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Clinical Impact of Extended-Spectrum β-Lactamase-Producing Bacteria

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1. Introduction

We have been forced to fight against the newly acquired antibiotic resistance of various bacteria. By the end of the 1970s, most *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) strains contained plasmid-mediated, ampicillin-hydrolyzing β-lactamases, such as TEM-1, TEM-2, and SHV-1, and could be eliminated by the use of third-generation cephalosporins. [1] TEM-1 and TEM-2 were detected mainly in *E. coli*, and SHV-1 was mainly detected in *K. pneumoniae*. [2] The emergence of *K. pneumoniae* strains with a gene encoding β-lactamase that hydrolyzes the extended-spectrum cephalosporins was first reported by a study from Germany in 1983. [3] The gene encoding the new β-lactamase harbored a single-nucleotide mutation, as compared to the parental *bla*SHV-1 gene. In 1986, *K. pneumoniae* strains resistant to the third-generation cephalosporins were detected in France. [4] The resistance was attributed to a new β-lactamase gene, which was closely related to TEM-1 and TEM-2. These newly detected β-lactamases capable of hydrolyzing extended-spectrum β-lactam antibiotics were named extended-spectrum β-lactamases (ESBLs). [5] In 1989, the CTX-M type was reported as a new ESBL family member not belonging to either the TEM or SHV types. [6] Notably, the origin of CTX-M ESBLs is totally different from that of TEM or SHV ESBL. [7] Until the end of the 1990s, most of the ESBLs detected were either the TEM or SHV types and were usually associated with nosocomial outbreaks caused by *K. pneumoniae.* [1] In the new millennium, the worldwide spread of CTX-M-producing *E. coli* has been dramatic, and they are now considered to be the primary ESBL producers that are almost always associated with community-acquired infections. [8] ESBL-producing *E.coli* and *Klebsiella* spp. are now listed as one of the six drug-resistant pathogens for which few potentially effective drugs are available. [9] This chapter will outline the genetic aspects of TEM, SHV, and CTX-M ESBLs, including molecular epidemiology and mobile elements. In addition, we will also consider the impact of their genetic evolution on clinical aspects, including mode of infection and antibiotic resistance.

2. ESBL definition/classification

There is no exact definition of ESBLs. ESBLs are generally defined as β-lactamases that confer resistance to bacteria against the penicillins, the first-, second-, and third-generation cephalosporins, and to aztreonam by hydrolyzing these antibiotics, and are inhibited by β-lactamase inhibitors. [1] Most of ESBLs are classified as class A on the basis of the scheme

devised by Ambler et al. [10] Class A ESBLs form a heterogeneous molecular group, which comprises β-lactamases sharing various identities, and consists of three major groups: the TEM, SHV, and CTX-M types. [7] TEM and SHV ESBLs genetically evolved from TEM-1, TEM-2, and SHV-1 progenitors (non-ESBLs), and CTX-M ESBLs developed independently from TEM and SHV ESBLs. Additional ESBL types, such as PER, VEB, and BES, are uncommon. [10] More than 130 TEM types and more than 50 SHV types are currently known. [10] The most common group of ESBLs not belonging to the TEM or SHV types is CTX-M, the name derives from the potent hydrolytic activity against cefotaxime. [1] More than 40 CTX-M types are now recognized and can be divided into five subgroups, CTX-M1, 2, 8, 9, and 25, according to their amino acid sequence similarities. [7]

3. Global epidemiology: dissemination of ESBLs

ESBLs were first detected in the first half of the 1980s in Europe, and they later disseminated worldwide. [1] Until the 1990s, the main producer of ESBLs was *K. pneumoniae* and nosocomial outbreaks caused by the organism were often reported. [1] The number of ESBL-producing *E. coli* isolates has been dramatically increasing during the 21st century. [11] A recent global surveillance database collected from Europe, North and South America, and Asia, showed that the detection frequencies for ESBL-producing *K. pneumoniae* and *E. coli* isolates were 7.5-44% and 2.2-13.5%, respectively. [12] The prevalence of ESBL-producing isolates increased to a greater degree, particularly in Asia than in other regions, and one study conducted in 2007 showed that the frequencies of ESBL-producing *K. pneumoniae* and *E. coli* isolates exceeded 30% in both bacterial populations. [13] A recent surveillance using samples collected from nine Asian countries showed ESBL producers accounted for 42.2% of *K. pneumoniae* isolates detected from patients with hospital-acquired pneumoniae. [14] Our data collected from one institution in Japan showed that the detection rate of the *E. coli* isolates increased first, followed by increased detection rates of the *K. pneumoniae* and *P. mirabilis* isolates. [15] (Figure1) These data suggest that *K. pneumoniae*, as well as *E. coli*, has been an important ESBL producer even in the last few years.

In the analysis of ESBL genotypes, TEM and SHV were predominantly observed until the 1990s, and it was most reported that SHV-producing *K. pneumoniae* strains showed clonal dissemination in hospitals. [1] Recent studies show that TEM and SHV types have been frequently detected up to the present day. Interestingly, in some cases, SHV has been found in isolates expressing other ESBL types, such as TEM and CTX-M. [16] Our study showed that multiple types of ESBLs, including TEM, SHV, and CTX-M, were most frequently detected in *K. pneumoniae* and *E. coli*. [15] (Table1) These findings suggest that the genetic mechanism underlying dissemination of ESBL genes has become more divergent and complicated. After the first half of the 2000s, it was often reported that the number of CTX-M ESBLs detected was on the rise, that the main carrier was *E. coli*, and that most of the CTX-M-producing *E. coli* strains were acquired in the community, not in hospitals. [11] The detection rate of CTX-M ESBLs has been dramatically rising, especially in the last 5 years. [17] The mechanism behind the spread of *bla*CTX-M genes differs from that observed in the case of *bla*TEM and *bla*SHV genes. *bla*TEM and *bla*SHV ESBL genes are associated with the dissemination of particular clones, known as an "epidemic" pattern; however, the mechanism by which *bla*CTX-M ESBL genes disseminate reflects the simultaneous spread of multiple specific clones, known as an "allodemic" pattern. [18] It has been indicated that various CTX-M-type ESBLs have spread

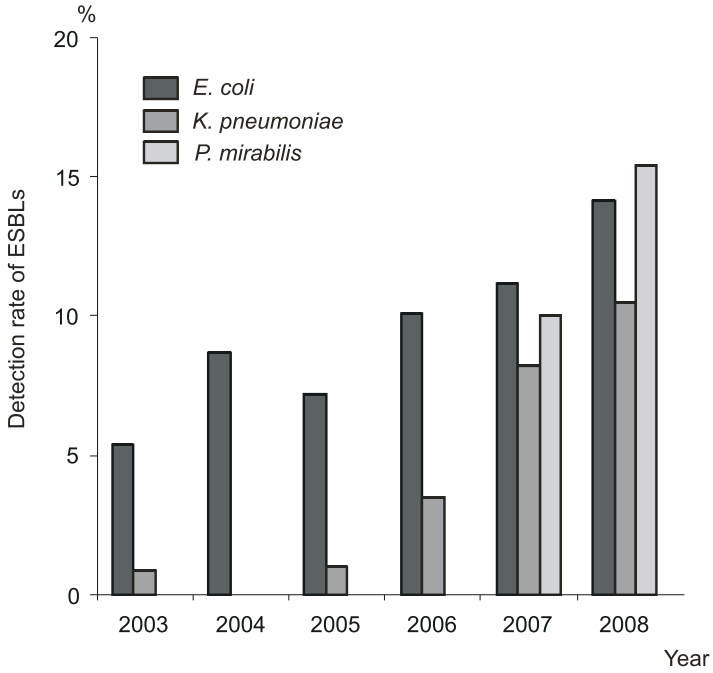

Fig. 1. Frequencies of ESBL-producing organisms at Hara-Sanshin Hospital in Fukuoka (Japan)

worldwide, and that specific CTX-M subgroups have been characterized in different geographic areas. [15,18,19] In contrast, CTX-M-15 ESBLs, which belong to the CTX-M-1 group, have been found worldwide. [18] Unlike in other countries, in the USA, ESBLs were rarely detected, until the first half of the 2000s; however, CTX-M ESBLs, specifically CTX-M-15, have frequently been encountered over the last 5 years. [20,21]

Year	Total no. of isolates	TEM/SHV	CTX-M	TEM/SHV+CTX-M
2003	11	0(0.0)	4 (36.4)	7(63.6)
2004	15	1(6.7)	5 (33.3)	9(60.0)
2005	15	0(0.0)	5(33.3)	10(66.7)
2006	20	0(0.0)	5 (25.0)	15(75.0)
2007	18	2(11.1)	7 (38.9)	9(50.0)
2008	25	5(20.0)	9(36.0)	11(44.0)
Total	104	8(7.7)	35(33.7)	61(58.6)

Table 1. Genotypes of ESBL-producing *Eschrichia coli* isolated from hospitalized patients

4. Genetic characteristics

Genes harboring ESBLs are associated with several specific genetic structures. A variety of mobile genetic elements, such as transposons, insertion sequences, and integrons, play important roles in the dissemination of ESBL genes. *bla*TEM-type ESBL genes are acquired by the mutation of plasmid-mediated, parent *bla*TEM-1 and *bla*TEM-2 genes, and the main producer of TEM-type ESBLs is *E. coli*; these genes occur within the earliest bacterial transposons identified. [2,22] *bla*SHV-type ESBL genes are the derivatives of chromosomal, parent *bla*SHV-1 genes, which occur mainly in *K. pneumoniae*,[23] and are likely acquired by the role of insertion sequences from chromosome to plasmid. [22] Notably, *bla*TEM-type and *bla*SHV-type ESBL genes located in the integron structures have never been identified. [22] The spread of *bla*CTX-M-type ESBL genes is associated with more complicated mobile elements, compared to that of *bla*TEM and *bla*SHV ESBL genes. *bla*CTX-M ESBL genes are not derivatives of *K. pneumoniae* or *E. coli* that contain original genes, as compared to *bla*TEM or *bla*SHV ESBL genes. *bla*CTX-M genes originate from the chromosomal β-lactamase genes of *Kluyvera* species, which are environmental bacteria found worldwide, and are captured mainly by insertion sequence elements translocated from chromosome to plasmid. [18] Original β-lactamase genes of *Kluyvera* species are identified in most CTX-M subgroups. [18] This differential origin might be involved in the characteristic spread of *bla*CTX-M ESBL genes, that is, an "allodemic" pattern of spread. All *bla*CTX-M genes are associated with insertion sequences. Well-studied, CTX-M-associated insertion sequence elements include IS*Ecp1* and IS*CR1*, which are involved in the mobilization of *bla*CTX-M genes by a transposition mechanism. [24,25,26] In addition, integron structures bearing insertion sequences and *bla*CTX-M genes can be linked to transposon elements, such as from the Tn*21* family, which has been intensively studied. Transposons of the Tn*21* family are disseminated worldwide in both environmental and clinical bacteria.[18,24] These highly efficient mobile genetic elements may have influenced the rapid and easy dissemination of *bla*CTX-M ESBL genes.

An antibiotic resistance plasmid itself is responsible for the efficiency of gene transfer, as well as the mobile genetic elements described above. It has been shown that ESBL gene-bearing plasmids can be transferred to different bacterial species by conjugation. [27,28] Previous studies have shown that *bla*TEM and *bla*SHV ESBL genes are associated with plasmids belonging to a few specific incompatibility (Inc) groups.[18] In contrast, *bla*CTX-M ESBL genes are carried by plasmids belonging to a variety of Inc groups including narrow- and broad-host-range types. [18,29] *bla*CTX-M-15 genes are located mainly on plasmids belonging to the IncF group. [29] Interestingly, a recent study has described the diversity of ESBL gene-bearing plasmids, including SHV types. [30] It was reported that a mosaic plasmid has been identified from a clonal CTX-M-producing *E. coli* isolate, suggesting genetic interactions among different plasmids. [31] In ESBL gene-bearing plasmids, the genetic diversity has been constantly increasing through the mechanism of gene transfer and gene shuffling.

5. Clinical impact

5.1 The mode of infection

5.1.1 Nosocomial infection

Up to the end of the 1990s, clinical infections caused by ESBL-producing bacteria were associated with nosocomial outbreaks, where the chief ESBL producer was *K. pneumoniae*,

but not *E. coli*. In addition, the ESBL genotypes detected in the nosocomial setting were almost always TEM and SHV, but not CTX-M types. [1] SHV-producing *K. pneumoniae* strains were intensively examined in the analysis of clonal dissemination in hospitals. Clonally related SHV-4-producing *K. pneumoniae* isolates were shown to have spread to multiple hospitals within the specific region. [32] This phenomenon indicates that, at that time, the mode of spread for SHV-producing *K. pneumoniae* was the dissemination of particular clones, that is to say, an "epidemic" pattern. The number of nosocomial outbreaks caused by TEM- or SHV-producing *K. pneumoniae* strains have been decreased during this century; however, as observed in many studies, these organisms are frequently identified in many hospitals worldwide. Interestingly, the derivatives of TEM and SHV types have been reported to be more divergent in *K. pneumoniae* strains isolated in European hospitals. [16,33] Moreover, the new variants of *bla*SHV genes were detected from an Algerian hospital. [34]

5.1.2 Community-acquired infection

The mode of ESBL-related infection has dramatically changed since the 2000s. Community-acquired infections caused by ESBL-producing bacteria have been increasingly documented. [8] CTX-M-producing E. coli strains are chiefly responsible for community-acquired infections, which are related to an increase in the number of ESBL carriers in the general population. [11,35] One report describes a significant increase in the prevalence of ESBL carriers in a specific population from 2001 to 2006. [36] The interfamilial dissemination of ESBL-producing bacteria has also been suggested. [37] Notably, animals used as food and or pets are reported to carry CTX-M ESBLs, [38,39,40,41] and this finding may explain the dramatic spread of ESBLs in the community. The community-onset dissemination of ESBLs in both humans and animals may suggest that *bla*CTX-M ESBL genes detected in pathogenic bacteria are acquired from environmental bacteria. Branger et al showed that many CTX-M ESBLs were associated with the phylogenetic group D2 that lacked a virulence factor. [42, 43] The specific features may be related to the colonization and spread among the general population. The spread of ESBLs in the community is linked to the emergence of ESBL-related infections in outpatients, in whom urinary tract infections are most often reported along with bacteremia. [44,45, 46] One study has described the detection of CTX-M-producing *K. pneumoniae* in outpatients, [33] A nosocomial outbreak was caused by CTX-M-producing *K. pneumoniae* isolates from foods, suggesting the influx of ESBL-producing *K. pneumoniae* into a hospital. [47] These reports may account for the dissemination of CTX-M ESBL genes from *E. coli* to other bacteria in the community.

5.2 Antibiotic resistance

Antibiotic resistance is of utmost importance for the clinical impact of ESBL-producing bacteria. A meta-analysis showed increased mortality and delay in effective antibiotic use in ESBL-related bacteremia, [48] indicating the importance of constant surveillance for an antibiotic resistance pattern in organisms with ESBLs. ESBL-producing bacteria are resistant to almost all β-lactam antibiotics, except carbapenems, as indicated by their definition. In addition, most ESBL-producing bacteria, particularly those with the TEM, SHV, and CTX-M genotypes, exhibit co-resistance to aminoglycosides, tetracyclines, and sulfonamides. [18] Organisms with CTX-M genotypes, such as those with CTX-M-9, -14, and -15, are reported to be resistant to fluoroquinolones. [18] This additional resistance is induced by the main

mechanism that *bla*CTX-M genes are directly linked to quinolone resistance genes, *qnr* genes. IS*CR1*, a mobile element for *bla*CTX-M genes, is associated with *qnr* genes, [26] indicating an effective transfer of quinolone resistance genes together with *bla*CTX-M genes. This genetic finding is interesting for clinical reasons. Selective pressure by the use of fluoroquinolones may induce the emergence of CTX-M ESBL-producing bacteria. As a consequence, the therapeutic options for infections caused by ESBL-producing bacteria may be more limited. Tigecycline has been shown to be microbiologically active against ESBL-producing *E. coli* and *K. pneumoniae,* [49,50] whereas, fosfomycin has been reported to be effective against urinary tract infections caused by ESBL-producing *E. coli.* [51,52]

6. Spread of CTX-M-15-producing ST131 *E. coli* clones

The dissemination of CTX-M-15 producing *E. coli* strains has become a major concern of research in antibiotic resistance. The first isolation of CTX-M-15-type ESBLs was reported in India in 2001. [53] CTX-M-15 is derived from CTX-M-3, belonging to the CTX-M-1 group, differing by one amino acid substitution. *bla*CTX-M-15 genes are transferred mainly by the IncF group plasmids, which are well adapted to *E. coli* and have acquired many antibiotic resistance genes. [54,55,56] Recently, Mnif et al reported that the IncF plasmids carrying *bla*CTX-M-15 genes contained many addiction systems, which could contribute to their maintenance in *E. coli* host strains. [57] The detection rate of the CTX-M-15 producing *E. coli* strains with multidrug resistance has been dramatically increasing worldwide since the 2000s. [56] This CTX-M-15-producing *E. coli* strain is often thought to be associated with ST131 clones. [56] Most of the CTX-M-15-producing *E. coli* strains isolated from three continents were O25:H4-ST131 clones that show highly similar PFGE profiles, suggesting a recent emergence of these clones. [58] The emergence of the CTX-M-15-producing ST131 *E. coli* clones is highly related to the recent dissemination of ESBLs in the USA. [59, 60] The worldwide spread of the multi-drug-resistant ST131 *E. coli* clones can be explained by the acquisition of IncFII plasmids harboring *bla*CTX-M-15 genes and many other antibiotic resistance genes. Interestingly, these ST131 *E. coli* clones belong to the highly virulent, phylogenetic group B2. [56] Over the past 5 years, CTX-M-15-producing ST131 *E. coli* clones have become an important causative agent for community-acquired ESBL infections, mainly urinary tract infections and bacteremia. [45]

7. Clinical impact on immunodeficient patients

The sufficient therapy for ESBL-related infections is important, especially in immunodeficient patients. One study has shown that approximately 13% of *E. coli*-related bacteremia cases detected in patients with cancer and neutropenia were caused by ESBLs, that CTX-M types were predominant among the ESBLs, and that the bacteremia induced by ESBL-producing *E. coli* strains was linked to inadequate empirical antibiotic therapy. [61] In our institution, the detection rate of ESBL-related bacteremia has been increasing in febrile neutropenic patients with hematological malignancies, and consequently, we have been forced to use carbapenems for the therapy. [62,63] In immunodeficient patients, such as those undergoing chemotherapy, serious ESBL-related infections may result in a poor prognosis owing to the failure of the initial therapy. Recently, M. D. Anderson Cancer Center has reported an interesting finding that pyomyositis was caused by ESBL-producing *E. coli* strains in neutropenic patients with hematological malignancies, and that the *E. coli* strains

were ST131 clones belonging to phylogenetic group B2. [64] This notable finding implies that ESBL-producing ST131 *E. coli* clones cause fatal damage in the case of immunodeficient patients because of their high virulence.

8. Conclusions

The spread of ESBL-producing bacteria in the community has begun influencing outpatient therapy. Community-acquired bacteremia, due to ESBL-producing *E. coli* strains, is becoming a critical concern for outpatients, because inappropriate use of empirical antibiotics, such as cephalosporins and fluoroquinolones, has resulted in high mortality. [65,66] One study has shown that the resistance of CTX-M-15-producing ST131 *E. coli* strains isolated from the community to fosfomycin has increased. [67] In the near future, we may be forced to use carbapenems as the first choice for the empirical therapy of patients with community-acquired infections due to ESBL-producing bacteria. The identification of carbapenemase-producing *E coli* and *K. pneumoniae* strains has been frequently documented as evidence for additional β-lactamases-producing bacteria other than the ESBL-producing bacteria. [68] The study of NDM-1-type carbapenemase-producing *E coli* and *K. pneumoniae* is currently a topic of much interest in multidrug-resistant bacteria research. Notably, some of the NDM-1-type-producing *E coli* and *K. pneumoniae* strains express *bla*CTX-M-15 ESBL genes in a single isolate. [69,70,71] A worldwide surveillance recently showed that many NDM-1-producing bacteria detected carried additional ESBL genes. [72] The acquisition of efficient mobile elements has accelerated the transfer of various antibiotic resistance genes. Potentially, a "super bug," resistant to almost all licensed antibiotics, may emerge in the future. Constant and careful worldwide surveillance for multidrug-resistant bacteria is urgently warranted.

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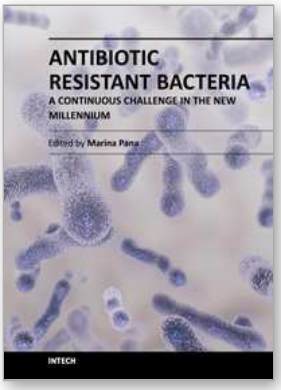

Antibiotic Resistant Bacteria - A Continuous Challenge in the New Millennium

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Antibiotic-resistant bacterial strains remain a major global threat, despite the prevention, diagnosis and antibiotherapy, which have improved considerably. In this thematic issue, the scientists present their results of accomplished studies, in order to provide an updated overview of scientific information and also, to exchange views on new strategies for interventions in antibiotic-resistant bacterial strains cases and outbreaks. As a consequence, the recently developed techniques in this field will contribute to a considerable progress in medical research.

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