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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!

Christa Ewers¹, Mirjam Grobbel¹ ², Astrid Bethe¹, Lothar H. Wieler¹, Sebastian Guenther³

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

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 bacteria in companion animals, 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; Pittout 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; Potta et al., 2008; Bonnedahl et al., 2009; Gquenther et al., 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., 2010; Rogers et al., 2011). However, compared to livestock, studies on the presence of ESBL-phenotype of 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 cephalosporins 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 (Norm-Vet 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 (EPFRUMA), 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” (BT&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 reporting 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 summarizes 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 (Svet 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. cefotaxime, ceftriaxime) 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 amino acid sequences (Ambler, 1980). The majority of ESBLs belong to Ambler class A and to the Bush group 2b.

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 (Sulphhydryl variable) -type beta-lactamases, CTX (cefotaximase) -M-type beta-lactamases and OXA (oxacillinase) -type beta-lactamases are currently regarded as 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 *Klebsiella* 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 (Bauerfeind 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-lactamas (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 (Yang 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 cephalosporinase 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 cephalosporinase-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 (Kittis et al., 1988). Shortly after that, Bauernfeind et al. (1989) reported on a clinical cephalosporin-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’Keeffe 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; Pye 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 clinical settings worldwide (Bernard et al., 1992; Gniadkowski et al., 1998; Fedorka-Cray, 2007), as specified in Table 1. 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’Keeffe 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; Pye 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])

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animal species</th>
<th>Sick/Healthy</th>
<th>Species</th>
<th>Country</th>
<th>Year of isolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsumoto et al., 1988</td>
<td>Dog</td>
<td>Healthy</td>
<td>Not specified</td>
<td>E. coli</td>
<td>Japan</td>
</tr>
<tr>
<td>Teschager et al., 2000</td>
<td>Dog</td>
<td>Recurrent UTI</td>
<td>1/1 (Case report)</td>
<td>SHV-12</td>
<td>E. coli</td>
</tr>
<tr>
<td>Terra et al., 2002</td>
<td>Dog</td>
<td>UTI</td>
<td>3 [11]/72 (4.2)</td>
<td>SHV; AmpC+</td>
<td>E. coli</td>
</tr>
<tr>
<td>Costa et al., 2004</td>
<td>Dog</td>
<td>Healthy</td>
<td>4/39 (10.3)</td>
<td>TEM-52 (75), CTX-M-1 (25)</td>
<td>E. coli</td>
</tr>
<tr>
<td>Carattoli et al., 2005</td>
<td>Cat</td>
<td>Not specified</td>
<td>Not specified</td>
<td>CTX-M-1 (76.5), SHV-12 (23.5), CMY-2 (11.8)</td>
<td>E. coli</td>
</tr>
<tr>
<td>Rankin et al., 2005</td>
<td>Horse</td>
<td>Sick</td>
<td>Outbreak isolate</td>
<td>SHV-12; TEM-1b; CMY-2</td>
<td>Salmonella Newport</td>
</tr>
<tr>
<td>Sidjabat et al., 2006</td>
<td>Dog</td>
<td>UTI, WI</td>
<td>11/11 (preselected)</td>
<td>TEM-1 (100); CMY-7 (100)</td>
<td>E. coli</td>
</tr>
<tr>
<td>Frye et al., 2007</td>
<td>Cat</td>
<td>Healthy</td>
<td>8/7/48 (20.8)</td>
<td>CTX-M group II; SHV; TEM^a; CMY-2</td>
<td>Salmonella enterica</td>
</tr>
<tr>
<td>Moreno et al., 2008</td>
<td>Cat</td>
<td>Hospitalized</td>
<td>10/not specified</td>
<td>CTX-M-1 (40), CTX-M-14 (60), PER-2 (50)</td>
<td>E. coli</td>
</tr>
<tr>
<td>Steen et al., 2007</td>
<td>Dog</td>
<td>UTI (2), UTI (1)</td>
<td>3/3 (100) (preselected)</td>
<td>CTX-M-type (100)</td>
<td>E. coli</td>
</tr>
<tr>
<td>Sidjabat et al., 2007</td>
<td>Dog</td>
<td>Sick (UTI, Osteomyelitis, WI, Abscess)</td>
<td>10/10 (preselected)</td>
<td>SHV-12 (90); OXA-10 (10); CMY-2 (10)</td>
<td>Enterobacter spp.</td>
</tr>
<tr>
<td>Vo et al., 2007</td>
<td>Horse</td>
<td>Not specified</td>
<td>3/3 (100)</td>
<td>TEM^b (100)</td>
<td>E. coli</td>
</tr>
<tr>
<td>Costa et al., 2004</td>
<td>Cat</td>
<td>Healthy</td>
<td>6/78 (7.8)</td>
<td>TEM^a (66.6)</td>
<td>E. coli</td>
</tr>
<tr>
<td>Ma et al., 2009</td>
<td>Cat &amp; Dog</td>
<td>UTI, RTI</td>
<td>36/not specified</td>
<td>CTX-M-9 group; CTX-M-1 group; DHA-1; CMY-2</td>
<td>E. coli</td>
</tr>
<tr>
<td>Pomba et al., 2009</td>
<td>Dog</td>
<td>UTI</td>
<td>1/41 (2.4)</td>
<td>CTX-M-15 (100)</td>
<td>E. coli**</td>
</tr>
<tr>
<td>Sun et al., 2010</td>
<td>Dog &amp; Cat</td>
<td>Sick &amp; Healthy</td>
<td>97/240 (40.4)</td>
<td>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)</td>
<td>E. coli</td>
</tr>
<tr>
<td>Ewers et al., 2010b</td>
<td>Dog</td>
<td>Horse</td>
<td>WI, UTI, GTI, WI, UTI, Eye</td>
<td>1/not specified</td>
<td>CTX-M-1; SHV^a</td>
</tr>
<tr>
<td>Ewers et al., 2010a</td>
<td>Dog</td>
<td>Cat</td>
<td>UTI, UTI, GTI, WI, UTI</td>
<td>1/not specified</td>
<td>CTX-M-1; SHV^a</td>
</tr>
<tr>
<td>Gibson et al., 2010</td>
<td>Cat</td>
<td>UGTI, WI, UGTI, WI, UGTI, WI, others</td>
<td>3 [34]/not specified</td>
<td>SHV-12 (2.9); CMY-2 (20); CMY-7 (77.1); CT (2.9); OXA-10 (2.9); CMY-2 (50); CMY-7 (50)</td>
<td>E. coli</td>
</tr>
<tr>
<td>O’Keefe et al., 2010</td>
<td>Dog</td>
<td>Cat</td>
<td>UTI</td>
<td>11/150 (7.3)</td>
<td>SHV-12 (9.1); CTX-M-14 (9.1); CTX-M-15 (81.8)</td>
</tr>
</tbody>
</table>

** Only representative number of isolates (n ~ 125) have been used for molecular characterization.

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

* 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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