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Extended-spectrum beta-lactamases-producing Gram-negative bacteria in companion animals: action is clearly warranted!

Extended-Spektrum Beta-Laktamase (ESBL)-bildende Gram-negative Bakterien bei Heimtieren: Zeit zum Handeln!

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Summary

Extended-spectrum beta-lactamases (ESBL)-producing Gram-negative bacteria pose a serious threat to Public Health in human medicine as well as increasingly in the veterinary context worldwide. Several studies reported the transmission of zoonotic multidrug resistant bacteria between food-producing animals and humans, whilst the contribution of companion animals to this scenario is rather unknown. Within the last decades a change in the social role of companion animals has taken place, resulting in a very close contact between owners and their pets. As a consequence, humans may obtain antimicrobial resistant bacteria or the corresponding resistance genes not only from food-producing animals but also via close contact to their pets. This may give rise to bacterial infections with limited therapeutic options and an increased risk of treatment failure. As beta-lactams constitute one of the most important groups of antimicrobial agents in veterinary medicine, retaliatory actions in small animal and equine practices are urgently needed. This review addresses the increasing burden of extended-spectrum beta-lactam resistance among *Enterobacteriaceae* isolated from companion animals. It should emphasize the urgent need for the implementation of antibiotic stewardship as well as surveillance and monitoring programs of multi resistant bacteria in particular in view of new putative infection cycles between humans and their pets.

Keywords: ESBL, companion animal, antibiotic, multi resistance, surveillance, review

Zusammenfassung

Extended-Spektrum Beta-Laktamase (ESBL) bildende Gram-negative Bakterien stellen weltweit ein Problem im Bereich der Public Health sowohl in der Humanmedizin als auch zunehmend in der Veterinärmedizin dar. Zwar konnte bislang bereits in einigen Studien für Lebensmittel produzierende Tiere eine direkte Übertragung von multiresistenten zoonotischen bakteriellen Erregern zwischen Mensch und Tier gezeigt werden, inwieweit jedoch Heimtiere wie Hunde, Katzen und Pferde einen Beitrag dazu leisten, ist nur unzureichend bekannt. Die sich in den letzten Jahrzehnten wandelnde soziale Rolle von Heimtieren hat zu einem engeren Kontakt zwischen Tieren und ihren Haltern geführt. Dies wiederum kann zu einer verstärkten Übertragung multiresistenter Erreger oder ihrer Resistenz-vermittelnden Gene, nicht nur von Lebensmittel produzierenden Tieren, sondern auch von Heimtieren führen. Daraus resultierend können diese multiresistenten Erreger zu bakteriellen Infektionen mit nur noch eingeschränkten Therapieoptionen führen. Vor dem Hintergrund der enormen Bedeutung von Beta-Laktam-Antiinfektiva in der Human- und Veterinärmedizin sind daher dringend eindämmende Maßnahmen gegen die Resistenzentwicklung und deren Verbreitung auch im Bereich kurativer Kliniken von Kleintieren und Pferden nötig. Dieser Übersichtsartikel beschreibt die Problematik des zunehmenden Auftretens Extended-Spektrum Beta-Laktamase bildender *Enterobacteriaceae* bei Heimtieren und unterstreicht damit die Notwendigkeit der Implementierung von Strategien

zum rationalen Einsatz von Antiinfektiva sowie von Surveillance- und Monitoring-Programmen von multiresistenten Bakterien, auch unter Einbeziehung möglicher neuer Infektionszyklen zwischen Haustieren und deren Haltern.

Schlüsselwörter: ESBL, Heimtier, Antibiotikum, Multiresistenz, Überwachung, Übersicht

Introduction

Extended-spectrum beta-lactamases (ESBL)-producing Gram-negative bacteria have become one of the major problems in terms of nosocomial infections in human medicine besides Methicillin resistant *Staphylococcus aureus* (MRSA) and Vancomycin resistant *Enterococcus* spp. (VRE) in terms of Gram-positive bacteria. Whilst according to the Annual report of European Antimicrobial Resistance Surveillance Network (EARS-Net, 2009) the proportion of MRSA remained stable in the last years, that of 3rd generation cephalosporin-resistant *E. coli* is on a continuous rise over the last decade, which suggests an incremental concern of infectious diseases caused by this microorganism.

So far, the production of ESBLs has mainly been documented for *Enterobacteriaceae* spp., and it confers resistance to the majority of the commonly used beta-lactam antimicrobials, including 3rd generation cephalosporins. However, the main therapeutic burden results from the multidrug phenotype of these bacteria which is caused by a frequent genetic linkage with other resistance mechanisms. This confers additional resistance to other antimicrobial classes including fluoroquinolones and aminoglycosides, which may result in therapeutic failures and possibly life-threatening bacterial infections (Hunter et al., 2010). The majority of beta-lactamases reported to date have been derived from clinical isolates of humans (Bradford, 2001; Bonnet, 2004). However, they are also increasingly recorded in community-acquired bacterial infections, a scenario which may reflect the evolution and spread of MRSA some decades ago (Arpin et al., 2005; Pitout et al., 2005).

In this context attention has initially been drawn to food-producing animals as a possible source of infection with ESBL-producing bacteria. Indeed it has been shown that beta-lactamases are frequently present in the microbiota and also in clinical samples of livestock, while there are also initial reports on the occurrence of ESBLs in wild animals, such as birds and rodents (Li et al., 2007; Poeta et al., 2008; Bonnedahl et al., 2009; Guenther et al., 2010a, b; Literak et al., 2010; Smet et al., 2010; Büchter, 2010). Several studies provide evidence for the transmission of zoonotic multidrug resistant bacteria between animals and humans (Guardabassi et al., 2004; Bertrand et al., 2006; Cloeckaert et al., 2007; Walther et al., 2009a; Walther et al., 2009b; Cuny et al., 2010; Smet et al., 2010; Vincze et al., 2010). Only recently, namely with the emergence of a clonally related group of CTX-M-15-type ESBL-producing *E. coli*, the role of companion animals in the evolution and epidemiology of ESBLs has gained proper attention worldwide (Nicolas-Chanoine et al., 2008; Pomba et al., 2009; Ewers et al., 2010b; Rogers et al., 2011). However, compared to livestock, studies on the presence of ESBL-producing bacteria in companion animals are still scarce, particularly in view of the close contact of owners with their pets and the resulting transmission scenarios one can assume. This review therefore focuses on the data currently available for the presence of ESBLs in companion animals, mainly dogs, cats, and horses. It aims to raise an awareness for the urgent need to quantify the significance of these animals as source of infection with ESBL-producing bacteria as well as the role of these multiresistant bacteria in diseases of pets.

Beta-lactams in the veterinary context

Beta-lactam antimicrobial agents prevent the bacterial cell wall from forming by interfering with the final stage of peptidoglycan synthesis through acting on penicillin-binding proteins. Although, in contrast to Gram-positive bacteria, in Gram-negative microorganisms the peptidoglycan constitutes only a thin layer between the outer membrane and the cytoplasmic membrane it maintains the cell shape and protects the bacterium against osmotic forces. The most common resistance mechanism of *Enterobacteriaceae* spp. against beta-lactams is the inactivation of the drug by hydrolytic cleavage of the beta-lactam ring system (Greenwood, 2000).

Beta-lactams constitute one of the most important groups of antimicrobial agents in veterinary medicine. Different substances of the penicillin family, first- to fourth-generation cephalosphorins and the beta-lactamase inhibitors, which are in principal identical to those used in human medicine, are recommended for the treatment of companion animal patients according to the species and the underlying disease (Guardabassi et al., 2008; Smet et al., 2010). Horses are basically regarded as food-producing animals and thus in most countries there is a legal restriction in the use of antimicrobial agents used for their treatment (1950/2006/EC; 2001/82/EC). However, horses may be also classified as companion or hobby animals, and these are allowed to be treated with a broader variety of substances. The use of carbapenems, such as imipenem and meropenem, should be restricted in that it may only be prescribed in the case of life-threatening infections and, if susceptibility tests performed in an approved diagnostic laboratory have demonstrated that the causative bacteria are resistant to all other antimicrobial agents registered for treatment in the animal species concerned (Smet et al., 2010).

Most countries are documenting the antimicrobial use in the treatment of animals in general but only few provide detailed information about the prescription for dogs, cats and horses. An EU-directive (2004/28/EC) now demands detailed prescription information from member states. In countries like Sweden and Denmark where the prescribed agents are surrendered by pharmacies, these data, basically reflecting the antimicrobial consumption, are already available and have been included in the annual resistance reports (DANMAP, 2009; SVARM, 2009). These reports confirm beta-lactam antimicrobials as the most commonly

prescribed antimicrobials in small animals (DANMAP, 2008; SVARM, 2009).

In livestock, a decrease in the use of beta-lactam antimicrobials could be observed over the last years (NormVet 2008), basically due to restrictions in prescription, also resulting in a shift from broad-spectrum cephalosporins to beta-lactamase susceptible penicillins. In small animal medicine the prudent use of antimicrobials should be a principal requirement. Thus, guidelines like those of the European Platform for the Responsible Use of Medicines in Animals (EPRUMA), representing a framework that was established in 2005 with the mission of promoting responsible use of antimicrobials in food-producing animals (2004/28/EC), should be likewise established for small animals. Some countries, like Germany, have already considered this in their "Guidelines for prudent use of antimicrobials and their implications on antibiotic usage in veterinary medicine" (BTK&AGTAM, 2010).

So far there are only few monitoring programs where the screening of bacterial isolates from dogs, cats and horses for the possession of ESBLs has been included. In Europe there are regular corresponding data in the national programs of Denmark (DANMAP) and Sweden (SVARM). The SVARM-Report 2009 includes a highlight section on ESBLs from isolates of diagnostic submissions which summarises the data since 2007. In Germany some aspects from a monitoring study on the antimicrobial resistances among Gram-negative bacterial clinical isolates from dogs, cats and horses (Grobbel et al., 2007a, b; Schwarz et al., 2007) were taken over by the annual national GERM-Vet, where the screening and confirmation of ESBL production will form one part of the program (data not yet published).

Beta-lactamases

A broad variety of different beta-lactamase enzymes, sharing the same resistance mechanism but differing in their range of substrates and susceptibility against inhibitory substances, has been identified in bacteria. To date, more than 400 enzymes have been reported worldwide and there is an ongoing emergence of new beta-lactamases (http://www.lahey.org/studies/). Of particular concern are the increasingly isolated ESBLs and plasmid-encoded AmpC-type-beta-lactamases, as well as carbapenemases. These enzymes display an extended substrate spectrum and lead to a global change of the epidemiology of beta-lactamases (Pitout, 2010). Broad-spectrum beta-lactamase-producing *Enterobacteriaceae* have increasingly been detected in humans since the early 1990s and in animals since 2000 (Smet et al., 2010).

The term extended-spectrum determines the ability of ESBLs to hydrolyze a broader spectrum of beta-lactam antimicrobials than the parent beta-lactamases they derived from. Whilst they are capable of inactivating beta-lactam antimicrobials containing an oxyimino-group such as oxyimino-cephalosporins (e. g. ceftazidime, cefotaxime) as well as oxyimino-monobactam (aztreonam), ESBLs are not active against cephamycins and carbapenems. They are usually inhibited by beta-lactamase-inhibitors like clavulanic acid and tazobactam, which marks a difference between ESBL- and AmpC-beta-lactamases producing bacteria (Bradford, 2001). Several different classification schemes for bacterial beta-lactamases have been described, including the system devised by Bush et al. (1995) which is based on the activity of the beta-lactamases against different beta-lactam antimicrobials, and the currently most widely used Ambler system, which divides beta-lactamases into four classes (A, B, C, and D), based on their aminoacid sequences (Ambler, 1980). The majority of ESBLs belong to Ambler class A and to the Bush group 2be.

Although ESBLs have been found in a wide range of Gram-negative bacteria, the vast majority of strains expressing these enzymes belong to the family of *Enterobacteriaceae*, including *Klebsiella* spp., *E. coli*, *Salmonella enterica*, *Citrobacter* spp., and *Enterobacter* spp. (Bradford, 2001). Four enzyme families, namely TEM (Temoneira)-type beta-lactamases, SHV (Sulfhydryl variable) -type beta-lactamases, CTX (cefotaximase) -M-type beta-lactamases and OXA (oxacillinase) -type beta-lactamases are currently regarded the most common ESBLs among *Enterobacteriaceae* spp.

TEM-type beta-lactamases are derivatives of TEM-1, which was first demonstrated in 1965 in an *E. coli* isolate from a patient in Athens, Greece, named Temoneira, and of TEM-2, and consist of more than 150 different enzymes. While the majority of TEM beta-lactamases are ESBLs, TEM-1, TEM-2 and TEM-13 are only able to hydrolyze penicillin derivates and thus are not regarded as ESBLs (Livermore, 1995). Similar to TEM-type enzymes the majority of SHV enzymes are ESBLs. All currently recognized SHV enzymes are derivatives of SHV-1 and SHV-2. Whereas SHV-1 merely confers resistance to broad-spectrum penicillins, SHV-2, which was first described 1983 in a *Klebsiella ozaenae* strain isolated in Germany, is able to hydrolyze cefotaxime (Paterson and Bonomo, 2005; Gupta, 2007). In contrast to TEM- and SHV-type beta-lactamases, most of the members of the OXA-type beta-lactamase family are not regarded as ESBLs because they do not hydrolyze 3rd generation cephalosporins with the exception of OXA-10, OXA-2, and their derivatives (http://www.lahey.org/studies/). However, distinct OXA-types (OXA-carbapenemases) play an important role in antimicrobial resistance e. g. of *Acinetobacter baumannii* (Pfeifer et al., 2010). Currently regarded as the most important ESBL enzyme family are the CTX-M-type beta-lactamases, named after their ability to hydrolyze cefotaxime. They are supposed to originate from beta-lactamases from *Kluyvera* spp. and currently comprise of more than 70 different CTX-M enzymes divided into five groups depending on their amino acid sequence (CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9, and CTX-M-25) (Pitout, 2010). AmpC beta-lactamases confer resistance to most of the beta-lactam antimicrobials with the exception of methoxy-imino-cephalosporins (cefepime) and carbapenems, while they are not inactivated by beta-lactamase inhibitors like clavulanic acid. The *ampC* gene is typically located on the chromosome of nearly all *Enterobacteriaceae* spp. except for *Klebsiella* spp. and *Proteus* spp., but it can also be located on plasmids. The constitutive expression of the intrinsic *ampC* gene in *E. coli* is weak but mutations in the promoter region or the acquisition of plasmid-borne *ampC* originating from other *Enterobacteriaceae* spp. can lead to enhanced gene expression (Caroff et al., 2000). Since the first description of CMY-1 in 1989 (Bauernfeind et al., 1989) a number of further plasmid-mediated AmpC-type beta-lactamases and variants, including MOX, FOX, DHA, MIR, BIL, and ACC have been described (Pfeifer et al., 2010).

Metallo-beta-lactamases (MBLs) are a molecularly diverse group of broad-spectrum beta-lactamases, conferring resistance to all beta-lactam antimicrobials including carbapenems but with the exception of aztreonam. Certain MBLs such as VIM (Verona integron-encoded MBL), KPC (*K. pneumoniae* carbapenemase), and GES (named after first detection in *K. pneumoniae from* Guiana) have recently been detected among *Enterobacteriaceae* spp. (Jacoby, 2006; Walsh, 2008). Since 2009, the appearance of the new MBL enzyme NDM-1 (New Delhi MBL), initially identified in *K. pneumoniae*, has gained worldwide attention (Yong et al., 2009). However, so far MBLs have not been reported from bacteria of animal origin.

ESBLs in humans

In human medicine a shift in the detected ESBL enzymes has taken place from the classic TEM and SHV enzyme families, which have been predominantly detected in the last two decades of the past century, to the CTX-M cefotaximase family (Livermore et al., 2007). Recent studies identified that out of the group of more than 70 different enzyme variants only certain CTX-M-types are circulating in Europe with some kind of geographical restriction. CTX-M-variants amplified locally are for example CTX-M-9 and -10 in Spain, CTX-M-14 in Portugal and Spain, and CTX-M-3 in eastern countries (Coque et al., 2008). Since the beginning of the 21st century *E. coli* producing CTX-M-15 have emerged and disseminated worldwide as an important cause of both nosocomial and community-onset urinary tract and bloodstream infections in humans (Coque et al., 2008; Pitout, 2010; Oteo et al., 2010; Hunter et al., 2010). A number of molecular epidemiological studies revealed that the sudden worldwide increase of CTX-M-15-producing *E. coli* is mostly due to the spread of one single clonal group of strains, namely B2:O25b:H4-ST131-CTX-M-15, across different continents (Nicolas-Chanoine et al., 2008; Rogers et al., 2011).

Apart from *E. coli*, other *Enterobacteriaceae* spp., including *Salmonella* serovars, *Citrobacter* spp., *Enterobacter* spp., and *Klebsiella* spp. have been identified as ESBL producers, with members of the latter genus being of particular importance in hospital-acquired infections (Bradford, 2001). There are several excellent review articles providing detailed insight into the occurrence and molecular epidemiology of ESBL-producing *Enterobacteriaceae* in humans (Bradford, 2001; Bonnet, 2004; Canton and Coque, 2006; Livermore et al., 2007; Coque et al., 2008; Pfeifer et al., 2010; Oteo et al., 2010; Pitout, 2010).

ESBLs in companion animals

The first CTX-M-type enzyme in animals, designated FEC-1 (Fujisawa *E. coli*-1), was discovered in a cefotaxime-resistant *E. coli* strain isolated from the fecal microbiota of a laboratory dog, which was used for pharmacokinetic studies of beta-lactam antimicrobials in Japan in 1986 (Matsumoto et al., 1988) (Tab. 1). At the same time, a nosocomial outbreak by CTX-M1-type ESBLs was recorded in an intensive care unit in a hospital in Paris, France (Kitzis et al., 1988). Shortly after that, Bauernfeind et al. (1989) reported on a clinical cefotaxime-resistant *E. coli* strain which produced a CTX-M1-type beta-lactamase at the beginning of 1989 in Germany. In the following ten years several studies reported about an explosive dissemination of ESBLs in human clinical settings worldwide (Bernard et al., 1992; Gniadkowski et al., 1998; Radice et al., 2002; Canton and Coque, 2006), whereas to the best of our knowledge an SHV-12-type beta-lactamase producing *E. coli* was the first clinical ESBL producing bacteria isolated from a dog with recurrent urinary tract infection in Spain in 1998 (Teshager et al., 2000). This was followed by the detection of ESBL producing *E. coli* (mostly TEM and SHV) in dogs from Italy, and Portugal (Feria et al., 2002; Carattoli et al., 2005). Since about 2000, the CTX-M enzymes have formed a rapidly growing family of ESBLs in human clinical and community settings (Bonnet, 2004; Pitout and Laupland, 2008; Mshana et al., 2009). Although based only on a limited number of available studies, one might assume that a similar development was observable in case of companion animals. Clinical as well as commensal isolates predominantly harbour enzymes of the CTY-M-type (ranging between 2.6% and 5.6% of all investigated isolates and between 25% and 76.5% of all ESBLs detected). Some of the studies reported relevant numbers of companion animals serving as hosts for ESBL producing *E. coli* worldwide (Vo et al., 2007; Carattoli, 2008; O'Keefe et al., 2010; Smet et al., 2010). The highest rate was observed for healthy dogs (7.8%) and healthy cats (12.1%) by a group in Portugal (Costa et al., 2008). Moreover the worldwide emergence and spread of the clonally related group of *E. coli* B2-O25b:H4-ST131-CTX-M-15 in human clinical settings is likewise reflected in the field of companion animals, as well (Pomba et al., 2009; Ewers et al., 2010b). Our group could confirm the presence of ST131, comprising 5.6% of ESBL-producing companion animal *E. coli* isolates recovered from a collection from eight European countries (Ewers et al., 2010b). This co-emergence of the pandemic ST131 clonal group in humans and companion animals sheds new light on possible novel infection cycles and clearly emphasizes the urgent need for surveillance of extended-spectrum beta-lactamase resistance in companion animals, as they might represent one major factor in the transmission of zoonotic bacteria due to their changing social role as mentioned above. To date, knowledge on ESBLs in *Enterobacteriaceae* other than *E. coli* of companion animals is very limited, but the presence of different CTX-M, SHV-12 or OXA-10 enzymes has been reported from *Citrobacter* spp. (Ewers et al., 2010a), *Enterobacter* spp. (Sidjabat et al., 2007; Ma et al., 2009; SVARM, 2009), *Klebsiella* spp. (Vo et al., 2007; Ma et al., 2009; SVARM, 2009) and *Salmonella* spp. (Rankin et al., 2005; Frye and Fedorka-Cray, 2007), as specified in Table 1.

Data published so far implicate a relatively small diversity of broad-spectrum beta-lactamases in *Enterobacteriaceae* of animal origin compared with what has been documented for humans. As the reported enzymes mostly reflect those which are also predominant in human samples of the respective geographical region one can assume that due to the relatively small number of veterinary studies only the most frequent enzymes have been detected while a bigger sample size would possibly also show less frequent variants. First evidence for the latter hypothesis has for example been given by a recent publication by Sun et al. (2010).

TABLE 1: *Presence of Extended-spectrum beta-lactamases-producing Enterobacteriaceae in companion animals in chronological order according to the date of publication (modified from Smet et al. [2010])*

Reference	Animal species	Sick/Healthy	No. of ESBL-producing isolates per total no. (%) of isolates investigated*	Beta-lactamase types (% of total no. of beta-lactamase-producing isolates)	Species	Country	Year of isolation
Matsumoto et al., 1988	Dog	Healthy	Not specified	FEC-1 (= CTX-M-type)	*E. coli*	Japan	1986
Teshager et al., 2000	Dog	Recurrent UTI	1/1 (Case report)	SHV-12	*E. coli*	Spain	1998
Feria et al., 2002	Dog	UTI	3 [11]/72 (4.2)	SHV[a]; AmpC[a]	*E. coli*	Portugal	Not specified
Costa et al., 2004	Dog	Healthy	4/39 (10.3)	TEM-52 (75), CTX-M-1 (25)	*E. coli*	Portugal	2003
Carattoli et al., 2005	Dog Cat	Not specified Not specified	15 [2]/226 (7.5) 3/72 (4.2)	CTX-M-1 (76.5); SHV-12 (23.5); CMY-2 (11.8) CTX-M-1 (66.6); TEM[a] (33.3)	*E. coli*	Italy	2001–2003
Rankin et al., 2005	Horse	Sick	Outbreak isolate	SHV-12; TEM-1b; CMY-2	*Salmonella* Newport	USA	2003–2004
Sidjabat et al., 2006	Dog	UTI, WI	11/11 (preselected)	TEM[a] (100); CMY-7 (100)	*E. coli*	Australia	1999–2001
Frye et al., 2007	Dog Cat Horse	Not specified Not specified Not specified	87/418 (20.8) 13/133 (9.8) 249/1300 (19.2)	CTX-M group III; SHV[a]; TEM[a,d]; CMY-2 CTX-M group III; SHV[a]; TEM[a,d]; CMY-2 CTX-M group III; SHV[a]; TEM[a,d]; CMY-2	*Salmonella enterica* *Salmonella enterica* *Salmonella enterica*	USA USA USA	1999–2003 1999–2003 1999–2003
Moreno et al., 2008	Dog Cat	Hospitalized Hospitalized	10/not specified 4/not specified	CTX-M-1 (40), CTX-M-14 (60), PER-2 (50) CTX-M-1 (100), PER-2 (75)	*E. coli* *E. coli*	Chile Chile	2006 2006
Steen et al., 2007	Dog	WI (2); UTI (1)	3/3 (100) (preselected)	CTX-M-type (100)	*E. coli*	UK	2007
Sidjabat et al., 2007	Dog	Sick (UTI, Osteomyelitis, WI, Abscess)	10/10 (preselected)	SHV-12 (90); OXA-10 (10); CMY-2 (10)	*Enterobacter* spp.	Australia	2001–2005
Vo et al., 2007	Horse	Not specified	3 [1]/not specified 3/not specified	CTX-M-1 (50); CMY-2 (25); unidentified (25) CTX-M-1 (100)	*E. coli* *K. pneumoniae*	The Netherlands	2003–2005
Costa et al., 2008	Dog Cat	Healthy Healthy	6/78 (7.8) 8/66 (12.1)	CTX-M-1 (33.3); TEM[a] (66.6) TEM[a] (100)	*E. coli* *E. coli*	Portugal	2003
Ma et al., 2009	Dog & Cat	GTI; RTI	36/not specified	CTX-M-9 group; CTX-M-1-group; DHA-1, CMY-2[b]	*E. coli,* *K. pneumoniae,* *C. freundii, E. cloacae*	China	2006–2007
Pomba et al., 2009	Dog	UTI	1/41 (2.4)	CTX-M-15 (100)	*E. coli***	Portugal	2004–2006
Sun et al., 2010	Dog & Cat	Sick & Healthy	97/240 (40.4)	CTX-M-14 (46.4); CTX-M-55 (24.7); CTX-M-27 (8.2); CTX-M-24 (8.2); CTX-M-15 (6.2); CTX-M-65 (6.2); CTX-M-3 (5.2); CTX-M-64 (3.1); CTX-M-9 (2.1); SHV-12 (1)	*E. coli*	China	2007–2008
SVARM, 2009	Dog Cat Horse 	WI UTI WI, UTI, GTI WI, UTI Eye	1/not specified 1/not specified 1/not specified 1/not specified 6/not specified 4/not specified 1/not specified	CTX-M-1 CTX-M-1; SHV[a] CTX-M-1 CTX-M-1 CTX-M1; SHV[a] CTX-M1; SHV[a] SHV[a]	*E. coli* *K. pneumoniae* *E. cloacae* *E. coli* *E. coli* *K. pneumoniae* *Enterobacter hormaechei*	Sweden	2007–2009
Ewers et al., 2010b	Dog Horse	UTI; WI, GTI UTI; WI, GTI	9 (ST131)/84 ESBL[c] 1 (ST131)/50 ESBL[c]	CTX-M-15 (10.7)[c]; SHV-12 (1.2)[c] CTX-M-15 (2)[c]	*E. coli***	Europe	2008–2009
Ewers et al., 2010a	Dog Cat Horse Degu Parakeet	RTI UTI, Pleuritis RTI, WI UTI GIT	1/not specified 2/not specified 4/not specified 1/not specified 1/not specified	CTX-M-1 SHV-12 (100) CTX-M-1 (100) SHV-12 SHV-12	*C. freundii*	Europe	2008–2010
Gibson et al., 2010	Dog Cat Horse	UGTI, WI, others UGTI, WI, others UGTI, WI, others	2 [34]/not specified [2]/not specified [3]/not specified	SHV-12 (2.9); CMY-2 (20); CMY-7 (77.1); CIT (2.9); OXA-10 (2.9) CMY-2 (50); CMY-7 (50) CMY-7 (100)	*E. coli*	Australia	1999–2007
O'Keefe et al., 2010	Dog & Cat	UTI	11/150 (7.3)	SHV-12 (9.1); CTX-M-14 (9.1); CTX-M-15 (81.8)	*E. coli*	USA	2004–2007

UTI: urinary tract infection; UGTI: urogenitary tract infection; RTI: respiratory tract infection, GTI: gastrointestinal tract infection; WI: wound infection;

[a] Not genotypically characterized;

[b] Ma et al. (2009) investigated companion animals as well as farm animals. No detailed information is provided about the distribution of the ESBL-encoding genes among these two groups.

[c] Only ESBL-producing *E. coli* have been investigated. Focus on identification and characterization of O25b:H4-ST131 CTX-M-15.

[d] Only representative number of isolates (n = 125) have been used for molecular characterization.

* Only in case that AmpC-beta-lactamases have been detected simultaneously with ESBLs in one study, they are included in the table (numbers are given in squared brackets).

** Multi locus sequence type ST131 (http://mlst.ucc.ie/mlst/mlst/dbs/Ecoli/).

Conclusion

The current situation of ESBLs in *Enterobacteriaceae* from companion animals almost reflects the situation in human medicine. In view of the changing social role of companion animals to within-household members and the putative transmission and infection cycles accompanied with that, retaliatory actions are urgently needed. National surveillance and monitoring of ESBLs producing bacteria should therefore not merely focus on livestock, but also on companion animals, which, on a small scale, is already realized in some national programs, like the Danish DANMAP, German GERM-Vet and Swedish SVARM. Additionally, consequent basic hygiene as well as infection prevention and control systems, should be adapted to veterinary clinics following those already implemented in human clinical settings. The prudent use of antimicrobials in small animal clinics according to "Antimicrobial Guidelines" should become second nature to practitioners. Furthermore the analysis of the mandatory documentation of antimicrobial consumption (2004/28/EC) with respect to antimicrobial class, host species and underlying disease in combination with the implementation of antimicrobial stewardship should facilitate immediate action to stem the suppression of the development and spread of resistance.

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