

Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* from livestock

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ABSTRACT

Extended-spectrum β -lactamases (ESBL) are enzymes produced in Gram negative bacterial plasmids that already have resistance to β -lactam antibiotics. Bacteria *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* are the most common ESBL-producing bacteria and are often detected as the cause of urinary tract infections, pneumonia and sepsis. ESBL-producing bacteria are generally known as infectious agents and considered as nosocomial pathogens. In the last decade the existence of livestock as animals transmitting and spreading ESBL has become a potential issue of new threats to humans. In this study, we describe the nature of ESBL, ESBL which produces type *E. coli* from livestock, factors that influence ESBL, transmission to human health, epidemiology of ESBL that produces *E. coli* in a global view, ESBL treatment, and ESBL control. Livestock provide animal protein in the form of meat and milk that are included in the global supply chain of trade and food. Feces animal waste production is a potential source of contaminants for the possible spread of ESBL bacteria to humans and the environment. ESBL treatment in humans is still very limited so preventing the spread of infection through the one health principle approach is the best way that can be done.

Keywords: ESBL, *Escherichia coli*, Livestock, One health

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INTRODUCTION

Extended-spectrum β -lactamases (ESBL) are enzymes produced in the Gram negative bacterial plasmid of the Enterobacteriaceae group that already have resistance to β -lactam antibiotics [1,2]. Most commonly known ESBL-producing bacteria [2] are *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) and are often considered as major cause of urinary tract infections (UTI), pneumonia and sepsis [2, 3]. CTX-M β -lactamase is most common ESBL enzyme in humans [5], while the variation of the subtype depends on the geographical area [6]. These ESBL-producing bacteria are nosocomial pathogens and increasingly found as infectious agents in the community [4]. The incidence of ESBL-producing bacteria has been widespread in the veterinary field, for example as a cause of mastitis in dairy cows [7] since 2000 [8, 9]. Research on these bacteria in livestock is important in order to ascertain the presence of these ESBL bacteria in sick and healthy cows, pigs and poultry farms [10-14]. The CTX-M group, has been found in many parts of Europe, especially CTX-M-1 β -lactamase which is often detected in cattle [6]. The risk of zoonotic migration from livestock to humans that is directly in contact with livestock is still largely unknown. There are several studies that have shown a link between the transfer of *E. coli* or ESBL-producing ESBL genes from poultry, pigs to humans in direct contact with these animals [15-18]. In addition to direct zoonotic transfer, food derived from animals can potentially be a risk factor for bacterial colonization or infection in humans [19, 20]. Bacteria, which produce ESBL are not only found in livestock, but are already widespread in pets [8, 21], zoo animals [22] and wildlife [23-25]. In this study, we describe the nature of ESBL, ESBL which produces type *E. coli* from livestock, factors that influence ESBL, transmission to human health, epidemiology of ESBL that produces *E. coli* in a global view, ESBL treatment, and ESBL control.

Nature of ESBL

ESBL can hydrolyze the antibiotic oxyimino- β -lactam which is currently an important therapeutic agent for the treatment of serious infections in humans and animals. ESBL was first detected in Enterobacteriaceae as a new taxonomy in 1983 and since then, scientific research has continued to examine the ESBL-producing Enterobacteriaceae (E-ESBL) as a real challenge to human lives. The incidence of 1700 deaths in the US due to treatment failure in severe infections in 2013 is inseparable from the increased ability of bacteria to hydrolyze antibiotics [26-28]. The occurrence of E-ESBL is not only limited to infections in the hospital environment, but has become a common human intestinal commensal disease [29, 30]. E-ESBL are present in various segments of ecosystem and are great concern to human, animals and environment. These segments of ecosystem can provide conducive environment for the spread of bacterial resistance. Animals become the transmission and distribution of E-ESBL because their position is directly related to the food chain in humans [31]. Livestock provide animal protein and are also source of meat and milk that is most consumed by humans, as well as being a major element in the food chain in humans [32]. Livestock are also the main source of compost through the resulting faecal mass [33]. All this puts livestock in an important position in the food chain and the environment, especially its role as a reservoir and transmission of the spread and threat of E-ESBL to the health of the world community. The inclusion of E-ESBL in ecosystems has raised concerns from various scientific communities and authorities involved in the One Health approach [34]. In Southeast Asia and Indonesia, based on several reports, E-ESBL has been found, the occurrence not only in humans but also in animals mainly livestock. Studies on milk samples from dairy farms have reported 8.75% positive ESBL [35]. In the beef cattle feces sample at the abattoir, 15.8% ESBL of *E. coli* bacteria were found and after 8.6%

CTX-M was identified [36, 37]. Molecular identification of rectal dairy swabs produced 5.21% positive ESBL *E. coli* with 6 blaCTX-M gene isolates and 2 blaTEM gene isolates [38]. Another study identified ESBL by the Vitek-2 method from a rectal dairy swab resulting in 6% positive ESBL *E. coli* [38]. Dairy cows can be potential as a reservoir for the spread of *E. coli* ESBL bacteria to humans. ESBL *e. coli* can be a threat to human health as well as a dangerous outbreak for the general public. Food chain contamination related to ESBL bacterial colonization is a risk that is difficult to deal with and control, especially in the era of globalization of trade, hygienic aspects and free of bacterial agents in food products of animal origin are important things to do so that the threat of the spread of *E. coli* ESBL from animals to humans can be finalized.

ESBL is an enzyme produced in bacterial plasmids that is globally classified into several variants, namely CTX-M, SHV and TEM. But there are also other types of ESBLs such as OXA, PER, VEB, BES, GES, SFO, TLA, and IBC [39]. CTX-M is common type of ESBL associated with the E-ESBL report [40]. Variants such as CTX-M-15 have been documented to be the cause of outbreaks of infection throughout the world, related to the clone that causes the antibiotic-resistant *E. coli* infection that is resistant to the antibiotic ST131 [41].

The emergence of ESBL variant enzymes mediated by plasmids such as CTX-M has also been reported since the 1980s [42]. ESBL type CTX-M can hydrolyze cefotaxime, ceftiofur, cefquinome, broad-spectrum cephalosporins of animals, and ceftriaxone. Unlike the previous variant ESBL enzyme namely TEM and SHV which only has penicillinase activity. Since around the 2000s, ESBL type CTX-M has been more widely studied throughout the world [5] than ESBL derivatives of TEM and SHV.

The CTX-M type ESBL was initially described as MEN1 [42], and Toho-1 [43], and later designated as the CTX-M-1 type, and CTX-M-44. CTX-M-type β -lactamases reported in *Kluyvera* species, members of the Enterobacteriaceae family intrinsically have unique genes on their chromosomes as encoding CTX-M-like β -lactamases such as KLUA-1, KLUA-2, KLUC-1 and KLUG-1. *K. georgiana* encodes an enzyme that is very similar (99%) to CTX-M-8 in amino acid sequence levels [44], which was first identified in Enterobacteriaceae isolated from humans in Brazil [45] and later found also in poultry and chicken meat samples worldwide [46, 47]. Because the β -lactamase-like CTXM gene mediated by the chromosome of the *Kluyvera* species has little or no promoter activity in the upper reaches of the gene, they tend to be silent. Therefore, *Kluyvera* species are usually susceptible to cefotaxime [48-51] despite having intrinsic genes such as blaCTX-M. However, the translocation of the β -lactamase chromosome gene from the *Kluyvera* species into several plasmids with sequence insertion functions, such as ISCR1 [52], and ISEcp1 [53], which has promoter activity provides resistance to oxymino-cephalosporin through constitutive and multicopy expression of the β - gene lactamase.

Besides the CTX-M type ESBL, there are other small ESBL groups such as GES-1 [54], VEB-1 [55], BES-1 [45], SFO-1 [56], TLA-1 [57], and PSE -2 / OXA-10 [58, 59] has also been reported from sick patients. This small ESBL also has a serine residue in the active site of each enzyme, and belongs to class A except for OXA type ESX types such as OXA-10 and OXA-11 which are classified into class D β -lactamase [60, 61]. As for type-G and β -lactamase type-GES, unique variants that have carbapenemase activity such as GES-5 [62, 63] and OXA-48 [64, 65], have appeared

in Enterobacteriaceae, and the identity of amino acids between OXA-10 ESBL and OXA-48 carbapenemases are 44% although including different clades.

ESBL Types Reported in *E. coli* From Livestock

Globally, researchers are currently focusing on identifying important components of the ESBL bacteria, for example the CTX-M type, which broadly has a wide variety of plasmid particles or certain bacterial clones [66]. Regardless of where the ESBL bacterial particles originate, the identical type of beta lactamase plasmid that occurs in humans and animals, has recently become the focus of global research [67, 68].

The most common types of ESBL are CTX-M-1, CTX-M-14, CTX-M-15, SHV-12, and CMY-2. CTX-M-14 and CTX-M-15, are found in humans. CTX-M-1 widely distributed in Europe among animals (pets, 28%; poultry, 28%; cattle and pigs, 72%). In general, CTX-M-14 is one of the most common types of beta lactamase in pets and poultry in Asia (30-33%), and to a lesser extent in cattle and pigs (14%). This is less common in cattle (4-7%) in Europe, and is not even found in pets [68].

The CTX-M-15 type has spread in a pandemic in humans [66], whereas in pet animals about 15% and cattle / pigs around 8% are related to this type. In spite ESBL diversity, CMY-2, is most common AmpC variant. Therefore, the similarity of ESBL type distribution patterns only applies to humans; but does not apply to groups of animals, where the distribution patterns observed are still very diverse.

CTX-M-1 is the main type of ESBL in cattle and pigs in Europe, with 72% of all ESBLs, as well as in poultry and pets also often found. In humans the type CTX-M-1 found 7% of all types of ESBL and this only applies in Europe. However, CTX-M-1 identified as the most common type of ESBL found in retail human, poultry and chicken patients, suggesting new cross-transmission between human and poultry hosts [69, 19]. In Indonesia there are some data on genetically confirmed sources of ESBL producing *E. coli* from cows, chickens and dogs [70-74].

The link between chicken meat contamination and the emergence of ESBL genes in humans, as well as the transmission of ESBL-producing bacteria from poultry to humans is a concern, although there is no evidence to confirm this. The literature on evidence of the spread of ESBL-carrying organisms through direct contact with livestock, is still limited [67]. Based on collective data from the available studies revealed that there are significant differences in the types of ESBL between poultry and humans in Europe, this all raises big questions for all parties about the role and contribution of livestock to the spread of ESBL in humans.

ESBL influencing factors

β -lactam based antibiotics most commonly use against bacterial infections [75]. β lactamase is major cause of antimicrobial resistance, especially *E. coli* bacteria [76]. β -lactamase enzymes are mutated continuously in response to the excessive use of antibiotics ESBL. There are several types of mechanisms that affect the resistance of ESBL bacteria to antibiotics, including through the enzymatic inactivation of antibiotics, changes in target sites, decreased porous permeability and active pumping of bacterial efflux [75]. Plasmid-mediated enzymes can originate from TEM point mutations in SHV β -lactamase which are widely distributed among Enterobacteriaceae [77, 39]. In recent years, several new ESBLs such as CTX-M, PER, VEB, and the GES lineage have emerged [78]. ESBL deactivates β -lactam antibiotics that contain oxymino

groups such as oxyimino-cephalosporin and oxyimino-monobactam [39]. Whereas cephamycins and carbapenem and are usually inhibited by β -lactamase inhibitors such as clavulanic acid, sulbactam, and Tazobactam [79, 80]. The emergence of ESBL-causing bacteria was first discovered in Japan, where *E. coli* bacteria produce CTX-M-2 which was detected in cattle dung from various important areas close to the center of the country [81]. E-ESBL has been reported in cattle in 39 countries, with concentrations occurring in Europe ($n = 16$) and Asia ($n = 13$) [82-83]. ESBL types were detected in cows, for example from the CTX-M type group with a higher prevalence of CTX-M-1, CTX-M-14 and CTX-M-15 types. Type CTX-M-1 was reportedly detected in 20 countries and most often found in European regions. CTX-M-1 type ESBL was first discovered in humans in 1989 in Germany [84-86]. The variant types CTX-M-15 and CTX-M-14 are the CTX-M enzymes because of their large and widely spread ability associated with severe outbreaks and extraintestinal infections [40, 41, 87]. The CTX-M-14 variant type is found in cattle in 13 countries, mainly in Europe and Asia. The CTX-M-14 type was first reported to be identified in humans in 2002 from a hospital in China [88, 89]. ESBL bacteria isolated from human types CTX-M-14 reported in European countries, Asia, North and South America, Africa and Oceania, are often associated with pandemic clones such as *E. coli* ST131 which is the cause of outbreaks in recent years. [66, 90-96]. The CTX-M-15 type was first reported in 2001 from the ESBL bacterial isolate in India. The CTX-M-15 type is the most widely found and most important ESBL variant of all types, because there are many important correlations in human health and ESBL clones [40, 41, 97-100]. The CTX-M-15 type is widely reported on all continents and has been detected in all major ecologies. The CTX-M-15 type is an example of the type of enzyme produced by the ESBL bacteria and it involves the circulation of groups of resistant bacteria along with resistance genes among ecological elements which are currently being controlled through the prism of the "One Health" approach [90, 101-108].

Transmission to human health

Humans with carrier status are the main factors spreading ESBL in the general public. Animals and the environment are other factors that support the ESBL occurrence in humans. Longitudinal studies and ongoing monitoring are needed, because the spread of ESBL is not possible independently without transmission to and from non-human sources such as animals and the environment. Humans with patient status will be at higher risk of being infected by ESBL bacteria, especially in patients with prolonged treatment and associated with invasive medical equipment [39]. Other risk factors for infection were also found in individual studies, including the presence of nasogastric tubes [109] gastrostomy or jejunostomy tubes [110,111] or arterial lines [112] total administration of parenteral nutrition [113] recent operations [114], hemodialysis [115], decubitus ulcers [116] and poor nutritional status [116]. Excessive misuse of antibiotic use is also a risk factor for the acquisition of ESBL-producing organisms [113,117,118]. Several studies have found an association between the use of third generation cephalosporins and the acquisition of ESBL-producing strains [109,110,117,119]. However, major risk factor for nosocomial acquisition of ESBL-producing organisms is accommodation in wards or rooms with other patients

with ESBL-producing organisms [120]. Risk factors for infection with CTX-M type ESBL-producing organisms are history of hospitalization, treatment with cephalosporins, penicillins and quinolones, age 65 years or higher, dementia and diabetes [39].

To date there is no evidence, a potential source of colonization and the incidence of ESBL in society derived from the use of oxyimino cephalosporins in animals such as ceftiofur in livestock [120]. However, infections caused by the ESBL bacteria have spread and occur in the general public, just as they did in the hospital environment [121,122]. ESBL bacteria have become a threat to human health and as a cause of epidemics that threaten the lives of people, especially the elderly. Most of the bacteria associated with human enteric diseases come from animals and can be transmitted directly from animals to humans or indirectly through food of animal origin, from contaminated water or through reservoirs [123, 124]. Foods of animal origin have a higher risk making it difficult to handle and control. In the global era of trade, the existence of ESBLs in products of animal origin is a threat that must be taken seriously.

Many sources of exposure have the potential to spread infection, causing epidemiological investigation to be very difficult. The interaction at the microbial level in humans and animals, especially between commensal bacteria with pathogenic bacteria, facultative bacteria and obligate bacteria in the same environment and the horizontal gene transfer of bacteria makes the distribution of resistance genes among various bacterial species becomes wider. To understand and identify the possibility of preventing the spread of resistance and infection in humans, an integrative approach such as 'One Health' is needed [125,126]. The application of the concept of global integration is assumed to accelerate the prevention and prediction of diseases as an effort to control zoonotic diseases [127,128].

Epidemiology ESBL Producing *E. coli* - a global view

The first E-ESBL occurrence in cattle was reported in Japan, CTXM-2 type *E. coli* bacteria were detected in cattle feces from the central region of the country [81]. Since it was first discovered until now, ESBL has been described in cattle in 39 countries, with more concentrations in Europe and Asia as shown in Figure 1. The origin of E-ESBL varies, isolated from healthy animals (faecal samples) or from clinical animal (mastitis, diarrhea, infection, or with other pathologists). Countries with the highest number of E-ESBL reports in cows include Britain, Germany, France and the United States, as well as the world's first to third largest cattle producers, all in Europe [82,83]. Of the five largest livestock producers in the world (United States, Brazil, European Union, China and India) have reported commensal or clinical E-ESBL detected in their livestock. ESBL types that are most often detected in cows, are included in the CTX-M type group with a higher prevalence, namely CTX-M-1, CTX-M14 and CTX-M-15 types. Type CTX-M-1 is reported in 20 countries, with the highest prevalence in Europe and is also found in Germany, Denmark, Spain, Finland, France, Hungary, Portugal, the Netherlands, United Kingdom, Czech Republic, Slovakia, Sweden, Switzerland and Turkey. Type CTX-M-1 was first reported as a type of E-ESBL production enzyme in humans in Germany precisely in 1989, then it was also reported in other European countries such as Spain, France, Italy and England as well as in Asia and North America [84-86].

Figure 1. World map illustrating the countries with description of E-ESBL in livestock [129]

The CTX-M-15 type was first discovered in 2001 from an E-ESBL isolate in a hospital in New Delhi, India. At present the CTX-M-15 type is the most widely spread enzyme type and is more important than all other types, because it is related to human health and E-ESBL clones [40,41,97-100]. The type of CTX-M-15 producing E-ESBL in cattle is found in 21 countries around the world, detected in most of Europe including Germany, France, Italy, the Netherlands, England, Sweden, Switzerland and Turkey. In Asia found in China, South Korea, India, Israel, Japan, Lebanon and Taiwan. Also found in North and South America (Brazil, Canada, and the United States) and Africa (Egypt, Tanzania, and Tunisia). The CTX-M-15 type has been reported on all continents (Europe, North America, South America, Asia, Africa, Oceania, and Antarctica with its main ecological detection including humans, animals and the environment. ESBL enzyme CTX-M-15 type is an example a serious threat to public health, the interaction of circulating bacterial resistance genes with environmental resistance genes makes the One Health approach important [85, 96-103] Virulence and multi-resistance type CTX-M-15 produced by *E. coli* clones. O25bST131 is one of the most adaptive circulant clones among E-ESBL, which causes epidemics and deaths worldwide, not only related to deaths due to infection, but also due to bacterial colonization in human and animal intestines and environmental contamination [29,130-139]

The choice of antibiotics for the treatment of infections due to ESBL-producing Enterobacteriaceae was reviewed in detail in 2008 [4], 2010 [140], and more recently in 2018 [140]. Carbapenems, including imipenem, meropenem, doripenem, and ertapenem, are the first choice agents used for the treatment of serious infections due to ESBL-producing Enterobacteriaceae [141]. Carbapenem is a group of antibiotics that are very stable against hydrolysis by ESBL. Carbapenem group antibiotics are distributed to various body tissues in high concentrations and there is a lack of inoculum effect that is when the MIC concentration (minimal inhibitory concentration) of antibiotics increases with increasing inoculum size or the number of bacteria tested, the ability of antibiotics to inhibit antibiotics will also decrease [140]. The potential weakness of the use of carbapenem antibiotics lies in the relatively high cost of antibiotics and diagnostic laboratory costs for determining the type of bacteria that is resistant to carbapenem.

Treatment of ESBL

ESBL-producing Enterobacteriaceae. The use of piperacillin-tazobactam and amoxicillin-clavulanic acid as a combination of β -Lactam- β -lactamase inhibitors has been shown to have activity against ESBL-producing bacteria and its role as an infectious treatment agent which was reviewed in detail during 2015 by Harris *et al.* [142], in 2017 by Muhammed *et al.* [143], and finally by Rodriguez-Bano in 2018 [141]. Based on retrospective data in the publication it was concluded that the combination of β -lactam- β -lactamase is not inferior to carbapenem and can be used as a therapeutic option other than carbapenem, especially if the source of infection comes from the urinary tract, namely urosepsis.

ESBL control

Efforts to control and prevent infection are very important to prevent the spread and epidemics of ESBL-producing bacteria. The agent for spreading the ESBL bacteria is in the digestive tract system. Alternative distribution agents can be in the form of oropharynx, colonized sores, and urine. Health workers' hands and medical devices are contaminated with agents an important factor in spreading infection among patients [76]. Important overall infection control efforts must be made including avoiding the use of unnecessary invasive devices, handwashing procedures for hospital staff, increasing prevention and isolation of patients indicated or infected by ESBL bacteria.

At the institutional or institutional level, prevention can be done by making some direct actions to minimize the spread of ESBL-causing organisms such as clinical and bacteriological supervision of patients treated in intensive care units and surveillance of antibiotic use cycles, as well as antibiotic use restriction policies, especially on empirical use of antimicrobial agents broad spectrum such as third and fourth generation cephalosporins and quinolones [39, 76, 144].

Some researchers have suggested using a combination of β -lactam / β -lactamase inhibitors rather than cephalosporins. The combination of β -lactam / β -lactamase inhibitors can work empirically in severe infections, it is suspected that there are specific agents against gram-negative bacteria that can control the formation of enzymes in ESBL bacteria [145-147]. However, many microorganisms now produce several types of β -lactamases, which can reduce the effectiveness of the β -lactam / β -lactamase combination [88,148-153].

Conclusion

Extended-spectrum beta-lactamases (ESBL) are enzymes produced by bacteria with the special ability to hydrolyze the antibiotic oxyimino-beta-lactam which is currently an important therapeutic agent for the treatment of serious infections in humans and animals. The year 1983 was the beginning of the discovery of the ESBL bacteria from the Enterobacteriaceae group of bacteria and since then scientific research has continued to conduct research on ESBL-producing bacteria (E-ESBL) as a real threat to human health. In its development the incidence of ESBL is not only limited to infections in the hospital environment, but has become a common human intestinal commensal disease in the wider community.

The existence of livestock being the transmission and distribution of ESBL animals is a potential new threat because it is directly related to the food chain in humans. Livestock are one of the main sources of animal protein, including the source of meat and milk that is most consumed by humans, as well as being a major element in

the food chain in humans. Livestock are also animals that produce a large capacity of faeces with the potential to transmit bacterial infectious agents to humans through contamination pathways. Most enteric diseases in humans originate from animals that are transmitted directly from animals to humans or indirectly through food derived from animals or faecal contaminated water.

The distribution pattern of the spread of ESBL enzymes globally in humans and animals can be a reference and consideration in efforts to prevent and treat ESBL bacterial infections. The CTX-M enzyme type is an enzyme variant that is widely found in various substances in humans, animals and the environment. The CTX-M-15 type has been widely reported on all continents and has been detected in all major ecological aspects including humans, animals and the environment. Treatment of ESBL-producing bacterial infections in clinical trials is still very rare. Until now most clinical studies are still observational or are a series of cases and are still limited to reports. Carbapenem antibiotics, are the first choice used for the treatment of serious infections due to the ESBL-producing Enterobacteriaceae, but the cost of treatment in this class of drugs is still relatively high. Treatment using a combination of β -Lactam- β -lactamase inhibitors such as piperacillin-tazobactam and amoxicillin-clavulanic acid as an infectious treatment agent based on retrospective data from several journals is not inferior to carbapenem class drugs, especially if used at sources of infection that originate from the urinary tract or urosepsis.

Given the many substances that affect the spread of infection and the danger posed by ESBL bacterial infections in humans, animals and the environment, prevention efforts are more important than treatment. Therefore, control and prevention through the principle of the "One Health" approach is the best way that can be done.

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