/14), C (1/5)</td>
<td>5 (4.4)</td>
</tr>
<tr>
<td>Nigeria [36,37]</td>
<td>Albinu, 2012</td>
<td>A (14/109)</td>
<td>14 (12.8)</td>
</tr>
<tr>
<td>Philippines [26]</td>
<td>Hawser, 2009</td>
<td>A (9/53), B (8/20), C (0/2)</td>
<td>17 (22.7)</td>
</tr>
<tr>
<td>Senegal [38]</td>
<td>Sire, 2007</td>
<td>A (38/1,010)</td>
<td>38 (3.8)</td>
</tr>
<tr>
<td>Singapore [26]</td>
<td>Hawser, 2009</td>
<td>A (17/51), B (12/32), C (0/1)</td>
<td>29 (34.5)</td>
</tr>
<tr>
<td>South Korea [44]</td>
<td>Ko, 2008</td>
<td>A (10/44), B (12/37), C (1/4)</td>
<td>23 (27.1)</td>
</tr>
<tr>
<td>Taiwan [45]</td>
<td>Chambers, 2005</td>
<td>A (33/260), B (30/164), C (2/14)</td>
<td>65 (14.8)</td>
</tr>
<tr>
<td>Tanzania [46]</td>
<td>Blomberg, 2005</td>
<td>A (9/36), B (9/92), C (1/37)</td>
<td>19 (15.2)</td>
</tr>
<tr>
<td>Thailand [29]</td>
<td>Hawkey, 2008</td>
<td>A (33/65), B (15/33), C (0/2)</td>
<td>48 (48.0)</td>
</tr>
<tr>
<td>Tunisia [47]</td>
<td>Ben Haj Khalifa, 2012</td>
<td>B (40/198)</td>
<td>40 (20.2)</td>
</tr>
<tr>
<td>Vietnam [48]</td>
<td>Jones, 2006</td>
<td>A (42/122), B (9/23), C (2/4)</td>
<td>53 (35.6)</td>
</tr>
</tbody>
</table>


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outbreaks are usually clonal, the strains are mainly spread through cross-transmission, and the risk factors are similar to those found for other multidrug-resistant pathogens. Each ESBL genotypes have different specificities for the various beta-lactam antibiotics. Some recent data suggest that infections related to ESBL-producing organisms might be a critical problem in outpatients worldwide, but detailed epidemiological data were not collected in most studies (Table 1) [26-48].

ESBLs were first reported in 1983 from Germany and England, in Europe [2]. Most ESBL-producing Klebsiella isolates harbored enzymes belonging to the TEM and SHV families. And the prevalence of ESBL differs with countries. In Netherlands, below 1% of E. coli and K. pneumoniae were identified as ESBL-producing pathogens [49]. In France and Italy, up to 40% of ESBL producing K. pneumoniae has been reported [50]. The studies on the genotypes of ESBLs also have been undertaken actively. In Sweden, 50-60% of ESBL-producing E. coli harbor CTX-M-15 followed by 10-15% of CTX-M-14 [51]. About 50% of genotypes in Norway and 20% in Denmark proved to be CTX-M-15 and CTX-M-14 [52,53]. In Finland, predominance of CTX-M-1 group (including CTX-M-15) was reported [54,55]. The different genotypes are found in other parts of Europe. In Spain, high prevalence of CTX-M-14 and CTX-M-9 is remarkable, and in Poland, CTX-M-3 has been frequently reported, which is similar to several countries in eastern Europe [56,57].

The first emergence of ESBL pathogen in USA was reported in 1988 [58]. Its prevalence rate ranges from 0-25% with average 3% [59]. In previous study of intensive care unit patients in USA, the rate of E. coli resistant to broad-spectrum cephalosporin increased 48% compared with that in the past 5 years. A recent study from the USA presents results from the SENTRY surveillance program including 26 hospitals from 20 states. The resistance levels to cephalosporins and/or aztreonam in invasive Enterobacteriaceae was 6.4%. CTX-M-15 is the most frequent and increasing in USA and Canada, where SHV phenotypes used to be the most common [60]. A Canadian study reported ESBL-production in almost 5% of the E. coli population—numbers similar to northern Europe. In Latin America, it seems that ESBLs are more common than other continents. The 8.5% of E. coli and 45% of K. pneumoniae were ESBL positive in large scaled, multicenter study [61]. South America stands out with a wide distribution of the CTX-M-2. Also the CTX-M-8 is found in South America which is rare on the outermost regions [62,63]. In the Africa and Australia, CTX-M-15 is predominant [63].

There are also several reports on the epidemiology of ESBL pathogens in Asia. Various differences are observed between Asian countries. The rate of multiresistant E. coli was 5% in Korea compared with 23.3% in Indonesia [64]. Contrastively, the rate of multiresistant K. pneumoniae was 48.8% in Korea and 20-40% in China and Japan. A single center study of 493 isolates in South Korea of Enterobacter, Serratia marcescens, Citrobacter freundii, and Morganella morgani revealed rates of ESBL-positive isolates of 12.8%, 12.4%, 4.9%, and 0%, respectively [65]. Some authors in South Korea described 22.4% of K. pneumoniae isolates and 10.2% of E. coli isolates as ESBL producers [44]. In Thailand, up to 52% of health workers carrying ESBL pathogen has been reported. In a recent study from Taiwan, 28.4% of K. pneumoniae from various body sites proved to be ESBL positive. A study in Vietnam reported that, of 350 isolates from specimens, 87.4% were GNB. The 88.9% of them were Enterobacteriaceae, of which 14.7% were ESBL positive [48]. In India, the reports are also alarming with high numbers seen among patients. A study from two hospitals in India collected isolates from patients with abscesses, UTI, blood and found ESBL pathogen in 69% of E. coli. Another study from India, the rate of ESBL-positive isolates was similarly elevated with 23.1% of ESBL positive [32]. Of the isolates, 48.4% were E. coli and 51.6% were K. pneumoniae. In Japan, the CTX-M-9 is dominant and in China, CTX-M-14 is more commonly reported [66,67]. In India, CTX-M-15 is exclusively found [68]. Notably, all of the ESBL-producing isolates were consistently susceptible to carbapenems, Asia is almost certainly a part of the world in which ESBLs have emerged, with early antimicrobial resistance studies showing elevated levels of ESBL phenotypes, particularly among Klebsiella isolates and particularly in China, South Korea, Japan, and India [29].

THE DISSEMINATION OF ESBL-PRODUCING PATHOGENS VIA VARIOUS FACTORS

ESBL-producing E. coli is spreading extensively and quickly in our community. Although a reliable explanation
Table 2. Outbreaks of infection due to ESBL-producing Enterobacteriaceae

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>ESBL: extended spectrum beta-lactamases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk patient</td>
<td>Intensive care units</td>
</tr>
<tr>
<td></td>
<td>History of transplantation</td>
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<tr>
<td></td>
<td>Long-term care facilities</td>
</tr>
<tr>
<td>Risk factor</td>
<td>Severity of disease</td>
</tr>
<tr>
<td></td>
<td>Length of hospital/intensive care units stay</td>
</tr>
<tr>
<td></td>
<td>Arterial/central venous catheter</td>
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<tr>
<td></td>
<td>Infusion of total parenteral nutrition</td>
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<td></td>
<td>Mechanical ventilator</td>
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<tr>
<td></td>
<td>Feeding tube</td>
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<tr>
<td></td>
<td>Urethral catheter</td>
</tr>
<tr>
<td></td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis</td>
</tr>
<tr>
<td></td>
<td>Bed sore</td>
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<tr>
<td></td>
<td>Altered nutrition</td>
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<td></td>
<td>Premature baby</td>
</tr>
<tr>
<td></td>
<td>Previous antibiotics treatment; fluoroquinolones, broad-spectrum cephalosporins, aztreonam, aminoglycosides, metronidazole</td>
</tr>
<tr>
<td>Reservoir</td>
<td>Hospital workers hand</td>
</tr>
<tr>
<td></td>
<td>Medical devices; thermometers, ultrasound gel, oxygen probes, liquid soap</td>
</tr>
</tbody>
</table>

is not yet known, different factors may explain this spread such as acquisition of ESBL-producing E. coli by food [69,70], person-to-person transmission from fecal carriers [71-73], dissemination of ESBL-producing E. coli in the environment [74], carriage by domestic [70,75,76] and wild animals [77-79], and the existence of reservoirs like long-term care facilities (Table 2) [80,81]. Sewage sludge is also a reservoir of ESBL-producing E. coli [74]. In 141 healthy individuals in Thailand, 51.8% had ESBL-producing E. coli in stool samples [82]. In China, the fecal colonization rate of ESBL-producing E. coli was 7% among 270 elderly people [71]. Seven of 105 healthy humans (6.7%) from Spain were carriers of ESBL-producing E. coli [72]. In healthy children from Portugal, the carriage rate was 2.7% [73]. In another study, the fecal carriage of ESBL-producing E. coli in patients with UTI caused by these pathogens was 67%, but the household members and the non-household relatives of these patients also had ESBL-producing E. coli in fecal samples, 27.4% and 15.6% respectively, while in healthy unrelated controls the fecal carriage rate was 7.4% [83].

Long-term care centers may also represent a significant reservoir for multi-resistant ESBL-producing E. coli isolates, and infection control efforts must be addressed in these settings. Among 294 nursing home residents in Northern Ireland, 119 nursing home residents (40.5%) were gut carriers of ESBL-producing E. coli [80], a carriage rate about 40 times higher than that for community patients with acute diarrhea in the same area; fluoroquinolones use and previous UTI were the risk factors for ESBL-producing E. coli carriage [80]. In Italy, 41.4% of residents and 11.6% of staff members in a long-term care facility were colonized with ESBL-producing E. coli [81].

RISK FACTORS OF ESBL-PRODUCING ESCHERICHIA COLI INFECTION

Treatment options for multi-resistant ESBL-producing pathogens are restrictive and initial empirical antibiotic therapy is occasionally inappropriate. As a result, the information of risk factors for ESBL-related infections is important for early detection and adequate initial treatment. In hospitalized cancer patients, 17 of 135 bacteremia caused by E. coli were ESBL-producing E. coli; several factors including female sex, hematological malignancy and previous antibiotic therapy were found to be remarkable for ESBL acquisition [84]. One control study in Switzerland found that previous antibiotic treatment and mechanical ventilation were risk factors for ESBL-related infection [85]. Typically, the most common risks factors for community acquired ESBL-producing E. coli infections are correlated to healthcare centers including recent admission history, residence in a long-term care facility, urethral catheterization. Other significant factors include recent use of antibiotics, older age, and diabetes mellitus. However, considerable cases of infections due to ESBL-producing E. coli occur without obvious risk factors [86]. This may be induced by increasing incidence of healthy carriers. One survey has reported the risk factors for ESBL-producing E. coli infections in 890 non-hospitalized patients. Remarkable risk factors were recent antibiotic use, residence in long-term care facilities, recent admission history, older age, and male sex [87].

Some studies on community acquired infections have been undertaken in Spanish hospitals [86]. The risk factors included older age, female sex, diabetes mellitus, recurrent UTIs, previous invasive procedures of urinary tract such as catheterization, and previous antibiotic use including cephalosporins, and fluoroquinolones. In the other study on community acquired bacteremia [86], long-term care facilities, urethral catheter, and previous antibiotic use (especially fluoroquinolones) were risk factors of ESBL-producing E. coli bacteremia [86]. Mostly, community-acquired ESBL-producing E. coli infections are originated in urinary tract.
in a recent study, over three UTI episodes in the last year, use of a beta-lactam antibiotic in the past 3 months and the history of prostatic disease were found to be associated with ESBL-producing *E. coli* [88]. The history of international travel as a risk factor for ESBL-producing *E. coli* has been reported in previous studies. In Switzerland, the beginning of symptoms, or recent antibiotic treatment in foreign country, proved to be a risk factor for ESBL-producing *E. coli*. In Calgary, 44% of patients with community acquired ESBL-producing *E. coli* infection had a history of trip abroad. Journey to India was the most dangerous factor [89]. In New Zealand, considerable patients suffered with UTIs by CTX-M-15producing *E. coli* had a history of travel or recent emigration from India [90].

**CONCLUSIONS**

The current epidemiology of ESBL-producing organisms is complex. Several species of the Enterobacteriaceae family with different types of enzymes are causing troublesome infections in patients in the hospital and outside of the hospital. The dominant subtype of ESBL organism is changing from SHV, TEM to CTX-M recently. Infection related to ESBLs occurs more commonly in Southern Asia than Eastern Asia, Southern Europe and Northern Europe in order. The cumulative effect of antibiotics on the dissemination and persistence of resistant bacteria should not be underestimated. To use appropriate antibiotics as far as possible, we need to understand how resistance arises and all the factors that influence dissemination, which allows practitioners to identify high-risk patients and avoid inappropriate empirical antibiotic therapy consequentially. Finally, there is an obvious goal to investigate the epidemiological aspect of the influx of ESBL-producing organisms in order to plan adequate infection management.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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