Antimicrobials and Resistance in Small Animals.

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How Does Antimicrobial Resistance Emerge?

Resistant bacteria emerge in our patients through horizontal spread, transfer of genetic elements carrying genes for resistance, and mutations arising during treatment. Inadequate antibiotic treatment consisting of doses too low, infrequent administrations, or selection of a poorly active drug, is an important contributor to emergence of drug resistance. An infection typically consists of a mixed population of susceptible wild type and resistant bacteria. The resistant strains can emerge and become dominant through selection and amplification. Antibiotics administered to dogs and cats do not necessarily *cause* resistance in bacteria. A more accurate description is that antibiotic exposure – if not adequate to suppress resistant bacterial strains – can select for resistant bacteria, which then can multiply and flourish. Resistant strains emerge because the competition from more susceptible bacteria is reduced, or eliminated, during antibiotic administration. Resistant bacteria potentially can be transferred to other animals, people, and the environment.

Over many years of antibiotic use, resistant bacteria have emerged that are encountered in small animal practice. Many of these resistant strains are now common and contributing to the difficulty in selecting effective antibiotics for some patients. The most common bacteria producing resistant infections in small animals are (not necessarily in order) *Escherichia coli*, *Pseudomonas aeruginosa,* methicillin-resistant *Staphylococcus* species, and *Enterococcus* species. The extent to which prescribing practices can influence this trend is not straight-forward. The notion that antibiotic treatment causes resistance is too simplistic and does not reflect the complexity of the issue. Previous antibiotic administration, hospitalization, and prolonged treatment are all risk factors. Some resistant strains were acquired by pets from human sources, the environment, or raw meat in the diet. Because of the co-selection and persistence of resistance genes, it is not entirely clear that a single antibiotic, or antibiotic class, is responsible for the emergence of resistance. A precise correlation between specific antibiotic class use and resistance is difficult to establish (Hawkey, 2008). Because data on the impact of restricting some classes of antimicrobial agents is conflicting, infection control may be more important than restricting some classes of antibiotics.

What are the Risks for Transfer of Resistant Bacteria From Small Animals to Humans?

There is some agreement on the effect of antibiotics on bacterial resistance in food-producing animals, but there is less known about these risks in small animals. This issue will require additional on-going investigation and surveillance. The risk of antibiotic-resistant bacteria transferred from pets to people has been reviewed by Schwarz et al (2017), Pomba et al (2017), and Guardabassi et al (2004). These reviews agree that more information is needed before making conclusions about these risks.

Published reports have indicated that resistant strains of fecal bacteria are found more frequently in animals that have been previously been hospitalized and/or treated with antibiotics (Ogeer-Gyles, et al. 2006; Hamilton et al, 2013; Gibson et al. 2008; Gibson et al. 2011). Healthy

dogs with a history of antibiotic treatment in the past year had a significantly higher risk of carrying ESBL- and/or AmpC-resistant *E. coli* (Belas, et al. 2014). However, it has been more difficult to associates this resistance with one particular agent or class of drugs. There is some evidence that oral administration of a fluoroquinolone may be more likely to select for antibiotic-resistant *E. coli* in dogs (Gibson, et al, 2011; Trott, et al. 2004); but, in experimental dogs, other classes of antibiotics studied (amoxicillin, amoxicillin-clavulanate, cephalosporins, and fluoroquinolones) were associated with detection of drug resistant bacteria (particularly *E. coli*) in fecal samples. We can conclude that antibiotic administration to pets can, at least transiently, increase the shedding of drug-resistant fecal bacteria, but it is uncertain if one antimicrobial, or particular class of antimicrobial, is more likely to be more responsible for this risk. The duration that antibiotic resistance persists after discontinuation of antibiotic treatment has varied among studies, but it may be transient and resolve to pre-antibiotic levels several days or weeks after antibiotics are discontinued (Trott, et al. 2004; Boothe, et al. 2011). Other risks that contribute to antibiotic-resistant bacteria recovered in feces of dogs are dogs from shelters/breeders (Belas, et al. 2014) and feeding of diets that contain raw meat (Leonard, et al. 2015).

As described above, there is evidence from clinical and experimental canine studies that antibiotic administration can increase the shedding of drug-resistant *E. coli* in dogs (studies in cats are not available). Are these transferred to people? Humans and pets in the same household can share *E. coli* and its virulence and resistance genes. Pets can shed resistant bacteria into the environment (Procter, et al. 2014). Virulence genes were identified in fecal *E. coli* from healthy dogs and their owners (Stenske, et al. 2009); however, it was unusual for both dogs and their owners to have the same bacterial genes. Analysis of paired samples from dogs and their owners in the same households in Japan showed that transfer of *E. coli* between owners and their dogs had occurred within 3/34 (8.8%) households (Harada, et al. 2012). Fecal samples were analyzed from pets and humans in households to determine the within-household transmission of *E. coli* (Johnson et al. 2008). They found that within household sharing of *E. coli* is common. They also found that 50% of the fecal *E. coli* from pets exhibit virulence characteristics suggesting pathogenic potential. At this time, the extent to which canine-origin *E. coli* is a public health risk is uncertain, but these studies, and others cited in reviews (Schwarz et al, 2017; Pomba et al. 2017, Guardabassi, et al.2004), suggest a *potential* for transfer of resistant fecal bacteria from animals to humans in the same household, as well as transfer from humans to pets.

Transfer of methicillin-resistant *Staphylococcus* spp. from pets to people also has raised concerns. Methicillin-resistant *Staphylococcus aureus* (MRSA) causes serious infection in people, and as reviewed by Harbarth & Samore (2008), there is a relationship between human antibiotic use and MRSA rates. The drugs most often cited for driving MRSA acquisition and transmission is the use of cephalosporins and fluoroquinolones (Harbarth & Samore, 2008; Dancer, 2008), both of which are frequently prescribed in small animals (Guardabassi et al. 2008).

Instead of MRSA, the most common drug-resistant *Staphylococcus* from pets is methicillin-resistant *S. pseudintermedius* (MRSP) – in older publications, referred to as *S. intermedius*. Methicillin-resistant staphylococci have been identified with increasing frequency in pets through the 1990s and 2000s, and are common in veterinary referral hospitals that receive patients previously treated with antibiotics (Bemis et al, 2009; Perreten, et al. 2010). Prior antibiotic administration can be a contributing factor for selection of MRSP in dogs (Schwarz, et al. 2017; Beck, et al. 2012; Eckholm, et al. 2013; Huerta, et al, 2011; Rota, et al. 2012; McCarthy, et al. 2014; Nienhoff, et al. 2011; Weese, et al. 2012). These resistant bacteria

present a therapeutic challenge to veterinarians because there are often very few antibiotics available to which these isolates are susceptible (Papich, 2012).

What is the risk to humans? Although it is possible for pets to transmit MRSP to humans, infection is unlikely. There may be rare cases of *S. pseudintermedius* infections in people, but these are isolated reports. Therefore, the reviews cited above have concluded that MRSP infection in pets is not a serious risk for humans. Methicillin-resistant *Staphylococcus aureus* (MRSA) is typically human origin. Pets may acquire, and serve as transient carriers of MRSA, but the source is most likely from an infected human or human carrier in the household. Therefore, there is a consensus among the reviews cited above that occurrence of MRSA in pets is most likely of human origin, but pets can serve as transient carriers that can potentially affect humans.

What are the Risks from Other Bacteria?

Transfer of drug-resistant bacteria from pets to humans has focused primarily on *E. coli* and *Staphylococcus* spp., as discussed above. Observations of *E. coli* resistance probably can be transferred to other bacteria of the Enterobacteriaceae. There appears to be less threat from other bacteria. The review by Pomba, et al (2017) discussed pet transmission of *Salmonella, Campylobacter, Clostridium difficile,* and other bacteria. Healthy pets can serve as carriers of these bacteria, but carriage is not the direct result of antibiotic administration. Transmission of *Campylobacter* is possible, but there are no reports indicating that pets are a source of drug-resistant isolates in people. Because this is a food-borne pathogen, transmission from contaminated meat is more likely. Animals can carry *Clostridium difficile*, and it is found in the environment. Although transmission of *C. difficile* from pets to humans is possible, it has not occurred as a result of antibiotic administration to pets. The environment and raw meat in pet diets is a more important source of *Salmonella* in dogs than antibiotic administration. Animals can be a source of *Salmonella* spp. transmission to humans and control measures should be taken when *Salmonella* outbreaks are identified. It has not been possible to evaluate the risk from antibiotic-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, but there is no evidence that pet-associated infections with these organisms presents a threat to people.

The summary from the Center of Disease Control on Antibiotic Resistance Threats in the U.S. (2013) provides a list of the most important drug-resistant bacteria considered a threat in the U.S. (https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf). None of the bacteria listed as “urgent threats” are pet-associated infections. *Campylobacter* infections from food-producing animals and extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are listed as “serious threats”, but the CDC limits the sources to food-producing animals.

Antibiotic-Resistant *Staphylococcus* Species in Small Animals

Staphylococcus isolated from small animals is most likely to be *S. pseudintermedius* rather than *S. aureus.* (Note that previously identified *Staph intermedius* probably have been misidentified and are now referred to as *S. pseudintermedius* by many laboratories. Other *Staphylococcus* species have also been reported – some of these being coagulase-negative *Staphylococcus*. When infection is caused by a typical wild-type strain, *Staphylococcus pseudintermedius* has a predictable susceptibility to ß-lactamase resistant ß-lactam antibiotics such as amoxicillin combined with a β-lactamase inhibitor (Clavamox), a first-generation cephalosporin such as cephalexin or cefadroxil, or the third-generation cephalosporins, cefovecin (Convenia) and cefpodoxime (Simplicef). Susceptible strains of *Staphylococcus* also are susceptible to oxacillin and dicloxacillin but these are not used as commonly in small animal medicine. Historically, *Staphylococcus pseudintermedius* retained susceptibility to commonly available drugs (Lloyd, et al, 1996; Pinchbeck et al, 2007). In addition to the β-lactamase stable β-lactam antibiotics listed above (cephalosporins and amoxicillin-clavulanate), most wild type strains are also susceptible (*in vitro)* to fluoroquinolones, lincosamides (clindamycin, lincomycin), trimethoprim-sulfonamides, or macrolides (erythromycin).

However, the incidence of methicillin-resistance among *S. pseudintermedius* has dramatically increased. The methicillin-resistant *Staphylococcus* spp. (including *Staph. pseudintermedius)* are isolated with increased frequency from animals with skin infections (Perreten et al, 2010; Bond & Loeffler, 2012; Weese, 2005; Weese & van Duijkeren, 2010). These infections are not confined to dermatology. Orthopedic surgeons have also encountered these strains as a cause of post-surgical orthopedic infections.

Methicillin-Resistant *Staphylococcus*

The most important resistance mechanism for *Staphylococcus* is methicillin-resistance. Methicillin-resistance presents a problem for veterinarians because, in addition to resistance to β-lactam antibiotics, most of these bacteria are also multi-drug resistant. The increased emergence of methicillin-resistant *Staphylococcus* in animals has been discussed in several publications and review articles (Bond & Loeffler, 2012; van Duijkeren, et al, 2011). The presence of the *mecA* gene and methicillin resistance appears to be increasing in veterinary medicine based on the number of reports in the last several years. Methicillin-resistant *Staphylococcus aureus* (MRSA) in human hospitals and in the community has reached alarming rates.

Staphylococcal methicillin resistance is caused by acquisition of the *mecA* gene, which encodes an altered penicillin-binding protein (PBP-2a). Although oxacillin is used as the surrogate for testing, these are referred to as methicillin-resistant staphylococci – MRS (Gortel et al, 1999; Deresinski 2005; Jones et al, 2007; Bemis et al, 2006). Methicillin has replaced oxacillin for testing in laboratories and resistance to oxacillin is equivalent to methicillin-resistance. If the pathogen is *Staphylococcus aureus* the term methicillin-resistant *S. aureus* (MRSA) can be applied. But *S. aureus* is an infrequent pathogen in dogs, and occasionally in cats.

If staphylococci are resistant to oxacillin or methicillin, they should be considered resistant to all other β-lactams, including cephalosporins and amoxicillin-clavulanate (eg, Clavamox), regardless of the susceptibility test result. Adding a β-lactamase inhibitor will not overcome methicillin resistance. Unfortunately, these bacteria often carry co-resistance to many other non- β-lactam drugs, including lincosamides (clindamycin, lincomycin), fluroquinolones,

macrolides (erythromycin), tetracyclines, and trimethoprim-sulfonamides. In the report by Bemis et al (2009), more than 90% of the methicillin-resistant isolates of *S. pseudintermedius* also were resistant to > 4 other drugs. The cause of the increased frequency of resistance has not been identified with certainty. Use of fluoroquinolones and cephalosporins has been linked to emergence of resistance of methicillin-resistant staphylococci in people (Dancer, 2008; Harbarth & Samore, 2008). In small animals, use of specific drugs have not been associated with methicillin-resistance, but administration of *any* antimicrobial within 30 days of prior to infection was identified as a risk factor in one study (Weese, et al, 2012). Dogs can carry these resistant strains for a long time after resolution of a clinical infection (Windahl, et al, 2012).

Antibiotic Choices for Methicillin-Resistant Staphylococcus

Because susceptibility to non-β-lactam antibiotics is unpredictable, a susceptibility test is needed to identify the most appropriate drug to administer for these infections. Susceptibility testing should always use CLSI standards (CLSI, 2018). Chloramphenicol, tetracyclines, aminoglycosides (gentamicin) and rifampin, are drugs to consider for these infections if a susceptibility test can confirm activity. These drugs are discussed in more detail below, but not all of these drugs are allowed in some countries, or there may be limitations on availability. Unlike the human strains of community-acquired *Staphylococcus aureus* (CA-MRSA), the veterinary strains of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) are usually not susceptible to trimethoprim-sulfonamides, clindamycin, or fluoroquinolones (Perreten et al, 2010; Bemis et al, 2009). However, a susceptibility test should always be used to confirm whether or not these drugs may have activity against isolates from animals. Topical drugs also should be considered for treatment of localized infections and shampoos and other topical treatment can be used to limit the need for antibiotics.

Rifampin (Rifampicin)

Rifampin, also known in some countries as rifampicin, is an older antibiotic that has seen recent interest because of its activity against methicillin-resistant *Staphylococcus*. Equine practitioners have been familiar with rifampin for many years because of its use for treating infections caused by *Rhodococcus equi.* Now, small animal veterinarians are becoming more familiar with this antibiotic because of its activity against mechicillin-resistant *Staphylococcus*. This antibiotic may be new to small animal veterinarians, but was originally discovered in the pine forests of France in the 1950s and was introduced into clinical medicine in the 1960s. Rifampin is the USP official name, and Rifampicin is the INN and BAN name; both names are synonymous. Rifamycin and rifabutin are structurally similar antibiotics – all in the group of rifamycins – but are not identical.

Rifampin is a bactericidal antibiotic that acts by inhibiting bacterial RNA polymerase. It is highly lipophilic, with a high volume of distribution and good absorption in practically all animal species studied. The intracellular penetration has made this drug valuable for treating intracellular bacteria in people and animals, including *Mycobacterium* and *Rhodococcus equi*. Rifampin is active against most strains of methicillin-resistant *Staphylococcus pseudintermedius*, (Perreten et al, 2010), although resistance among canine isolates has been identified (Kadlec et al, 2011). Rifampin has been effective for treatment of canine pyoderma caused by *Staphylococcus pseudintermedius* at a dose of 5 mg/kg once daily for 10 days (Senturk et al, 2005). Another study had success with 5-11 mg/kg twice daily (DeLucia, et al, 2012). A dose of

10 mg/kg per day, usually split into two doses, 12 hours apart has been recommended (Papich 2016). Higher doses recommended in some veterinary formularies are discouraged.

Resistance occurs through mutations and clonal spread of a resistant strain. To reduce rate of mutation, combination therapy with other agents has usually been recommended in human guidelines (Liu et al, 2011), as was the recommendation from a veterinary study (Kadelec et al 2011). However, in a review of the evidence from clinical trials of eradication of *S. aureus* in humans, rifampin was an effective agent for eradication of *S. aureus*, whether administered as monotherapy or as a combination (Falagas et al, 2007). Addition of a second antibiotic did not seem to confer additional effectiveness to rifampin monotherapy for eradication of methicillin-resistant *Staphylococcus*. As the authors pointed out, "…the decrease in the development of resistance to rifampin with the use of combination therapy has been mainly validated in clinical situations in which long-term therapy with rifampin was necessary (eg, tuberculosis) and may not be the same for short-term treatment for *S. aureus* carriage eradication".

Rifampin is a strong inducer of drug metabolizing enzymes (Reitman et al, 2011). Induction can significantly increase the metabolism and clearance of other co-administered drugs that are affected by these proteins. The consequence of induction is diminished effect of the co-administered drug and may require a higher dose or more frequent administration. For example, rifampin co-administration significantly affects the exposure to prednisolone (Lee, et al, 1993). In people 4 weeks is required for full recovery of the rifampin effect after discontinuation (Reitman et al, 2011). Rifamin may also have dual effects in which it can be an inhibitor of intestinal transport, as well as an inducer of other proteins.

Adverse effects, which are associated with high doses, include liver injury and GI disturbance. A study reported in 2012 indicated that among dogs treated with 5-11 mg/kg twice daily, there were elevations in liver enzymes in most dogs, and GI and hepatic abnormalities in some dogs (De Lucia et al, 2012). In a study (Bajwa et al, 2013) 16% of dogs had adverse events associated with rifampin, and 26% had elevations in liver enzymes. In dogs, hepatotoxicosis is the most common adverse reaction and 20%-25% of dogs receiving 5-10 mg/kg develop increases in liver enzymes and some develop hepatitis. To avoid adverse effects, it is recommended not to exceed a dose of 10 mg/kg per day. Rifampin has an unpalatable taste. It also may produce a discoloration (orange-red color) to the urine, tears, and sclera. Owners should be warned of this possibility.

Tetracyclines (Doxycycline, Minocycline)

Occasionally, some methicillin-resistant *Staphylococcus pseudintermedius* are susceptible to tetracyclines (Maaland et al, 2013; Hnot et al, 2015). Because the choices of oral tetracyclines are limited for small animals, either doxycycline or minocycline should be used. The human susceptibility testing breakpoint of ≤ 4 µg/mL is too high for testing bacteria from animals. The doxycycline breakpoint has been revised for animals and is now ≤ 0.12 µg/mL for testing doxycycline, and is ≤ 0.5 µg/mL for testing minocycline (CLSI, 2015).

Doxycycline administration to small animals is usually accomplished with tablets (50, 75, 100 mg) or oral suspension (5 mg/mL suspension and 10 mg/mL syrup) at doses of 5 mg/kg twice daily. When compounded in a suspension in a more concentrated form (either 33.3 mg/mL or 167 mg/mL) in an aqueous-based vehicle, the formulation was stable for 7 days, but declined to only 20% of the initial potency at 14 days.

Adverse effects from doxycycline have been rare. Renal injury, intestinal disturbances, or hepatic injury is uncommon. Unlike other tetracyclines, it has little affinity for calcium and

does not cause the dental enamel discoloration known for other tetracyclines, and does not chelate with calcium-containing oral products. It has been mixed with chocolate milk for administration to children with no interference with absorption.

Minocycline also should be considered when a susceptibility test indicates that the *Staphylococcus* is susceptible to a tetracycline, and especially when the test shows a MIC ≤0.5 µg/mL. Minocycline is a reasonable substitute for doxycycline and a dose of 5 mg/kg oral, twice daily will reach therapeutic targets. Toxicology studies have indicated a good safety profile and was well tolerated at doses recommended for clinical use. Recent studies in dogs indicate that some MRSP isolates may be susceptible to minocycline, yet resistant to other tetracyclines (ie, those that carry the *TetK* resistance). If used in cats, the dose of 8.8 mg/kg once daily (or 50 mg per cat once daily) will reach therapeutic targets.

Chloramphenicol

Chloramphenicol was discovered in 1947. It was in popular use decades ago, but gradually replaced by safer alternatives. The small animal formulation is approved by the FDA (Chloromycetin) but is not actively marketed. The use of chloramphenicol diminished in the 1970s and 80s because other active and safer drugs became available. Chloramphenicol has the disadvantage of a narrow margin of safety in dogs and cats, and necessity of frequent administration in dogs to maintain adequate concentrations (three or four times daily oral administration). These disadvantages still exist, but the activity of chloramphenicol against bacteria that are resistant to other oral drugs (eg, staphylococci and enterococci) has created increased use of chloramphenicol in recent years.

Chloramphenicol has FDA approval in the U.S. for use in dogs as 100, 250, and 500 mg tablets (Chloromycetin). The oral suspension of chloramphenicol palmitate is rarely available. Although chloramphenicol is poorly soluble (< 5 mg/mL), the poor solubility does not interfere with oral absorption. Chloramphenicol is absorbed orally with- or without food (except some formulations in cats). Tablets and capsules have similar oral absorption in dogs.

Plasma concentrations of chloramphenicol were published in several studies. Using Monte Carlo Simulations and the pharmacokinetic parameters listed above, at a dose of 50 mg/kg PO to dogs, every 8 hours there is a 90% probability that the plasma concentrations are above the MIC of 8 µg/mL for 25% of the dosing interval. Because this dose appears to have clinical efficacy in dogs, plasma concentrations may need to be above the MIC for only a short time during the dosing interval to be effective, or chloramphenicol may be more bactericidal against *Staphylococcus* than previously thought.

Significant disadvantages of chloramphenicol are adverse effects and drug interactions. As cited above, chloramphenicol has a narrow margin of safety. High doses easily produce toxicity in dogs (Clark, 1978). Gastrointestinal disturbances are rather common. A decrease in protein synthesis in the bone marrow may be associated with chronic treatment. This effect is most prominent in cats, but can occur in any animals. Idiosyncratic aplastic anemia has been described only in humans. The incidence is rare but the consequences are severe because it is irreversible. Because exposure to humans can potentially produce severe consequences, veterinarians should caution pet owners about handling the medications, and to ensure that accidental exposure does not occur at home (eg, to young children).

An important adverse effect that has emerged with recent experience treating dogs is a syndrome of ataxia, and hind-limb weakness that has been attributed to a peripheral neuropathy.

This problem appears to be more common in large breed dogs. It is reversible if the medication is discontinued.

Chloramphenicol is notorious for producing drug interactions. Chloramphenicol is a Cytochrome P450 - CYP2B11 inhibitor, and possibly other enzymes, in dogs (Aidasani et al, 2008; KuKanich et al 2011). Therefore, chloramphenicol can decrease the clearance of other drugs that are metabolized by the same metabolic enzymes. Chloramphenicol will inhibit the metabolism of opiates, barbiturates, propofol, phenytoin, salicylate, and perhaps other drugs (KuKanich et al, 2011; Akesson & Linero PEM, 1982; Sanders et al, 1979; Adams & Dixit 1970).

Aminoglycosides (Gentamicin)

Aminoglycosides – specifically gentamicin and amikacin – have *in vitro* activity against *Staphylococcus,* including methicillin-resistant strains of *Staphylococcus pseudintermedius*. Amikacin also has good activity, but it is less available commercially, is more expensive, and clinical advantages over gentamicin for *Staphylococcus* spp. treatment are not apparent, even though some strains may show *in vitro* susceptibility to amikacin but resistant to gentamicin (Gold et al, 2014). The disadvantage of gentamicin administration is the need for daily injection, the potential for kidney injury in animals with prolonged use, or high risk of toxicity if animals have evidence of kidney disease.

Gentamicin sulfate has been administered IV, IM, or SC. Because it is a water-soluble formulation, it is well absorbed from SC and IM injection sites, although these routes may produce pain in some patients. In-hospital the route is usually IV, but owners have been trained to administer SC or IM injections at home.

Once-daily regimens are used based on pharmacokinetic-pharmacodynamic principles (Drusano et al, 2007) that presume that treatment is aimed at gram-negative bacilli. Aminoglycosides have rapid bactericidal activity against gram-negative bacilli because they act to disrupt the outer membrane of these organisms. Gram-positive cocci lack this feature; therefore, aminoglycosides are not considered as effective for treating *Staphylococcus* species as compared to gram-negative bacilli (Llanos-Paez., et al. 2017). More frequent administration may be needed for optimum efficacy. Because efficacy has not been confirmed with clinical studies using aminoglycosides to treat pyoderma, this property of their action should be considered before selecting an aminoglycoside for treatment.

The MIC values for *Staphylococcus* spp. are usually below 2 µg/mL. The current CLSI breakpoint for susceptible bacteria (CLSI 2015) is $\leq$ 2 µg/mL. This breakpoint assumes a dose of 10 mg/kg, q24h, IM in dogs, but higher dose or IV use would produce higher plasma concentrations for which this breakpoint also would apply. Activity of aminoglycosides is diminished in the presence of pus and cellular debris (Konig et al 1998). This may be important for some skin infections. These conditions may decrease the usefulness of gentamicin for the treatment of wound and ear infections.

The most serious adverse effect associated with aminoglycoside therapy is nephrotoxicity. Toxicity initially affects the renal proximal tubules because of active up-take in these cells. Eventually, the entire nephron can be affected. Animals that are dehydrated, have electrolyte imbalances (for example low Na^+ or K^+), septicemic, or have existing renal disease are at a higher risk for toxicity than healthy animals. Nephrotoxicity is related to persistent drug levels (especially high trough concentrations). Therefore, extended dosing intervals will decrease risk of nephrotoxicosis (Drusano et al, 2007). To decrease the risk of drug-induced

nephrotoxicosis, therapeutic drug monitoring and careful evaluation of renal function during its use is recommended.

Glycopeptides (Vancomycin)

Of the glycopeptides, vancomycin is the only one used in veterinary medicine, but is restricted from use in some countries. Vancomycin is not a new drug – although it may be new to many veterinarians. It is difficult to administer to small animals because of the need to administer IV. Therefore, its use is rare and will probably remain so. Despite is long history of use, resistance to vancomycin among *Staphylococcus aureus* is extremely rare with only a few cases described worldwide.

Vancomycin is slowly bacteridical for staphylococci by inhibiting the cell wall in a time-dependent manner. Vancomycin is poorly absorbed orally and this route should not be used except to treat intestinal infections. Intramuscular administration is painful and irritating to tissues. The usual dosage for small animals is 15 mg/kg q8h, IV, via slow infusion. Therapeutic drug monitoring (TDM) can be performed to ensure that trough concentrations are maintained above 10 µg/mL for skin, soft-tissue infections.

If vancomycin is administered according to the recommended dosing rates, adverse reactions are rare. Early formulations of vancomycin were associated with a high incidence of adverse effects. Most of these effects resulted from rapid IV administration, which induced flushing of the skin, pruritus, tachycardia and other signs attributed to histamine release. Nephrotoxicity and ototoxicity also was reported. Newer formulations are safer because impurities have been removed.

What about other human-label drugs?

In response to the emergence of resistant gram-positive bacteria in humans – primarily methicillin-resistant *Staphylococcus* and drug-resistant *Enterococcus* spp. – the pharmaceutical industry has responded with new antibiotics. These drugs are generally expensive, and most of them must be administered by the intravenous route, in some cases via a central vein. They have primarily a gram-positive spectrum, but in some instances can be used for bacteria other than *Staphylococcus* or *Enterococcus*. Because of the expense, or the difficult administration, the use of these drugs has not been described in clinical veterinary patients. These drugs include streptogramins (combination of 30:70 quinupristin:dalfopristin called Synercid); daptomycin (Cubicin), a cyclic lipopeptide antibiotic; telavancin, another glycopeptides; tigecycline (Tygacil), a unique tetracycline; linezolid (Zyvox), the first in the class of oxazolidinones, telithromycin (Ketek), the first of a class of drugs called ketolides (currently restricted because of toxicity risk in humans); and a new generation of cephalosporins, ceftaroline fosamil (Teflaro) and ceftobiprole. The only one of these agents that has been used in veterinary patients, to the author's knowledge, is linezolid, which is discussed briefly below.

Oxazolidinones

Linezolid (Zyvox) is the first in the class of oxazolidinones to be used in human medicine. It is currently being used in people to treat methicillin-resistant Staphylococcus and vancomycin resistant gram-positive infections caused by enterococci and streptococci. It has excellent activity against staphylocci and enterococci. Resistance can occur, but several sequential mutations are needed for development of resistance because of the redundant nature of

the 23S rRNA gene, which codes for the target of this drug. Consequently, resistance has been rare in human patients and not documented in veterinary patients.

Linezolid is absorbed orally and also is administered IV. Oral absorption is practically 100% in all animals tested (Slatter et al, 2002), and is not affected by food. Linezolid is metabolized similarly across species (Slatter et al, 2002) and pharmacokinetic parameters scale allometrically across species, allowing accurate prediction of doses for both dogs and cats of approximately 10 mg/kg twice daily (Bhamidipati et al, 2004).

Because of the high expense, linezolid has been used very infrequently in veterinary medicine. The brand-name tablets may cost over $120 per tablet in retail pharmacies. However, the availability of a generic tablet may reduce this cost by approximately 10-fold less. The use at this time has only been reported in unpublished anecdotal canine and feline cases, which have responded with good outcomes.

Toxicokinetic studies in dogs at high doses showed that linezolid was well tolerated and did not accumulate (Slatter et al, 2002). Linezolid is a mild, reversible inhibitor on monoamine oxidases A and B. In the 10 years of clinical use of linezolid in people, these theoretical interactions with adrenergic agents have not been significant. Whether or not linezolid will produce interactions in dogs administered adrenergic agents (eg, phenylpropanolamine, selegiline), or other drugs metabolized by monoamine oxidases (eg, serotonin reuptake inhibitors or tricyclic antidepressants) has not been studied. Long-term use (>14 days) can cause bone marrow suppression (eg, thrombocytopenia) in people, but this has not been reported in dogs or cats. If it occurs, myelosuppression is mild and reversible.

Resistant Gram-Negative Infections

After a susceptibility report is available, one may find that the only antimicrobials to which some gram-negative bacilli are sensitive, including *Pseudomonas aeruginosa,* are extended-spectrum cephalosporins, penems (carbapenems), piperacillin-tazobactam, amikacin, or tobramycin.

Cephalosporins

Cefpodoxime is more active than many other third-generation cephalosporins against *Staphylococcus,* and pharmacokinetic properties allow for once-daily dosing (Papich et al, 2010). However, it is not active against *Pseudomonas aeruginosa*, *Enterococcus*, or methicillin-resistant *Staphylococcus*.

In the spring of 2008 cefovecin (Convenia) was approved was registered by the FDA-CVM for use in dogs and cats for treatment of skin infections. In December of 2006 cefovecin (Convenia) was introduced to small animal medicine in Europe and in Canada in October 2007. There have also been pharmacokinetic studies (Stegemann et al 2006ab) published for dogs and cats, pharmacodynamic studies published (Stegemann et al, 2006c), and clinical efficacy studies in dogs and cats (Stegemann et al, 2007ab; Passmore et al, 2007; Six et al, 2008). In the clinical studies, cefovecin was compared to another active antimicrobial (cefadroxil, cephalexin, or amoxicillin-clavulanate) and non-inferior to these other drugs.

In dogs and cats, cefovecin is registered in Europe and Canada for treatment of skin infections. In dogs it is also registered for urinary tract infections. In Europe, but not Canada, it is also registered for urinary tract infections in cats. The approved label dose in these countries

is 8 mg/kg SC, once every 14 days. The studies published show efficacy with a 14 day interval for administration. The injection may be repeated for infections that require longer than 14 days for a cure (eg, canine pyoderma). The approval for the United States lists treatment of skin infections in dogs and cats and therapeutic concentrations are maintained for an interval of 7 days, but drug concentrations persist long enough for a 14 day interval for some indications.

There are currently not any CLSI approved standards for susceptibility testing established for cefovecin (CLSI 2013). Based on the distribution of organisms reported (Stegemann et al. 2006c) ≤ 2.0 µg/mL should be considered. It has equal or greater activity against *Staphylococcus* spp. isolates and gram-negative bacteria of the Enterobacteriaceae (eg, *E. coli, Klebsiella).* However, activity against *Pseudomonas aeruginosa* is poor and it will not be effective against methicillin-resistant staphylococci.

Cefovecin is a third-generation cephalosporin and is more active with lower MIC values than first generation cephalospsorins. This was demonstrated for pathogens from Europe and the United States (Stegemann et al, 2006c, Six et al, 2008). Cefovecin MIC_{90} values were 0.25 µg/mL for *Staphylococcus intermedius* compared to 2 µg/mL for cephalexin and cefadroxil. As a 3rd-generation cephalosporin, it is expected to have even greater activity against gram-negative bacteria as was demonstrated by the MIC_{90} values of 1 µg/mL compared to 16 µg/mL for cephalexin and cefadroxil (Six et al, 2008). Other MIC comparisons are provided in the tables in the paper by Stegemann et al (2006c).

Although cefovecin and cefpodoxime are technically considered 3rd-generation cephalosporins, the activity of cephalosporins within these arbitrary "generations" are not always similar. Cefovecin and cefpodoxime are *not* as active against gram-negative bacteria compared to injectable 3rd-generation cephalosporins used in human medicine, such as ceftazidime or cefotaxime. When other injectable cephalospsorins are considered for small animals, the most often used are cefotaxime and ceftazidime, although individual veterinary hospitals have utilized others in this group. These drugs are injectable, and must be administered frequently. Of the cephalosporins, only the 3rd-generation cephalosporins, ceftazidime (Fortaz, Tazidime), cefoperazone (Cefobid), or cefepime (Maxipime), a 4th-generation cephalosporin, have predictable activity against *Pseudomonas aeruginosa.* Ceftazidime has greater activity than cefoperazone and is the one used most often in veterinary medicine. These drugs must all be injected, and are usually given IV, although SC, and IM routes have been used.

Carbapenems:

The β-lactam antibiotics with greatest activity against resistant strains of the Enterobacteriaceae (*E. coli, Klebsiella,* etc.) and *Pseudomonas aeruginosa* are the carbapenems. The carbapenems are β-lactam antibiotics that include imipenem-cilastatin sodium (Primaxin), meropenem (Merrem), ertapenem (Invanz) and most recently, doripenem (Doribax). All drugs in this group have activity against the enteric gram-negative bacilli. Ertapenem does not have anti-*Pseudomonas* activity. Resistance (carbapenemases) among veterinary isolates has been very rare. Imipenem is administered with cilastatin to decrease renal tubular metabolism. Imipenem has become a valuable antibiotic because it has a broad spectrum that includes many bacteria resistant to other drugs. Imipenem is not active against methicillin-resistant staphylococci or resistant strains of *Enterococcus faecium*. The high activity of imipenem is attributed to its stability against most of the β-lactamases (including ESBL) and ability to penetrate porin channels that usually exclude other drugs (Livermore 2001). The carbapenems

are more rapidly bactericidal than the cephalosporins and less likely to induce release of endotoxin in an animal from gram-negative sepsis.

Some disadvantages of imipenem are the inconvenience of administration, short shelf-life after reconstitution, and high cost. It must be diluted in fluids prior to administration. Meropenem, a more recent generation carbapenem (some experts consider it a 2nd –generation penem) and has antibacterial activity greater than imipenem against some isolates. One important advantage over imipenem is that it is more soluble and can be administered in less fluid volume and more rapidly. For example, small volumes can be administered subcutaneously with almost complete absorption. There also is a lower incidence of adverse effects to the central nervous system, such as seizures. Based on pharmacokinetic experiments in our laboratory (Bidgood & Papich, 2002), the recommended dose for Enterobactericeae and other sensitive organisms in dogs is 8.5 mg/kg SC every 12hr, or 24 mg/kg IV every 12 hr. For infections caused by *Pseudomonas aeruginosa*, or other similar organisms that may have MIC values as high as 1.0 mcg/mL: 12 mg/kg q8h, SC, or 25 mg/kg q8h, IV. For sensitive organisms in the urinary tract, 8 mg/kg, SC, every 12 hours can be used. In our experience, these doses have been well-tolerated except for slight hair loss over some of the SC dosing sites. For cats, published studies recommend 10 mg/kg IM, SC, or IV (SC is easiest) every 12 hours.

Penicillin Drugs

Penicillin G and the amino-derivatives ampicillin and amoxicillin have little activity on gram-negative bacteria. This is true also for ampicillin-sulbactam (Unasyn) and amoxicillin-clavulanate (Clavamox) combinations. When resistance is encountered among Enterobcteriaceae, *Pseudomonas aeruginosa*, and other gram-negative bacteria, other penicllins can sometimes be useful.

This group includes the ureidopenicillins (mezlocillin, azlocillin, piperacillin) and the carboxylic derivatives of penicillin (carbencillin, ticarcillin). Ticarcillin and ticarcillin-clavulanate (Timentin) was once popular for use in many veterinary hospitals. However, this product has been removed from the market and is no longer available. The most consistently available drug, and one for which we have pharmacokinetic and susceptibility data to support the use is piperacillin-tazobactam (Piperacil, or "Pip-Taz"). This is a very active drug against a broad spectrum of bacteria, including ESBL. However, it has a very short half-life in dogs and must be given frequently (eg, 50 mg/kg every 6 hours IV) or via constant rate infusion (4 mg/kg IV loading dose, followed by 3.2 mg/kg per hour CRI). There are no orally effecive formulations in this class.

Aminoglycosides

Aminoglycosides, discussed in a previous section, are active against most wild-type strains of *Pseudomonas aeruginosa*. Against resistant isolates, amikacin and tobramycin are more active than gentamicin, and resistance is less likely to these drugs (Petersen et al, 2002). For *Pseudomonas aeruginosa,* tobramycin can be used as an alternative. Aminoglycosides are valuable for treating gram-negative bacilli that are resistant to other drugs. They are rapidly bactericidal, less expensive than injectable drugs listed above, and can be administered once-daily. Among these, amikacin and tobramycin are the most active and the first choice in small animal medicine when resistant or refractory infections are encountered. Both drugs are administered once-daily IV, IM, or SC. Important disadvantages to systemic use of aminoglycosides are the adverse effects (primarily kidney injury) that increases if treatment must

extend for at least two weeks or longer. Risk of nephrotoxicosis is greater with longer duration of treatment. To decrease the risk of drug-induced nephrotoxicosis, therapeutic drug monitoring and careful evaluation of renal function during its use is recommended. Activity of aminoglycosides is diminished in the presence of pus and cellular debris (Konig et al 1998). This may decrease their usefulness for the treatment of wound and ear infections caused by *Pseudomonas aeruginosa.*

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