

# Enterobacteriaceae Producing ESBLs in the Community: Are They a Real Threat?

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Organisms that produce extended-spectrum  $\beta$ -lactamases (ESBLs) remain an important cause of failure of therapy with cephalosporins and have serious infection control consequences. *Klebsiella pneumoniae* and *Escherichia coli* remain the major ESBL-producing organisms isolated worldwide. *Klebsiella* species that produce ESBLs (such as the SHV and TEM types) are a major cause of hospital-acquired infections, while *E coli* that produce ESBLs (the CTX-M enzymes) have emerged as an important cause of community-onset urinary tract infections in some areas. These bacteria are often associated with resistance to other classes of antibiotics, especially the fluoroquinolones. A heightened awareness of clinicians and the enhanced testing by laboratories, including molecular surveillance studies, are required to reduce treatment failures, limit the introduction of these bacteria into hospitals, and prevent the spread of these emerging pathogens. [*Infect Med.* 2007;24:57-65]

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■ Community-onset infections

**A**ntimicrobial-resistant organisms are an emerging global health problem that will likely evolve into one of the most significant challenges facing medical practice.<sup>1</sup> Infections with resistant organisms lead to increased patient morbidity as a result of antibiotic treatment failures. Costs incurred by prolonged hospital stays are only a small portion of the additional expenses associated with these infections. It has been estimated that mi-

crobial resistance could add \$0.1 billion to \$10 billion annually to health care costs in the United States.<sup>2</sup>

Moreover, once generated, resistance does not disappear quickly. This leads to dramatic increases in costs of care and infection prevention efforts and the need for more effective antimicrobial agents.<sup>3</sup> Of most concern, however, is that the rates of the development of resistance among some organisms are challenging the ability of the phar-

maceutical industry to design effective new agents.<sup>4</sup> It is quite conceivable that in the near future, organisms will have developed resistance to all available antimicrobial agents.

For Gram-negative pathogens,  $\beta$ -lactamase production remains the most important contributing factor to  $\beta$ -lactam resistance.<sup>5</sup> One important group of  $\beta$ -lactamases—the extended-spectrum  $\beta$ -lactamases (ESBLs)—is an increasingly significant cause of treatment failure. In this article, I will discuss the clinical significance and emergence of the ESBLs in the community setting.

## Extended-spectrum $\beta$ -lactamases

$\beta$ -Lactamases are bacterial enzymes that inactivate  $\beta$ -lactam antibiotics by hydrolysis, which results in ineffective compounds.  $\beta$ -Lactamases can differ from one another in their substrate profile (the different types of antibiotics they can inactivate), inhibitor profile (which compounds inactivate them), and sequence homology (amino acid composition).<sup>6</sup> At least 450 different types of  $\beta$ -lactamases originating from clinical isolates have been described, and a Web site has been specifically created to monitor the latest developments (<http://www.lahey.org/studies/webt.htm>).

ESBLs have the ability to hydrolyse various types of the newer  $\beta$ -lactam antibiotics.<sup>7</sup> Organisms, such as *Escherichia coli* and *Klebsiella* species,

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that produce ESBLs remain an important cause of cephalosporin treatment failures and have serious infection control consequences. It is recommended by some authorities to isolate patients infected with these types of organisms for the prevention of crossover infections, although this is not always done on a routine basis. It is therefore important that clinical microbiology laboratories detect and report ESBL-producing organisms.

Most ESBLs can be divided into 4 groups: TEM, SHV, OXA, and CTX-M types.<sup>6</sup> *Klebsiella pneumoniae* and *E coli* remain the major ESBL-producing organisms isolated worldwide, but these enzymes have also been identified in several other members of the family Enterobacteriaceae, as well as certain non-fermentors. In a recent report, the Infectious Diseases Society of America (IDSA) listed ESBL-producing *Klebsiella* species and *E coli* among the 6 priority drug-resistant microbes for which new therapies are urgently needed.<sup>4</sup>

Organisms (mostly *Klebsiella* species) that produce SHV and TEM types of ESBL have traditionally been responsible for serious nosocomial infections; they are often multidrug-resistant, and the therapeutic options are limited.<sup>8</sup> Specific risk factors for acquisition of these bacteria include length of hospital stay, severity of illness, time in the ICU, intubation and mechanical ventilation, urinary or arterial catheterization, and previous exposure to antibiotics.<sup>7</sup>

Most patients infected with ESBL-producing organisms have been admitted to ICUs, but infections can also occur in almost any area of the hospital. These organisms are also isolated with increasing frequency from patients in extended-care facilities.<sup>9</sup> Less than 20 years after the first description of ESBLs, organisms producing these enzymes have become

important players in antimicrobial resistance.

Organisms that produce CTX-Ms have become the most prevalent type of ESBLs described during the past 5 years, especially in certain European and South American countries.<sup>10</sup> Organisms that produce specific CTX-Ms have been isolated from different countries: CTX-M-9 and CTX-M-14 are mostly present in Spain; CTX-M-14 in Canada and China; CTX-M-1 in Italy; CTX-M-3 in Poland; and CTX-M-2 in several South American countries, Japan, and Israel. CTX-M-15 has been described on all continents except Antarctica.

The CTX-M enzymes usually have greater activity against cefotaxime than against ceftazidime and are associated with mobile elements, such as *ISEcp1*.<sup>11</sup> The epidemiology of organisms that produce CTX-M enzymes is very different from that of those organisms that produce TEM- and SHV-derived ESBLs.<sup>12</sup> CTX-M enzymes are not limited to nosocomial infections caused by *Klebsiella* species, and their potential to spread beyond the hospital environment has exacerbated public health concerns. *E coli* that produce CTX-M  $\beta$ -lactamases seem to be true community ESBL producers, and the current emergence and spread of these bacteria will have important implications.

#### **Treatment of infections caused by ESBL-producing Enterobacteriaceae**

The choice of drugs for treating serious infections caused by ESBL-producing bacteria is limited to the carbapenems (imipenem, meropenem, and ertapenem).<sup>7</sup> The mortality rate for patients with infections treated with a carbapenem was significantly lower than that for patients who received other antibiotics reported to have in vitro activity against ESBL-

producing bacteria.<sup>13</sup>

Treatment failures have been described when cephalosporins and combinations of a  $\beta$ -lactam with a  $\beta$ -lactam inhibitor were used for serious infections caused by ESBL-producing Enterobacteriaceae.<sup>14</sup> These treatment failures are most likely attributable to the inoculum effect, in which minimal inhibitory concentrations rise as the number of bacteria increases. The cephamycins, such as cefoxitin, should be avoided when treating such infections because of the relative ease with which these bacteria decrease the expression of outer membrane proteins, thus creating resistance.<sup>14</sup>

Antibiotics from other classes, particularly the fluoroquinolones, trimethoprim/sulfamethoxazole (TMP/SMX), and the aminoglycosides, can be used if susceptibility testing shows in vitro activity. Several studies have demonstrated a significant increase in resistance to the fluoroquinolones among community isolates, especially the CTX-M producers; this will influence the future use of antibiotics in the treatment of community-onset infections, especially empiric treatment of urinary tract infections (UTIs).<sup>15</sup>

It is possible that the widespread use of antibiotics, such as extended-spectrum cephalosporins, fluoroquinolones, and TMP/SMX, in the hospital and in community settings will continue to select for the emergence of isolates that possess mutations in the genes responsible for ESBL production.

#### **Community-onset infections and ESBL-producing bacteria**

Community-onset infections are defined infections that have an onset within 48 hours of hospital admission or that present in the outpatient setting. Such infections can be divided into 2 groups.<sup>16</sup>

■ The first group is associated with

health care institutions and includes patients receiving intravenous treatment or specialized care, those who have attended a hospital clinic within the previous 30 days, those who have been admitted to a hospital within the previous 90 days, and residents of nursing homes or long-term-care centers.

■ The second group represents truly community-acquired infections in patients who do not meet the above-mentioned criteria.

Most community-onset infections caused by ESBL-producing bacteria are health care-associated. The first possible community acquisition of an ESBL-producing isolate was reported in 1998 in Ireland: a nalidixic acid-resistant *E coli* that produced an ESBL was isolated from the urine of an elderly patient who had not been recently hospitalized.<sup>17</sup> This was followed by several case reports and larger studies from Israel, the United Kingdom, Canada, and different countries in Europe.<sup>15</sup> The characteristics of community-onset infections that are caused by ESBL-producing bacteria are summarized in the Table.

There is a “chicken versus egg” issue concerning ESBL-producing bacteria in the community. Did these bacteria originate in hospitals and were then introduced into the community, or did they originate within the community setting? Evidence of a community origin includes the fact that CTX-Ms (the most common ESBL in the community) evolved from environmental organisms (such as *Kluyvera* species) and the fact that these enzymes are associated with mobile elements (therefore, they can be maintained and spread within the community with relative ease).<sup>11</sup>

Furthermore, several studies have shown that farm and domestic animals from different parts of the world are colonized with ESBL-pro-

ducing bacteria.<sup>15</sup> This is further supported by studies from Spain and the United Kingdom that showed that up to 4% of the general population are colonized with ESBL-producing bacteria.<sup>18,19</sup>

**Consequences for the medical community**

The emergence of ESBL-producing bacteria in the community has important consequences for the medical community in general but especially for the clinical microbiology laboratory, clinicians, and infection control practitioners. The clinical microbiology laboratory plays a critical role in detecting and reporting ESBL-

producing bacteria, but many laboratories may not be fully aware of the importance of these organisms and how best to detect them.<sup>20</sup> One consequence of this lack of awareness is that there have been several treatment failures in patients who received inappropriate antibiotics and outbreaks of multidrug-resistant, Gram-negative pathogens that required expensive control efforts.

Although several guidelines are available, including those from the Clinical and Laboratory Standards Institute (CLSI) in the United States, this remains a contentious issue, since many laboratories have difficulty in detecting ESBL-mediated re-

**Table – Characteristics of community-onset infections caused by ESBL-producing bacteria (*Escherichia coli*)<sup>15</sup>**

**Type of ESBL**

CTX-M (especially CTX-M-15)

**Infections**

Most often UTIs; bacteremia and gastroenteritis

**Susceptibilities**

Resistance to all penicillins and cephalosporins; high-level resistance to other classes of antibiotics, especially fluoroquinolones and trimethoprim/sulfamethoxazole

**Molecular epidemiology**

Most isolates often not clonally related, although clusters have been described in Canada, the United Kingdom, Italy, and Spain

**Risk factors**

- Recurrent UTIs and underlying renal pathology
- Previous use of antibiotics, including cephalosporins and fluoroquinolones
- Previous hospitalization
- Nursing home residence
- Older age
- Diabetes mellitus
- Underlying liver pathology

ESBL, extended-spectrum β-lactamase; UTI, urinary tract infection.

sistance because of cost-cutting practices, while others are unaware of the relevant CLSI guidelines. Proficiency testing shows that compliance among clinical laboratories varies widely throughout the world.<sup>5</sup> A study published in 2003 showed that only 8% of clinical laboratories from rural hospitals in the United States routinely screened for ESBL-producing organisms.<sup>21</sup>

The second major consequence affects clinicians who are confronted with bacteria that typically cause nosocomial infections causing infections in patients in the community. The presence of ESBLs complicates antibiotic selection, especially in patients with serious infections, such as bacteremia.<sup>7</sup> The reason for this is that ESBL-producing bacteria, including those originating in the community, are often multiresistant to various antibiotics; an interesting feature of CTX-M-producing isolates is the co-resistance to the fluoroquinolones.<sup>15</sup> Antibiotics that are regularly used for serious community-onset infections, such as the third-generation cephalosporins, are often not effective against ESBL-producing bacteria.<sup>14</sup> A recent study from Israel has demonstrated that up to 15% of cases of non-nosocomial bacteremia are caused by ESBL-producing bacteria.<sup>22</sup>

The final major consequence for the medical community is the possible introduction of ESBL-producing bacteria from the community into the hospital setting. The above-mentioned study from Israel showed that 11% of patients admitted to a general medical ward were positive for ESBL-producing bacteria on fecal screening.<sup>22</sup>

### Combating ESBL-producing bacteria in the community

Four important issues need to be addressed if the spread of ESBL-producing bacteria is to be curbed.

■ *Should all Enterobacteriaceae isolated in the clinical laboratory from community specimens be tested routinely for ESBL-production?* The clinical laboratory acts as an early-warning system, alerting the medical community to new resistance mechanisms in clinically important bacteria. The detection of ESBL-producing organisms in laboratories is a critical requirement for appropriate treatment of patients, for infection prevention and control efforts, and for tracking these organisms in surveillance systems. All clinical microbiology laboratories should rule out ESBL production in Enterobacteriaceae, regardless of the specimen type or the location of the patient (in the community, hospital, or nursing home setting). An appropriate approach to initially screening organisms from the community is to use resistance to cefpodoxime followed by confirmation disk tests using both cefotaxime with and without clavulanate and ceftazidime with and without clavulanate.<sup>23</sup>

■ *Should a carbapenem routinely be used for the treatment of serious community-onset infections?* The routine use of a carbapenem for empiric therapy for serious community-onset infections is not indicated, but additional studies are needed to further define the risk factors for such infections. It is evident that most infections are health care-associated, but the risk factors for the truly community-acquired infections need to be established.

■ *Should all patients be screened for ESBL-producing bacteria via rectal specimens before or during hospital admission, and must barrier precautions be instituted when taking care of these patients?* Limiting the introduction of ESBL-producing organisms into the hospital setting might prove difficult, since routine rectal screening of patients admitted from the community may be impractical. However, it

is important to investigate fecal colonization among the general population, especially in North America. This will help identify patients who are at risk for colonization with ESBL-producing bacteria, so that barrier precautions can be initiated on hospital admission. This approach will help prevent the spread of these organisms.

■ *What future investigations are needed?* Investigations are needed to study the microbiologic and ecologic factors that make certain CTX-M producers (especially CTX-M-15) such successful pathogens. A simple standardized and cost-effective typing protocol should be established for monitoring the spread of different clusters of CTX-M-15-producing *E coli* throughout the world. This protocol can be distributed to different laboratories, and typing images can be forwarded to a center for comparison purposes to ensure the tracking of these important CTX-M-producing bacteria. Additional molecular surveillance studies are necessary to track CTX-M-producing *E coli* in the community and to investigate their influx into hospitals. A more accurate evaluation of the origin of CTX-M  $\beta$ -lactamases, including the distribution of *Kluyvera* species, is also required.

### Summary

It is clear that the epidemiology of ESBL-producing bacteria is becoming more complex, with increasingly blurred boundaries between hospitals and the community. *E coli* that produce CTX-M  $\beta$ -lactamases seem to be true community ESBL producers with different behavior than *Klebsiella* species that produce TEM- and SHV-derived ESBLs. These bacteria have become widely prevalent in the community in certain areas and are likely to be imported into the hospital setting.

Because of the significant public

health implications, including the treatment of community-acquired UTIs, the spread of organisms that produce ESBLs (especially CTX-Ms) in the community merits close monitoring with enhanced surveillance efforts. This will help prevent infections caused by these emerging pathogens. It is important for clinicians to be aware of the emergence of ESBL-producing bacteria in the community. Not all clinical laboratories necessarily test for ESBLs in bacteria isolated from community patients. Clinicians can play a major role in helping to curb the spread of these organisms by making clinical laboratories that perform testing on their patients aware of the importance of ESBLs in this setting. ♦

## Therapeutic agents mentioned in this article

Cefotaxime  
 Cefoxitin  
 Cefpodoxime  
 Ceftazidime  
 Clavulanate  
 Ertapenem  
 Imipenem  
 Meropenem  
 Trimethoprim/sulfamethoxazole

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