Review Article

Extended-Spectrum β-Lactamase-Producing *Enterobacterales*

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Abstract

Extended-spectrum β-lactamases-producing *Enterobacterales* is one of the global health concern due to rapid global spread and threatening infections. It is known as "superbugs" causing both hospital-acquired and community-acquired infections. ESBL genes dissemination is associated with mobile genetic elements on plasmid resulting in rapid transmission. Emerging of ESBL producers can occur by horizontal gene transfer. It is suggested that screening for ESBL colonization should be carried out in the high-risk groups. Moreover, appropriate antibiotic use for treatment is imperative to prevent development of bacterial resistance against new antibiotics. Global surveillance of extended-spectrum β-lactamase producing *Escherichia coli* is currently carried out with a tricycle protocol. It is crucial to encourage active surveillance and infection control to prevent ESBL genes transmission.

Keywords: Extended-spectrum β-lactamases-producing *Enterobacterales,* ESBL genes, Transmission, Risk factors, Prevalence and surveillance

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Introduction

Nosocomial infections are caused by many resistant bacteria, including carbapenem-resistance in *Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacterales,* Extended-spectrum β-lactamase-producing *Enterobacterales* (ESBL-E), vancomycin-resistant *Enterococcus faecium,* methicillin-resistant *S. aureus*, clarithromycin-resistant *Helicobacter pylori*, fluoroquinolone-resistant *Campylobacter* spp., fluoroquinolone-resistant *Salmonellae*, cephalosporin-resistant *Neisseria gonorrhoeae*, penicillin-non-susceptible *Streptococcus pneumoniae*, ampicillin-resistant *Haemophilus influenzae,* and fluoroquinolone-resistant *Shigella* spp.

High rates of antibiotic resistance among these bacteria have frequently been observed worldwide. The Global Antimicrobial Resistance and Use Surveillance System (GLASS) showed reports of resistance to carbapenem in *K. pneumoniae* and to fluoroquinolone antibiotics in *E. coli,* which were used for urinary tract infection. At present, the only effective drug for carbapenem resistant bacteria is colistin.[1] The antibiotic resistance of bacteria severely affects public health and causes economic problems worldwide, as reported by the Centers for Disease Control and Prevention (CDC).[2]

ESBL-E has emerged globally and spread rapidly. This causative agent resulted in failure of treatment due to the extended-spectrum β-lactamases. This review focuses on genetic characteristics, dissemination and transmission of ESBL genes. In addition, prevalence, risk factors and recent surveillance by multisectoral approach for antimicrobial resistance are included for an overview.

Characteristics of ESBL - E and Dissemination of ESBLs

ESBL-E first emerged in healthcare settings and then spread to communities.[3] They have become a global health concern. ESBL-EC is most commonly found in urinary tract infections; however, this bacteria can also cause infections in blood streams and central nervous systems.[4] Mortality of patients with ESBL-EC infection in their blood streams is significantly higher than that of patients with non-ESBL producing *E. coli* in their blood, as reported previously.[5]

ESBLs were first described in 1983. The ESBLs are able to hydrolyze penicillins, oxyimino-cephalosporins, and aztreonam, but not cephamycins or carbapenems.[6] ESBL enzymes are inhibited by β-lactamase inhibitors such as clavulanic acid.[7] ESBL producers have become resistant to a wide variety of penicillins and cephalosporins due to their extended-spectrum β-lactamase. The only remaining β-lactam agent for treatment is carbapenem. More than 200 variants of ESBLs were characterized by George Jacoby and Karen Bush (http://www.lahey.org/studies/webt.htm). ESBLs have proliferated worldwide, as reported from many countries.

After introducing the third-generation, or oxyimino cephalosporins in the early 1980s, the first report of an extended-spectrum β-lactamase was SHV-2. ESBL-E, particularly *K. pneumoniae* containing SHV and TEM types, have been a major cause of hospital acquired infections. Since the late 1990s, ESBL producers have caused community acquired infections, as reported in patients with urinary tract infections and diarrhea.[3,7] The mutation of TEM- and SHV-type ESBLs resulted in failure of oxyimino cephalosporins hydrolysis. SHV-type ESBLs are most frequently found in *K. pneumoniae* and *E.coli*.[8] Variants of TEM- and SHV- type ESBLs are regional prevalent in USA and Europe.[9,10] However, prevalence of TEM and SHV mutants β-lactamases may be underestimated because they are not detectable by any screening methods used in routine laboratories.[10]

The CTX-M enzymes are the second largest group of ESBLs. There are many reports of them causing infection in community settings and they have frequently been identified worldwide.[11] CTX-M-type ESBL among *Enterobacterales* have spread globally and have become a major public health concern.[4,12] Mutations generated over 172 different CTX-M enzymes due to antibiotic selective pressure. The CTX-M was predominant as reported previously.[13-17] In contrast, in a recent study, CTX-M type was the least detected in both ESBL-PE and ESBL-KP. This indicates the CTX-M type had not yet widely spread among the strains in the hospital (S. Kondo, et. al., unpublished data).

OXA type was predominant in *Pseudomonas aeruginosa* but also found in other gram-negative bacteria.[18] Others including GES/IBC, VEB and PER β-lactamases were rarely detected.[3]

Transmission of ESBL Genes

Transmission of ESBL enzymes encoding genes can take place either by emerging bacterial clones or by horizontal gene transfer. The horizontal ESBL genes transfer is plasmid mediated resulting in spreading between the same and or different species. Insertion sequence common regions (ISCR), mobile genetic elements found on plasmids, are associated with ESBL genes dissemination.[4] A study in Thailand reported almost all isolates carried integrase *(intI1)* gene, a marker of multiple antibiotic resistance class 1 integron elements. This study indicated that the transmission of resistance genes occurred in both hospital and community settings.[19]

Many gram-negative bacteria produce chromosomally mediated β-lactamase. The SHV-1 -lactamase is chromosomally encoded in the majority of isolates of *K. pneumoniae* but is usually plasmid mediated in *E. coli.* CTX-M variants of β-lactamases are often found in *E. coli* causing hospital-acquired infection. TEM-1 was found to be the first plasmid-mediated β-lactamase in gram-negatives, as described in the early 1960s.[6] Since then, it has spread globally. ESBL encoding genes are located on large plasmids which also carry other antimicrobial resistance genes.[20]

Prevalence and Risk Factors

High prevalence of ESBL-E was caused by antibiotic usage in humans and animals. These strains are colonized in guts and capable of disseminating the resistant strains in the environment. ESBL-producing *K. pneumoniae* and ESBL-EC are the most prevalent isolates in Asia.[21-24] The correlation between antimicrobial resistance and antibiotic usage have been reported as a risk factor.[25] A report from Thailand indicated that the highest prevalence of ESBL-E was significantly associated with improperly using antibiotics after purchasing them without a prescription.[26] Another report indicated that duration of hospitalization and types of contact such as sharing food or hugging by family members were higher risk factors than healthcare workers of ESBL-producing *Enterobacterales* acquisition.[27] Rectal colonization with ESBL-producing gram-negative bacteria (ESBL-GNB) was detected in 86% of carriers.[28] Other sites of colonized patients detected 10-30% of ESBL-GNB.[29, 30] Therefore, the initial site of infection should be included for screening and follow-up.[28] Another report revealed risk factors of CTX-M-producing *E. coli* infection associated with underlying diseases, previous antibiotic usage, previous hospitalization, nursing home residents and elderly people.[31]

More reports suggested gut colonization is one of the risk factors for developing ESBL-EC infection.[32] Retrospective meta-analysis for prevalence of ESBL-E colonization in healthy individuals with identifying risk factors was associated with rising acquisition of ESBL resistance. In addition, international travel and antibiotic use were identified risk factors for ESBL-E fecal colonization.[33] This report revealed that global ESBL-EC was prevalent in 14% of patients with colonized ESBL-E. Fecal ESBL-EC carriage in patients with hematological malignancies was associated with blood stream infection resulting in longer stay in hospital and high costs.[34] A study in a 750-bed, tertiary-care hospital revealed that surgical site infection was associated with ESBL colonization and dirty wound classification.[35] Nutman and colleagues suggested screening for ESBL-E carriage before colorectal surgery.[36] In addition, personalizing prophylaxis for carriers is effective to lower the risk of surgical site infections.[37] However, screening for ESBL-E carriage is an expensive approach. Hence, surveillance screening and antimicrobial stewardship in the carriages who are particularly high risk groups is recommended.[38]

Surveillance by Multisectoral Approach for Antimicrobial Resistance

Due to the development of resistant bacteria caused by misuse and overuse of antimicrobial agents, antimicrobial resistance has become a global public health threat. Antimicrobal resistance involves in human, the food chain and the environment. The complex problem of antimicrobial resistance has led to a "One Health" approach for development of National Action Plans on integrated surveillance of antimicrobial resistance.

The "One Health" approach involves specialized agencies to work together for development and implementation of programs, policies, legislation and research for better public health solutions. This approach requires multisectoral action for Sustainable Development Goals (SDGs).

Global Action Plan to tackle antimicrobial resistance (GAP-AMR) was approved in the year 2015. This plan is to ensure successful treatment and prevention of infectious diseases. It is essential to have surveillance for drug resistance to provide data for policies, prevention and infection control, and AMR spread control and to monitor the impact of local, national and global strategies. Hence, GLASS, the first global collaboration for standard AMR surveillance, was established to provide a standardized approach to collection, analysis, interpretation and sharing of data. In addition, surveillance approaches based on laboratory data, including epidemiological, clinical, and population-level data, have been monitored for resistance and usage of antimicrobial agents for treatment. Data of AMR in the food chain and the environment are also incorporated with the data of AMR in humans.[1]

Recently, a tricycle protocol was developed for global surveillance of ESBL-EC.[39] This protocol is a simplified and multisectoral surveillance system for detection and estimation of the prevalence of ESBL-EC in three different sectors: humans (hospital and community), the food chain (animals), and the environment. In addition, genomic analysis is also performed. Prevalence trends are predicted from these data at regional and global levels. Data of ESBL-EC resistance of each sector combined with molecular characterization for the flow direction of resistance elements provide vigorous support for magnitude of selection pressure in each sector. The composition of ESBL-EC Tricycle protocol (eight work packages; WPs) are listed and methodology are briefly reviewed as follows.

- WP1: Surveillance in humans includes patients in hospitals with bloodstream infections and pregnant women (carriage) in communities
- WP2: Surveillance in the food chain includes chicken caeca from live bird open markets in major cities
- WP3: Surveillance in the environment includes rivers (upstream and downstream), animal slaughter wastewater, and human communal wastewater
- WP4: Molecular characterization
- WP5: Epidemiology design and analysis
- WP6: Management at country Level and regional levels
- WP7: Linkage with Global Antimicrobial Resistance Surveillance System (GLASS)
- WP8: Links with Antimicrobial consumption/ Antimicrobial use surveillance systems

WP1: Surveillance in Humans

Isolation, confirmation, and characterization of ESBL-EC in humans are performed to calculate the proportion of ESBL-EC strains among all *E.coli* in hospitalized patients with bacteremia, and in healthy pregnant women for the prevalence of fecal ESBL-EC colonization at pre- and peri-natal healthcare settings, during delivery, or at their last routine visit before delivery.

WP2: Surveillance in the Food Chain

Isolation, confirmation, and characterization of ESBL-EC in poultry (chicken) is carried out by collecting intact caeca by clipping at the ileocaecal junction and at the caecal-colon junction, and placing each entire cecum plus its contents in a separate, sterile, container. The sample should be transported to laboratory immediately in an ice-filled cooler and kept at 4°C for analysis within 48 hours.

WP3: Surveillance in the Environment

Selection of sampling sites are suggested as follows.

1. Sampling sites selection should be aligned with the human and food chain WPs.
2. Sampling locations for human wastewater should be selected.
3. Sampling sites selection should be aligned with poliovirus environmental sampling.
4. Investigated rivers should be sampled upstream and downstream of locations where humans and animals discharge into the river.
5. In case of no river, suitable sampling locations for analyses in human and animal wastewater is allowed.
6. In cases of a seashore or a similar large coastal marine area, downstream samples can be collected at the river mouth discharge into the ocean or large lake, ideally during low tide.

WP4: Molecular Characterization

Genomic analysis including genotyping and/or whole genome sequencing for molecular characterization are performed in order to scrutinize more detailed information of the isolates.

WP5: Epidemiology Design and Analysis

Metadata are collected from human sources including bloodstream and fecal samples. The data from blood include (1) Patient ID, (2) Hospital name (blood stream) and Clinic/hospital name (fecal), (3) Date of admission (blood stream only), (4) Date of sampling, (5) ID specimen number, (6) Sex (bloodstream), (7) Age, (8) Isolate number, (9) ESBL screening result, (10) Isolate ID confirmation, (11) Antimicrobial susceptibility testing results.

WP6: Management at Country Level and Regional Level

Training Microbiologist(s), Epidemiologist and National coordinator for participation and national coordination for implementation of ESBL-EC Tricycle surveillance.

WP7: Linkage with Global Antimicrobial Resistance Surveillance System (GLASS)

Antimicrobial resistance data have been collected from enrolled countries in GLASS. Tricycle data will be sent to GLASS IT platform and supported by WHONET.

Genomes for ESBL-EC should be submitted in public domain including National Center for Biotechnology Information (NCBI) or European Nucleotide Archive (ENA).

WP8: Links with Antimicrobial Consumption (AMC)/ Antimicrobial Use (AMU) Surveillance Systems

Analysis for AMC and AMU relation in humans is available from surveillance programmes in GLASS and Tricycle.

Discussion

ESBLs and variants are disseminated worldwide. The variants caused by mutations resulting in resistance to antibiotics and ineffective treatment. As CTX-M type ESBL have been classified as CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, and CTX-M-25 based on their amino acid composition.[40] A new CTX-M variant found in *K. pneumoniae* from clinical specimen showed impaired permeability leading to increased MIC of meropenem (8 mg/L). The isolates carried two CTX-M enzymes with different resistance mechanisms which limited the efficacy of the antibiotics used, including meropenem and new antimicrobial agents[41]. In addition, more bacterial strains become resistant and rapidly spread both in hospital and community settings. Constant vigilance in prevention and infection control is crucial to stop the spread of antibiotic resistance.

Antimicrobial agents, including ciprofloxacin, amoxicillin/clavulanate, nitrofurantoin, and fosfomycin are currently recommended for the treatment of ESBL-E infection causing community-onset urinary tract infections. Ertapenem and other carbapenems are effective for serious infections caused by ESBL-E.[41] However, the effective drugs for treatment of the ESBL-E infections are running out due to the rapid spread of variants strains harboring ESBL resistant genes. Treatment of infections has become more difficult and new antimicrobial agents are urgently needed. Appropriate empirical antibiotic and punctual treatment are essential. Failure of treatment in serious infections is associated with long hospitalization, higher costs and increasing mortality. Therefore, guideline for an appropriate antibiotic for treatment is important to prevent new antibiotics from becoming ineffective.

The necessity of screening for ESBLs colonization to prevent transmission is still controversial. A meta-analysis report showed that an active surveillance program resulted in a significant reduction of resistance transmission,[42] however, another report revealed no benefits.[43] It is, therefore, suggested to have active surveillance and infection control programs to prevent the spread of resistant ESBL genes in ESBL patients at high risk of infection.

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