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Antimicrobial resistance in companion animals

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Abstract

Antimicrobial resistance (AMR) is an emerging problem in companion animals, because of difficult-to-treat infections, possible pressure to use antimicrobials that are important in human medicine, and potential zoonotic transmission. The extent and importance of AMR in companion animals are poorly understood, in part because of limited surveillance; however, it is clear that resistance is problematic in many pathogens and commensals, including staphylococci, enterococci, *Escherichia coli* and *Salmonella*.

Keywords: antimicrobial, infectious diseases, zoonotic

Introduction

Antimicrobial resistance (AMR) amongst companion animals, particularly household pets and horses, is a complex area that is of increasing importance because of both patient factors and public health issues. In this context, a unique and critical aspect of AMR in companion animals is their close contact with humans. This creates opportunities for interspecies transmission of bacteria, including multidrug resistant (MDR) bacteria, so that it is possible and likely that the increasing rates of MDR bacterial infection and colonization in humans may be reflected in their close contacts, including companion animals. Despite the close contact of many people with companion animals and concerns about the animal and human health risks associated with MDR infections, there has been surprisingly little investigation of many aspects of this field, so that current knowledge is limited.

Evaluation of the scope of AMR in companion animals is difficult, as there are few formal surveillance programs, particularly compared to the data available for food animal species. Much of the available data come 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 can be geographical variation in pathogen and susceptibility patterns, as well as global differences in antimicrobial drug usage that can limit the applicability of results to other areas. Few prospective, population-based studies are available, and many are relatively small. It is an important area for future research, particularly because of the potential for bi-directional infection with humans, and of amplification of resistance in veterinary clinics with subsequent infection of humans.

AMR is a concern in a wide range of bacterial pathogens and commensals. Detailed examination of several aspects of the relevant concerns is beyond the scope of this review. Specific information on AMR in selected bacterial species is provided below.

Staphylococcus aureus and *Staphylococcus pseudintermedius*

AMR has been a problem historically with staphylococci, an important group of opportunistic pathogens. Penicillin resistance, associated with beta-lactamase production, is very common amongst clinical companion animal staphylococcal isolates, with resistance rates of up to 74% (Hoekstra and Paulton, 2002). Although beta-lactamase producing staphylococci can be treated successfully with beta-lactam/beta-lactamase inhibitor combinations, beta-lactamase resistant beta-lactam antimicrobials, and other drug classes, much recent attention has been paid to the emergence of methicillin-resistance, particularly in *S. aureus* (MRSA) and *S. pseudintermedius*

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(MRSP). Methicillin-resistance is mediated by the *mecA* gene, which resides on a staphylococcal cassette in the chromosome (SCC*mec*). Expression of *mecA* results in production of an altered penicillin-binding protein, PBP2a, which has low affinity for all beta-lactam antimicrobials (penicillins, cephalosporins and carbapenems), rendering methicillin-resistant strains clinically resistant to this broad class of antimicrobials. Clinical MRSA infections have been reported in various species, including dogs, cats, rabbits and horses. MRSA can also be isolated from the nasal passages or intestinal tract of a small percentage (0–5%) of healthy individuals (Baptiste *et al.*, 2005; Weese *et al.*, 2005b; Kottler *et al.*, 2008). MRSA isolates often possess a variety of other resistance genes, and some may even be resistant to most available antimicrobials. There have only been limited studies describing and characterizing other AMR genes amongst MRSA. Macrolide resistance is common and typically mediated by *erm*(*C*) (O'Mahony *et al.*, 2005; Rich *et al.*, 2005; Bagcigil *et al.*, 2007). Inducible resistance to clindamycin is also a concern because of the inability to detect resistant strains using routine testing. For example, a British study reported inducible resistance in 71% of veterinary isolates (Rich *et al.*, 2005), whereas a North American study identified inducible resistance in 55% of erythromycin resistant isolates from dogs and cats (Faires and Weese, 2008). Tetracycline resistance is common among canine and equine *S. aureus* (methicillin-sensitive *S. aureus* [MSSA] and MRSA) in most regions (Baptiste *et al.*, 2005; O'Mahony *et al.*, 2005; Weese *et al.*, 2005a; Bagcigil *et al.*, 2007) and is most commonly mediated by the *tet*(*K*) gene (Schwarz *et al.*, 1998). Highly variable (3–79%) trimethoprim-sulfonamide resistance has been reported (Weese *et al.*, 2005a; Morris *et al.*, 2006; Rich and Roberts, 2006). There are also variable rates for aminoglycoside resistance, with some studies reporting very low rates (3–8%) (Morris *et al.*, 2006; Rich and Roberts, 2006) and others up to 100% (Baptiste *et al.*, 2005; Weese *et al.*, 2005a; O'Mahony *et al.*, 2005). The highest rates have been reported for equine isolates, which could reflect the more common use of this drug class in horses. There are similarly variable (0–100%) rates for fluoroquinolone resistance, with higher rates in small animal studies (Morris *et al.*, 2006; O'Mahony *et al.*, 2005; Weese *et al.*, 2005a; Rich and Roberts, 2006). Some of the variations in reported resistance rates likely involve the presence of different MRSA clones in different geographic regions and between different animal species.

Although MRSA receives the most attention, largely because of its significance in human medicine and the potential for zoonotic transmission, other staphylococci may be of equal or greater clinical concern in companion animals. *S. pseudintermedius* (previously misidentified as *Staphylococcus intermedius*), is an important pathogen, particularly in dogs and cats. Methicillin-resistant strains (MRSP) have been reported (Sasaki *et al.*, 2007; Schwarz *et al.*, 2007) and anecdotally there has been a dramatic increase in infections worldwide in recent years. Like MRSA, methicillin-resistance in MRSP is mediated by the *mecA* gene, and MRSP isolates are resistant to all beta-lactam antimicrobials. Multidrug resistance among MRSP may be very common. While data are limited, there is anecdotal information of highly drug resistant MRSP isolates, which are susceptible to few antimicrobials, and which are more resistant than most MRSA isolates. The largest most recent study, from a Japanese veterinary teaching hospital, reported 100% resistance to erythromycin, clindamycin, trimethoprim-sulfa (TMS) and levofloxacin (Sasaki *et al.*, 2007). In contrast to MRSA, inducible resistance to clindamycin is very rare in MRSP (unpublished data) and macrolide resistance tends to be mediated by *erm*(*A*) (Schwarz *et al.*, 2007). Tetracycline resistance is common (Sasaki *et al.*, 2007), as in MRSA, but is most often mediated by *tet*(*M*) (Schwarz *et al.*, 1998).

Enterococci

Enterococci are opportunistic Gram-positive pathogens that are commonly found in the gastrointestinal tract of many animal species. The two species most often involved in disease are *Enterococcus faecium* and *Enterococcus faecalis*. Enterococci are inherently resistant to a variety of antimicrobial classes, including cephalosporins, some penicillins, clindamycin and trimethoprim, which makes the implications of acquired resistance even greater.

In human medicine, vancomycin resistant enterococci (VRE) are a tremendous concern, particularly *E. faecium* and *E. faecalis* strains carrying the transferable *vanA* and *vanB* genes. Currently, VRE are rare in companion animals (Rice *et al.*, 2003; Damborg *et al.*, 2008; Ossiprandi *et al.*, 2008); however, there have been sporadic reports of infection or colonization in household pets (Devriese *et al.*, 1996; de Niederhäusern *et al.*, 2007). A link between VRE carriage in dogs and avoparcin use in food animals has been suggested as an explanation for high rates in some European studies, such as the 48% vancomycin resistance among canine enterococci in the Netherlands (van Belkun *et al.*, 1996). While the link to avoparcin has not been proven, a subsequent Dutch study, performed 5 years after avoparcin use was banned, reported no VRE in 100 dogs, so that there was an apparent marked decline in canine fecal carriage (Wagenvoort *et al.*, 2003). VRE colonization has also been reported in horses, with a 6.7% colonization rate reported in a study of Italian horses (de Niederhäusern *et al.*, 2007).

Although VRE infections are rare in companion animals, other MDR enterococci are of greater importance. It is not unusual to encounter enterococci in clinical specimens that are resistant to most antimicrobials, except vancomycin. However, population-based studies provide conflicting reports of resistance to other

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antimicrobials. For example, studies of healthy dogs in Denmark and dogs with antimicrobial exposure in Finland reported low prevalences of resistance to various antimicrobials (Rantala *et al*., 2004; Damborg *et al*., 2008), whereas a study of healthy dogs in the community in Portugal reported higher rates of resistance to most antimicrobials (Poeta *et al*., 2006) and a study of dogs presented to a veterinary hospital in Italy reported frequent resistance to fluoroquinolones, tetracyclines, macrolides, rifampin and tetracycline (Ossiprandi *et al*., 2008). High rates of tetracycline and macrolide resistance in *E. faecalis* were also reported in dogs from private homes and kennels in Belgium (De Graef *et al*., 2004).

These examples highlight the need to consider the study population when evaluating resistance data. Recently, ampicillin-resistant CC17 *E. faecium*, an important strain in humans, was identified in a surveillance study of dogs in Denmark, a country with a relatively low prevalence of MDR enterococci in humans (Damborg *et al*., 2008). This strain is of concern because of its role in human disease and typical resistance to ampicillin, potentiated penicillins, first generation cephalosporins, potentiated sulfonamides and fluoroquinolones, the main first line treatments for urinary tract and many other infections in pets.

Streptococci

Streptococcus zooepidemicus and *Streptococcus equi* are important pathogens in equine medicine and *Streptococcus canis* is an uncommon but potentially important pathogen in small animals. In general, AMR amongst equine streptococci is rare and streptococci are assumed to have relatively predictable patterns of susceptibility. Beta-lactam resistance is rare (Clark *et al*., 2008) despite widespread use of beta-lactam antimicrobials for streptococcal infections over many years. TMS resistance is a somewhat controversial area that requires further study. Feary *et al*. (2005) investigated a decrease in *S. zooepidemicus* susceptibility from close to 100% to 50% over a few years, and concluded that there was false reporting of resistance because of the use of an inappropriate culture medium and quality control strain. However, a recent study reported that only 55% of *S. zooepidemicus* isolates were susceptible despite the use of CLSI guidelines and appropriate control strains (Clark *et al*., 2008). This is potentially important, particularly in light of a study indicating that TMS administration was unable to prevent *S. zooepidemicus* infection and abscess formation following experimental inoculation (Ensink *et al*., 2005).

Resistance is uncommon in *Streptococcus canis* from dogs. Resistance rates of 0% have been reported for penicillin, ampicillin, amoxicillin/clavulanic acid, gentamicin and chloramphenicol, with low rates of resistance to erythromycin (12%) and clindamycin (12%) among isolates from the ears of dogs with and without otitis (Lyskova *et al*., 2007). Another study reported no resistance to penicillin, cephalothin or trimethoprim/sulfonamides with 27% resistance to tetracycline, 14% to enrofloxacin, 14% to clindamycin and 11% to erythromycin (Pedersen *et al*., 2007). Macrolide resistance in canine isolates has been associated with *erm*(*B*) in two canine *S. canis* isolates, whereas *mef*(*A*) and *msr*(*D*) were identified in macrolide resistant *Streptococcus dysgalactiae* ssp. *equisimilis* from one dog (Lüthje and Schwarz, 2007). There has been minimal investigation of other mechanisms of resistance amongst companion animal streptococci. While not related to resistance, there is an interesting association between fluoroquinolone administration and streptococcal toxic shock syndrome and necrotizing fasciitis in dogs (Ingrey *et al*., 2003). This occurs through enrofloxacin-mediated induction of a mitogen-encoding bacteriophage. The prevalence of this bacteriophage in *S. canis* strains is unknown; however, the severity of this potential complication indicates that fluoroquinolones should not be used when *S. canis* infection is known or likely.

Escherichia coli

E. coli is an important pathogen and common component of the commensal intestinal microflora. The vast reservoir of *E. coli* in the intestinal tract is of potential concern as a pool of AMR. Various studies have evaluated susceptibility patterns amongst *E. coli* isolates from healthy animals and infected sites (Table 1). The marked diversity in *E. coli* and the inherent biases in clinical-specimen-based reporting complicate understanding of AMR in *E. coli* at the population level.

The main area of focus regarding AMR in *E. coli* involves beta-lactamase production, because of the importance of beta-lactam antimicrobials in the treatment of infections of animals and humans and concerns about transmission of resistant strains between animals and humans. Of particular concern is extended spectrum beta-lactamases (ESBLs), which hydrolyze a broad range of beta-lactam antimicrobials. These include the plasmid-encoded AmpC-type CMY beta-lactamases and Class A ESBLs (mainly TEM and SHV derivatives, and CTX-M ESBLs) which are emerging animal and human health concerns (Li *et al*., 2007). Studies of isolates from dogs and cats have identified $bla_{\text{CMY-2}}$, $bla_{\text{CTX-M}}$, bla_{TEM} and $bla_{\text{SHV-12}}$ (Teshager *et al*., 2000; Sanchez *et al*., 2002; Carattoli *et al*., 2005; Costa *et al*., 2008), whereas $bla_{\text{CMY-2}}$, $bla_{\text{CTX-M}}$, bla_{TEM} and $bla_{\text{SHV-1}}$ have been reported in horses (Vo *et al*., 2007a; Dolejska *et al*., 2008).

Other studies have evaluated different molecular aspects of AMR. Studies of integrons and associated resistance genes reported identification of *aac*(3)-II, *aad*A1, *aad*A2, *aad*A4 and *aad*A5 (aminoglycoside resistance), *dfr*A1, *dfr*A12 and *dfr*A17 (trimethoprim resistance), *est*X, *sat*2 and *sat*12 (streptothricin resistance),

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Table 1. Susceptibility patterns of *E. coli* isolates from companion animals

Region	Canada (Clark *et al.*, 2008)	Italy (Frontoso *et al.*, 2008)	Canada (Weese *et al.*, 2008)	Sweden (Weese *et al.*, 2008)	Portugal (Costa *et al.*, 2008)	Canada (Authier *et al.*, 2006)	Denmark (Pedersen *et al.*, 2007)
Species (*n*)	Equine (82)	Equine (64)	Equine (102)	Equine (161)	Canine and feline (144)	Canine (205)	Canine (499) diagnostic samples
Amp	62	38	40	31	88	67	74
Ceft	94		84	100			98
Ceph	50					89	95
Enro	91	78	91	96		97	
Gen	80	74	71		98	99	97
Tet	65	39	48	94	81	86	80
TMS	62	74	42	81	97	92	80
Co-Am	84	72			96	84	96
Ami	100		90		100		
Chl			70		97		95

Amp, ampicillin; Ceft, ceftiofur; Ceph, cephalothin; Enro, enrofloxacin; Ge, gentamicin; Tet, tetracycline; TMS, trimethoprim-sulfonamide; Co-Am, amoxicillin–clavulanic acid; Ami, amikacin; Chl, chloramphenicol.
The data are presented as percentage of isolates that are susceptible to the anti-microbial

*cat*B3 (chloramphenicol resistance), and *sul1* (sulfonamide resistance) from canine and feline isolates (Kadlec and Schwarz, 2008; Costa *et al.*, 2008). *tet*(*A*) and/or *tet*(*B*), encoding tetracycline resistance, have been found in isolates from dogs and cats, with *tet*(*A*) being more common in dogs and *tet*(*B*) more common in cats (Costa *et al.*, 2008). Studies of resistance determinants have often focused on populations of isolates with specific phenotypes (i.e. cephalosporin resistance) so the population prevalence is not well understood. Regardless, it is clear that MDR *E. coli*, including various combinations of beta-lactamase and other resistance determinants, can be found in isolates from both healthy animals and clinical cases. Further, the topic of AMR in *E. coli* in household pets may be of considerable public health significance because of the potential for interspecies transmission as was highlighted by a study raising concern that dogs could be sources of uropathogenic *E. coli* in humans (Starcic *et al.*, 2002).

Salmonella

Salmonellosis is an important disease in many companion animals, and is also a zoonotic threat. MDR *Salmonella* have been widely reported in horses; these include serovars Infantis (Tillotson *et al.*, 1997), Anatum (Zhao *et al.*, 2007), Heidelberg (Amavisit *et al.*, 2001), Krefeld (Ikeda and Hirsh, 1985), Newport (Zhao *et al.*, 2007), Saint Paul (Ikeda and Hirsh, 1985), and Typhimurium (Ward *et al.*, 2005) including Typhimurium DT104 (Weese *et al.*, 2001). Outbreaks of MDR *Salmonella* infections have been widely reported in horses in veterinary teaching hospitals (Ikeda and Hirsh, 1985; Tillotson *et al.*, 1997; Ward *et al.*, 2005). However, MDR *Salmonella* can also be found in horses in the general population, both in horses with salmonellosis and subclinical carriers. Risk factors for MDR *Salmonella* colonization or infection have been poorly defined.

MDR *Salmonella* can also be a problem in dogs and cats, with sporadic cases and outbreaks amongst animals and humans in veterinary clinics and households (Cherry *et al.*, 2004; Wright *et al.*, 2005).

Various AMR genes have been identified in *Salmonella* from horses and household pets (Rankin *et al.*, 2002; Gray *et al.*, 2004; Vo *et al.*, 2007b; Zhao *et al.*, 2007). As with *E. coli*, ESBL producing strains of *Salmonella* are of concern. Ceftiofur resistance was identified in 9.8% of feline and 20.8% of canine *Salmonella* isolates in one study (Frye and Fedorka-Cray, 2007). Various resistance genes, including $bla_{\text{CMY-2}}$, bla_{SHV}, bla_{TEM} and $bla_{\text{CTX-M}}$, were identified. $bla_{\text{CMY-2}}$, bla_{SHV}, bla_{TEM} and $bla_{\text{CTX-M}}$ have been identified in canine, feline and equine *Salmonella* in studies of cephalosporin resistant isolates (Rankin *et al.*, 2002; Gray *et al.*, 2004; Vo *et al.*, 2007b). Various integron-associated resistance genes have been identified in equine isolates, including *aad*A21, *aad*A1 and *aad*A2 (aminoglycoside resistance), *dfr*A1, *dfr*A7 and *dhrf*XII (trimethoprim resistance) and $bla_{\text{PSE-1}}$ (ampicillin resistance) (Rankin *et al.*, 2002; Vo *et al.*, 2007b; Zhao *et al.*, 2007).

Pseudomonas

Multidrug resistance is a common problem in *Pseudomonas* spp. and MDR *Pseudomonas* infections can be encountered in companion animals in veterinary hospitals and in the community. They can be of particular concern in hospitals because of strong environmental persistence and innate resistance to many antiseptics (Deplano *et al.*, 2005; Bonomo and Szabo, 2006).

AMR can be variable, with some isolates resistant to a large number of antimicrobials. A study of canine isolates

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reported resistance to from 8 to 28 of 32 tested antimicrobials (Rubin *et al*., 2008). Pan-resistant *Pseudomonas aeruginosa* has been reported in humans (Deplano *et al*., 2005), but not yet in animals. Beta-lactam resistance, almost all of it innate resistance, is very common. A Canadian study of isolates from canine ear and skin infections reported 100% resistance to ampicillin, cefazolin, cefoxitin, cephalothin and cefpodoxime, 99% resistance to amoxicillin/clavulanic acid, and 97% resistance to ceftiofur, with lesser resistance to ceftriaxone (39%), cefotaxime (26%) and cefotaxime/clavulanic acid (20%) (Rubin *et al*., 2008). Acquired resistance to gentamicin (7%) and amikacin (3%) was uncommon but there were high rates against chloramphenicol (100%), tetracycline (98%) and trimethoprim-sulfamethoxazole (57%). Resistance to fluoroquinolones was moderate with 16% resistant to ciprofloxacin, 31% resistant to enrofloxacin and 52% resistant to orbifloxacin. Twenty-two different alterations in *gyrA* sequences were identified among 102 naladixic acid resistant isolates, particularly mutations at Thr83 and Asp87. Alterations in *gyrB* and *parC* were also found amongst naladixic acid resistant isolates, but were less common. Similar resistance patterns were reported in a smaller study of clinical isolates from dogs in Denmark (Pedersen *et al*., 2007), whereas similar rates of resistance to enrofloxacin (53%) and ciprofloxacin (25%) were reported in an American study of ear and skin isolates (Wildermuth *et al*., 2007). Thirty-three percent resistance to marbofloxacin was also reported in the latter study. Less information is available regarding isolates from horses. A study of equine *P. aeruginosa* isolates reported 100% resistance to ampicillin, ceftiofur, penicillin, cephalothin, tetracycline and trimethoprim-sulfonamide, with 87% resistance to amoxicillin/clavulanic acid, 44% to gentamicin, 70% to enrofloxacin, and 8% to amikacin (Clark *et al*., 2008). Resistance to beta-lactams was less common in other *Pseudomonas* spp., with 76% resistance to ampicillin, 67% to ceftiofur and 84% to penicillin, however, there was 32% resistance to enrofloxacin, 44% to gentamicin, 60% to tetracycline, 48% to trimethoprim-sulfonamide and 0% to amikacin. An earlier study reported no resistance to gentamicin and amikacin, 36% resistance to enrofloxacin, 14% resistance to tetracycline, 71% resistance to chloramphenicol and 100% resistance to beta-lactams (Hariharan *et al*., 1995). Studies of isolates from pseudomonal keratitis have reported high rates of susceptibility to gentamicin, tobramycin and ciprofloxacin, with variable resistance to chloramphenicol (Moore *et al*., 1995; Keller and Hendrix, 2005).

Acinetobacter

Members of the Gram-negative genus *Acinetobacter* are potentially important and highly drug resistant pathogens, mainly in hospital environments. They are opportunistic pathogens that can cause a range of infections in various species, including dogs, cats and horses (Francey *et al*., 2000; Boerlin *et al*., 2001). Hospital-associated infections are probably most commonly based on the opportunistic nature of *Acinetobacter* spp. and the ability of this organism to persist in the hospital environment for prolonged periods of time.

Much attention has been paid recently to *Acinetobacter baumanii* infections in humans because of the increased incidence and very high level of AMR (Krcmery and Kalavsky, 2007; Naas *et al*., 2007; Perez *et al*., 2007). *Acinetobacter* spp. tend to possess large collections of mobile resistance determinants and also have a high endogenous mutation rate that allows for *de novo* development of resistance (Fournier *et al*., 2006). Emergence of resistance even during a single course of therapy has been reported (Reid *et al*., 2007). Some *Acinetobacter* spp. strains from humans possess resistance mechanisms against all known antimicrobial classes (Perez *et al*., 2007; Reid *et al*., 2007). Little information has been published regarding antimicrobial susceptibility amongst companion animal isolates, however anecdotal information indicates that highly drug resistance isolates are being encountered in veterinary hospitals. Reports involving small numbers of isolates have indicated common susceptibility *in vitro* to amikacin, imipenem and enrofloxacin amongst equine and canine isolates (Francey *et al*., 2000; Boerlin *et al*., 2001).

Conclusion

Emergence and dissemination of AMR in companion animals will undoubtedly continue to be a challenge in veterinary medicine, from both patient health and public health standpoints. More organized surveillance is required to better understand the scope of the problem, and to identify measures that may be used to decrease the impact of this problem.

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