Current status of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae in animals

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The emergence and spread of extended-spectrum beta-lactamases (ESBLs) among members of Enterobacteriaceae family originating from food-producing animals and pets is a major public health issue worldwide. In food-producing animals, the off-label use of cephalosporins as prophylaxis treatment to prevent bacterial infections (i.e., early mortality in day-old chicks) has been regarded as s an important risk factor, contributing to the selection and spread of ESBL-producing Enterobacteriaceae. In pets, urinary tract infections (UTIs) caused by ESBL positive bacilli are a serious problem, since carbapenem antibiotics (last resorts for human infections due to ESBL-producing bacteria) are prescribed as an extra-label drug without a standardized treatment schedule. Moreover, companion animals can represent a possible source for the dissemination of ESBL-encoding genes to humans. Regarding ESBL variants, CTX-M-type enzymes have been widely identified in *Escherichia coli* and *Salmonella* spp. strains from both healthy and diseased animals. In this regard, detection of the international CTX-M-15-producing *E. coli* clone O25-ST131 has been an epidemiological concern. In this chapter, we summarize the more recent findings in ESBL epidemiology in animals in order to understand the recent increase of these enzymes.

Keywords extended-spectrum cephalosporins; antibiotic resistance; CTX-M; pets; food-producing animals.

1. Introduction

1.1. Antibiotics in veterinary medicine and extended-spectrum beta-lactamase production

Antimicrobial agents in veterinary medicine are used to treat bacterial infections, including life-threatening contagious diseases. In food-producing animals, broad-spectrum antibiotics have been widely used off-label for prophylactic treatment. Indeed, cephalosporins have been used to prevent and control colibacillosis infections, in day-old chicks (early chick mortality) and turkey poults, associated with *Escherichia coli* [1]. In this regard, ceftiofur, cefquinome, cefalonium, cefoperazone, cefovecin and cefuroxime are the most frequently used cephalosporins, and are approved exclusively for the treatment of infections in veterinary medicine worldwide [2,3].

Use of antibiotics in food-producing animals has been widely discussed and subjected to criticism by the community, since contamination of meat and milk by residues of antibiotics has been documented in Europe and China [4].

Antimicrobial use in production animals has been shown to lead to the emergence of resistant bacteria throughout the food chain. Most likely, the use of low doses of antibiotics by the modern food animal industry as growth-promoting substances in farm animals to promote animal growth and to prevent infections rather than cure infections is responsible for drug-resistant bacteria emerging on farms which reach the general population through human or animal carriers, and through the food consumers eat [5]. So, the misuse and overuse of broad-spectrum antibiotics, mainly cephalosporins, must be contributing to selection and spread of ESBL-producing Enterobacteriaceae in animals.

Gram-negative bacteria (GNB) that produce extended-spectrum β-lactamases (ESBLs) have become a common problem in veterinary medicine across the world. These enzymes have been identified in a wide range of Enterobacteriaceae, including *Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli, Proteus mirabilis, Enterobacter cloacae, Morganella morganii, Serratia* spp., *Shigella* spp., *Citrobacter* spp., and *Salmonella* species [6-7,8,9,10,11,12] around the world.

Although acquisition of ESBLs confers resistance to penicillins, cephalosporins and monobactams, isolates remain susceptible to carbapenems, and *in vitro*, these enzymes are inhibited by beta-lactamase inhibitors, such as clavulanic acid, sulbactam, and tazobactam [13].

ESBL-encoding genes are often carried on plasmids, which can easily be transferred between isolates, bearing additional resistance determinants for other classes of antimicrobial agents, mainly fluoroquinolones, aminoglycosides and sulfonamides, contributing to the multidrug-resistant phenotype [14].

1.2. ESBL-producing Enterobacteriaceae in companion animals

Companion animals represent potential sources of spread of multidrug-resistant bacteria. Meyer *et. al*. [15] showed that previous contact with pets increases by almost seven-fold the chance to be colonized with ESBL positive bacteria. The close contact of companion animals with humans offers favorable conditions for the transmission of bacteria by

direct contact (petting, licking, physical injuries, etc.) or through the domestic environment (furnishings, contamination of food, etc.). Moreover, the extensive use of antimicrobial agents in animals can create an opportunity for colonization by multidrug-resistant bacteria allowing horizontal transference of antibiotic resistance genes to commensal gut microbiota [16].

Epidemiological data on global resistance in members of the Enterobacteriacea family have been neglected by antimicrobial surveillance programs and current information on this topic is restricted to individual reports. On the other hand, much of the data comes from retrospective studies of clinical isolates, with the inherent potential bias for overestimation of resistance because clinical specimens could represent both the most serious infections and those that had failed to respond to antimicrobial therapy. Also, there exists geographical variation in pathogen and susceptibility patterns, as well [17]. National monitoring programs on antimicrobial resistance in animals generally do not provide data on companion animals. So, more efforts must be undertaken to obtain reliable data of the antimicrobial susceptibility of bacteria from pet animals.

In human medicine, the first beta-lactamase encoded by a mobile genetic element was identified in the early 1960s, from an *E. coli* strain isolated from a patient named Temoniera, so the enzyme was designated TEM-1 [18]. Whereas in veterinary medicine, the first report of an ESBL from an animal was described in Japan in 1988. It was a CTX-M-type enzyme, designated FEC-1 (Fujisawa *E. coli*-1). The cefotaxime-resistant *E. coli* strain was isolated from the faecal microbiota of a laboratory dog, which was used for pharmacokinetic studies of beta-lactam antimicrobials and had received beta-lactams drugs [19]. Since that time a number of cases of ESBL-positive isolates from animals have been described.

Europe

Most reports of ESBL positive GNB isolated from pets come from Europe. In 1998,for the first time a resistant *Escherichia coli* strain was isolated from a urine specimen from a dog with a recurrent urinary tract infection (UTI), in Madrid, Spain. This strain showed resistance to amoxicillin, cephalothin, cefotaxime, ceftazidime, and aztreonam and the ESBL enzyme was confirmed as SHV-12 variant [20]. Subsequent studies conducted in Portugal reported the identification TEM-1-, SHV, and OXA-1-type enzymes in uropathogenic *E. coli* strains isolated from dogs [21].

Among CTX-M-type ESBLs, CTX-M-15 has currently been shown to be the most prevalent variant all over the world and, being successfully spread among *E. coli* isolates belonging to the pandemic clone sequence type (ST) ST131, serotype O25, causing community and hospital-acquired infections in humans [22]. Surprisingly, the international O25-ST131 CTX-M-15-producing *E. coli* was already identified in dogs with urinary tract infection, in Portugal and Germany [23, 24]. More recently, CTX-M-15 uropathogenic *E. coli* strains belonging to ST533 were identified in companion animals in Swiss [25].

Also, ESBL producing bacteria have been identified in commensal microbiota of pets. Costa et al., [26] reported the occurrence of $bla_{\text{CTX-M-1}}$ (25%) and $bla_{\text{TEM-2}}$ (75%) in faecal samples from healthy dogs in Portugal, and a significant prevalence of ESBL-producing *E. coli* (mainly SHV-12 and CTX-M-1) was found in sick and healthy dogs and cats, in Italy [27].

The first report of *E. coli* CTX-M positive in the United Kingdom was described in 2007. The isolates came from three cases: two from wound dogs infection and one from preputial discharge and urine of the same animal [28]. Later, *E. coli* CTX-M-15 positive was identified in 2011 from bile in dogs with hepatobiliary disease [29].

Latin America

In South America, the first report of ESBL in pets occurred in 2008 from Chile, and it was from *E. coli* strains isolated from faecal samples of dogs and cats untreated and treated with enrofloxacin. In this study, ESBL enzymes belonged to CTX-M-1-, CTX-M-9- and PER-2-type variants [30]. In Brazil, mostly ESBL have been identified in *E. coli* isolated from pets with UTI at a university veterinary hospital in Southeastern Brazil, where CTX-M-15, CTXM-8 and CTX-M-2 β-lactamases were confirmed by sequencing. Curiously enough, in this country ESBL enzymes have been not limited to *E. coli* and, indeed, CTX-M-8 and CTX-M-2 ESBLs have been identified in *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, respectively, where the high prevalence of clonally unrelated CTX-M-producing *E. coli* belonging to low-virulence phylogenetic groups A and B1 suggested that most extraintestinal infections caused by ESBL-producing *E. coli* could be endogenous [31].

North America

In the United States, the largest threat from ESBLs has come from *Salmonella* spp. and *Escherichia coli*. In 2007 Frye *et al.* [32] found *Salmonella enterica* harboring CTX-M, SHV, TEM and CMY-2 β-lactamases. From 1999 to 2003, 34,411 *Salmonella* spp. strains were isolated from cattle, avian, horses and dogs and the proportion of ceftiofur-resistant isolates for each *Salmonella* serotype varied widely. *S.* Newport had a significantly high-level of ceftiofur

resistance with a few strains, recovered from pets, carrying bla_{TEM}- or bla_{SHV}-type genes. The first report of CTX-M- and SHV-type ESBLs in *E. coli* in the US was described in 2010 [33]. In this study, eleven *E. coli* strains isolated from dogs and cats with UTI produced SHV-12 (n= 1), CTX-M-14 (n= 1) and CTX-M-15 (n= 9) β-lactamases. According to Shaheen *et al.,* [34] 6% of clinical *E. coli* isolates from companion animals in the USA have reduced susceptibility to extended-spectrum cephalosporins, where CTX-M-1-type ESBLs appears to be endemic.

Asia

In China, while Ma *et al.* [35] reported a high prevalence of $bla_{CTX\text{-}M\text{-}9}$ and $bla_{CTX\text{-}M\text{-}1}$ in *E. coli* strains from dog faeces, in Japan the presence of O25b-ST131 CTX-M-27-producing *E. coli* was confirmed in companion animals. Moreover, *E. coli* isolates had harbored $bla_{CTX\text{-}M\text{-}14,}$ $bla_{CTX\text{-}M\text{-}15}$, and $bla_{CTX\text{-}M\text{-}55}$ genes [36]. Also, faecal samples from apparently healthy pups (≤ two months of age) from Japan kennels, with no history of antimicrobial use, were found to harbor multidrug-resistant *E. coli* isolates, including ESBL producers [37]. Those findings showed the identification of ESBL-bacteria from commensal microbiota in dogs. In the Republic of Korea, the production of ESBL in *E. coli* strains isolated from stray dogs has been related with the presence of $bla_{CTX\text{-}M\text{-}14}$, $bla_{CTX\text{-}M\text{-}24}$, $bla_{CTX\text{-}M\text{-}3}$, $bla_{CTX\text{-}M\text{-}55}$, $bla_{CTX\text{-}M\text{-}27}$, and $bla_{CTX\text{-}M\text{-}65}$ genes [38].

Africa and Australia

In Northern Kenya, dogs, cats and their owners were investigated with an emphasis on extended-spectrum beta-lactamases. Rectal swabs of 216 dogs, 50 cats and 23 humans were collected. Totals of 47 (22%), 2 (4%), and 4 (17%) ESBL-positive *E.coli* isolates were obtained from dogs, cats, and humans, respectively. Three dogs were found to harbor the international clone B2-O25-ST131. Moreover, genes $bla_{CTX\text{-}M\text{-}15}$ and $bla_{OXA\text{-}1}$-type were found in all ESBL-producing *E. coli* isolates [39]. Finally, *E. coli* harboring the $bla_{CTX\text{-}M\text{-}1}$ gene was isolated from a faecal sample of a healthy pet in Tunisia [40].

ESBLs (SHV-12-type) in Australia have been identified in *Enterobacter* spp. isolated from dogs with opportunistic infections (i.e., UTIs, post-surgery infection, osteomyelitis and multiple abscess) [41].

1.3. ESBL-producing Enterobacteriaceae in hobby animals

Horses can be classified as companion or hobby animals, since they are involved in equestrian sports or as transport, and in some countries they are considered food animal and processed for human consumption. These animals have close contact with humans and, like dogs and cats, they may share microbiota with humans suggesting an important reservoir of resistant bacteria. Antimicrobial resistance data for these animals is sparse. The first report of ESBL was published by Rankin *et al.* in 2005 [42], where *Salmonella enterica* serovar Newport expressing TEM-1B and SHV-12 was isolated from affected animals during an outbreak of salmonellosis that led to a 3-month closure of one of the largest equine hospitals in the United States. Later, Frey *et al*., (2007) [33] reported on the identification of *Salmonella enterica* carrying $bla_{CTX\text{-}M\text{-}3}$-, bla_{SHV}- and bla_{TEM}-type genes from horses in the USA.

In the Netherlands, the presence of ESBL (mostly CTX-M-1) among *Escherichia coli* and *Klebsiella pneumoniae* isolates from horses (including horses foals of one month old) was detected in clinical (pus, stomach, uterus, synovial liquid) and faecal samples [43]. The highly virulent CTX-M-15-producing *E. coli* clone B2-O25b-ST-131 was isolated from a horse present eye infection, in Germany [24].

In Brazil, the detection of CTX-M-15-producing *E. coli* (ST2179) was reported in 2012 from a foal that had died after a septic shock [44].

The occurrence and genetic background of cefotaxime-resistant *E. coli* from faecal samples in horses receiving broad-spectrum antimicrobial prophylaxis was previously investigated [45]. In this study, the authors reported a proliferation of *E. coli* producing either CTX-M-1 or CTX-M-14 enzymes. Shedding of CTX-M-producing *E. coli* was intermittent in some horses and can persist for weeks following antimicrobial treatments.

Besides the use of broad-spectrum antimicrobial agents, prolonged hospitalization time may contribute to the selection of ESBL producers in horses [46]. On the other hand, a cross-sectional study, performed in the UK, on faecal carriage of microbial drug-resistant *E. coli* amongst horses in the general equine community, revealed that prevalence of ESBL-producing *E. coli* was 6.3% [47].

1.4. ESBL-producing Enterobacteriaceae in food animals

In humans, antibiotic use has been established as a strong risk factor for colonization and infection due ESBL-producing organisms [48]. In companion animals, many analyses indicated that risk for multidrug-resistant *E. coli* rectal colonization of dogs was increased following prior treatment with several antimicrobial agents [49].

In food-producing animals, colonization with ESBL-producing bacteria must be considered a public health concern, since the transmission to humans cannot be ignored. Among the reasons for this unusual colonization, the off-label use

of cephalosporins as prophylaxis treatment to prevent bacterial infections (i.e., early mortality in day-old chicks and turkey poultries), could be considered as an important risk factor [2, 3, 50]. In this regard, ESBL-producing *E.coli* and *Salmonella* species have been isolated from farm animals (mainly poultry and pigs) in different countries [2, 51].

1.4.1. Livestock

The epidemiology of CTX-M-type-producing *E. coli* was studied on a commercial dairy farm located in the United Kingdom and results suggested that husbandry, antimicrobial usage and hygiene may play a significant role on a farm, with regards to the increased prevalence of the CTX-M-15 *E. coli* in certain cattle groups and farm environments including calving pens [52]. Watson et al. [53], reporting that 82.8% of calves were colonized by CTX-M-producing *E. coli* strains. These high rates were directly related to the feed and waste milk (milk unfit to human consumption generally contaminated with antibiotic residues) provided to calves, which may select ESBL-producing bacteria in calves' microbiota [53, 54].

According to Department for Environment, Food and Rural Affairs (DEFRA) in the UK, since July 2006 the presence of *E. coli* and other Enterobacteriaceae members carrying $bla_{\text{CTX-M-type}}$ genes, including $bla_{\text{CTX-M-1}}$, $bla_{\text{CTX-M-14}}$ and $bla_{\text{CTX-M-15}}$ gene variants has been confirmed in different cattle farms. Furthermore, some *E. coli* isolates carrying the $bla_{\text{CTX-M-15}}$ gene have been identified as serotype O25, a common human pathogen [55].

Plasmidial $bla_{\text{CTX-M}}$ is currently the most prevalent ESBL gene variant present in livestock. Studies conducted in France, Italy, Germany, USA and Brazil support this data. CTX-M-1- and CTX-M-14-producing *E. coli* and *K. pneumoniae* strains have been isolated from dairy cattle with symptomatic or asymptomatic mastitis, in France and Italy [56, 57]. Surprisingly, in France, same *E. coli* clones (ST10, ST23 and ST58) carrying $bla_{\text{CTX-M-14}}$ and $bla_{\text{CTX-M-1}}$ have been identified in humans, food-producing animals and food from animal origin [56].

A study conducted in Germany sought the presence of ESBL-producing *E. coli* in different dairy cattle, beef cattle and mixed farms (both dairy and beef). The results showed a high prevalence of CTX-M-1, CTX-M-2 and CTX-M-9 ESBLs [58].

In the Americas, ESBL-producing bacteria isolated from cattle have been reported in some countries. In 2010, *Salmonella* spp. harboring $bla_{\text{CTX-M-1}}$ and $bla_{\text{CTX-M-79}}$ genes were isolated from cattle in the US. This was a serious concern because broad-spectrum cephalosporins are considered the choice treatment for invasive infections due to GNB, including human salmonellosis. *E. coli* strains carrying $bla_{\text{CTX-M}}$ variants have also been isolated from cattle in the USA [59].

An epidemiological surveillance study conducted in Brazil, reported for the first time the presence of CTX-M-8- *E. coli* producing in buffaloes. In this regard, 55% ESBL producers belonged to the low-virulence phylogenetic groups A and B1, which reinforces the hypothesis of endogenous selection of commensal microbiota in food-animals, due to the selective pressure caused by broad-spectrum antibiotic use and/or horizontal transference of resistance genes. In this study, the MLST (multilocus sequence typing) analysis revealed clonal diversity, with common ancestors in Asia, Africa, South America, North America and Europe [32].

Studies conducted in Asia (Japan and China) also have shown the presence of ESBL-producing bacteria in food-producing animals. In China, intestinal *E. coli* obtained from healthy food animals, including dairy and beef cattle, were tested for the presence of ESBL genes. *E. coli* isolates showed reduced susceptibility to cefotaxime and different $bla_{\text{CTX-M}}$ variants were detected, including $bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-55}}$, $bla_{\text{CTX-M-65}}$, $bla_{\text{CTX-M-27}}$, $bla_{\text{CTX-M-15}}$, $bla_{\text{CTX-M-98}}$, $bla_{\text{CTX-M-24}}$, $bla_{\text{CTX-M-3}}$, $bla_{\text{CTX-M-102}}$ and $bla_{\text{CTX-M-104}}$ [60]. In Japan HIROI et al. [61] evaluated the diversity of ESBL genes among food-producing animals. To achieve this objective, 48 isolates of ESBL-producing *E. coli* isolates were obtained from rectal samples of broilers, layers, beef cattle and pigs, at the slaughterhouse level. ESBL-producing *E. coli* were isolated from 60.0% of individual broiler rectal samples, 5.9% of layers, 12.5% of beef cattle and 3% of pigs. ESBL-positive *E. coli* isolates from broilers harbored $bla_{\text{SHV-12}}$, $bla_{\text{CTX-M-2}}$, $bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-15}}$ and $bla_{\text{CTX-M-44}}$ genes.

1.4.2. Pigs

Antimicrobial resistance in commensal Enterobacteriaceae from pigs may play an important role in the ecology of resistance, constituting an important reservoir for these transmissible resistance genes. In this respect, in some Danish farms, the production of CTX-M-1 β-lactamase in *E. coli* strains recovered from faeces of pigs, has been associated with ceftiofur use [50]. On the other hand, significant decreases in the carriage prevalence of CTX-M-producing *E. coli* and faecal counts of CTX-resistant coliforms were detected during the pig production cycle [62]. Escudero, et al., [63] investigated the prevalence of ESBL-encoding genes in *E. coli* recovered from faecal samples from healthy pigs, in different farms distributed in Spain. Among 29 *E. coli* strains showing reduced susceptibility or resistance to extended-spectrum cephalosporins, 72% (n= 21) *E. coli* isolates were confirmed as ESBL producers, reporting the presence of SHV-12-, CTX-M-1-, CTX-M-9- and CTX-M-14-encoding genes. Wu et al. [64], in a similar study conducted in Denmark, reported the detection of a single isolate of CTX-M-1-producing *E. coli* from healthy pigs. On the other hand, Tian et al. [65] reported the detection of CTX-M-15, CTX-M-22, and SHV-2 in *E. coli* strains isolated in faecal samples from commercial pigs farms in China.

While in Switzerland, CTX-M-1, CTX-14 and a novel TEM-186 variant were identified in *E. coli* isolates from healthy pigs [66], in Spain, *E. coli* isolates carrying genes encoding TEM-1, CTX-M-1, CTX-M-14, CTX-M-32 or SHV-12 have been isolated from sick and healthy pigs [67, 68].

1.4.3. Poultry

The first reports of ESBL-producing bacteria in poultry were performed in Europe. In this regard, in Spain, *E. coli* strains isolated from faecal samples of healthy and sick poultry were found to harbor $bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-9}}$, or $bla_{\text{SHV-12}}$. [69]. Genes encoding CTX-M-1 also were detected in *E. coli* and *Salmonella enterica* isolates recovered from sick hen (septicaemia) and healthy poultry, in France [70, 71, 72]. In Portugal, cefotaxime-resistant *E. coli* was obtained from faecal samples from broilers at slaughterhouse level and the followed ESBLs were detected: TEM-52, CTX-M-14 and CTX-M-32 [73]. Another work had characterized *E. coli* isolates with reduced susceptibility to cefotaxime or ceftiofur obtained from healthy broilers in Italy farms, confirming the presence of $bla_{\text{CTX-M-1}}$, $bla_{\text{CTX-M-32}}$ and $bla_{\text{SHV-12}}$ [74]. The German National *Salmonella* Reference Laboratory (NRL-Salm), reported the production of CTX-M-1 in *S.* Typhimurium and *S.* Paratyphi B in chicken meat and chicken, respectively [75]. In Switzerland, CTX-M-1, SHV-12 and TEM-52 ESBls were detected in *E. coli* strains recovered from faecal samples of healthy chicken [66]. In Henan province, in China, presence of ESBL genes $bla_{\text{TEM-57}}$, $bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-24}}$ and $bla_{\text{CTX-M-65}}$ was reported in chicken farms [76]. Moreover, genes encoding SHV-12, CTX-M-27, CTX-M-55, CTX-M-24, CTX-M-105, CTX-M-14 and CTX-M-24 were identified in fecal samples of healthy ducks and environmental samples from a duck farm in South China [77]. Most recently in Korea CTX-M-3 and CTX-M-14 positive *Salmonella* spp. were identified in poultry slaughterhouses [78].

Curiously, the identification of ESBL in chicken from Brazil was reported in a study performed in the UK, where chicken breast fillets imported from Brazil and other countries, such as France, Poland and Netherlands, were positive for CTX-M-2-producing *E. coli* [79]. Later, in another study, *E. coli* strains isolated from raw chicken meat imported into the UK from Argentina, Chile and Brazil, were found to carry $bla_{\text{CTX-M-2}}$ and $bla_{\text{CTX-M-8}}$ genes [80]. More recently, the emergence of CTX-M-2-producing *Salmonella enterica* serovars Schwarzengrund, Agona and Typhimurium have been reported in Brazilian poultry farms [81, 82].

2. Final comments

The global emergence and spread of $bla_{\text{CTX-M}}$ genes is the main problem associated with resistance to cephalosporins in *E. coli* and *Salmonella* strains isolated from companion and food-producing animals. In this regard, the identification of CTX-M-15-producing *E. coli* belonging to the international clone O25-ST131 is an epidemiological concern. In food-producing animals, the off-label use of cephalosporins as prophylaxis treatment to prevent bacterial infections has been considered as an important risk factor contributing to the selection and spread of ESBL-producing bacteria. Epidemiological data reports about antimicrobial resistance in animals are important tools to be used in clinical management of infectious diseases leading to the rational use of antimicrobial agents. Thus food-producing and pets can become an important source for the dissemination of ESBL-encoding genes to humans, further studies are needed to clarify the reason why clinically relevant ESBL-producing Enterobacteriaceae are emerging worldwide.

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