Antibiotic Treatment of Resistant Infections in Small Animals

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KEYWORDS

• Antibiotics • Resistance • Infection • Small animals

KEY POINTS

- There are few veterinary clinical studies to support a recommended use and dose for treating drug-resistant infections in small animals and many of these details have been extrapolated from human medicine.
- If the organism is *Pseudomonas aeruginosa*, *Enterobacter* species, *Klebsiella* species, *Escherichia coli*, or *Proteus* species, resistance against many common antibiotics is possible and a susceptibility test is advised using Clinical and Laboratory Standards Institute standards.
- Infections caused by *P aeruginosa* presents a special problem because so few drugs are active against this organism.
- *Staphylococcus* isolated from small animals is most likely to be *Staphylococcus pseudintermedius* rather than *Staphylococcus aureus*.
- The most important resistance mechanism for *Staphylococcus* is methicillin resistance.
- Enterococci are gram-positive cocci that have emerged as important causes of infections, especially those that are nosocomial.
- Isolation of *Enterococcus* species from a site does not always indicate that treatment is needed.
- After a susceptibility report is available, the only antimicrobials to which some gram-negative bacilli are susceptible, including *P aeruginosa*, may be extended-spectrum cephalosporins, carbapenems (penems), selected penicillin derivatives, amikacin, or tobramycin.
- 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.
- 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 for treating these infections in people, but there has not been an equal response in veterinary medicine.

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INTRODUCTION

Treatment guidelines are established in textbooks and consensus documents available for treating routine infections in small animals. Dosage regimens have been established and drug manufacturers have produced several important drugs to treat these common infections encountered in small animals. But these regimens and approved antibiotics for animals are designed for susceptible (wild-type) infections and are often not active against bacteria that carry resistance mechanisms. When the patient has an infection that is refractory to treatment, and/or caused by a resistant organism, other strategies and drugs may be necessary. As with many new treatments, there are few veterinary clinical studies to support a recommended use and dose, and many of these details have been extrapolated from human medicine.

WHAT BACTERIA ARE LIKELY TO BE RESISTANT?

Resistant Gram-negative Bacteria

If the organism is *Pseudomonas aeruginosa*, *Enterobacter* species, *Klebsiella* species, *Escherichia coli*, or *Proteus* species, resistance against many common antibiotics is possible and a susceptibility test is advised using Clinical Laboratory Standards Institute (CLSI) standards.[1] For example, a report showed that among nonenteric *E coli* only 23% were sensitive to a first-generation cephalosporin and less than half were sensitive to ampicillin. In the same study, 13% and 23% were intermediate or resistant to enrofloxacin and orbifloxacin, respectively.[2] In urinary tract infections,[3] half of the *E coli* were resistant to cephalexin, and only 22% were susceptible to enrofloxacin. There was a high incidence of resistance in *E coli* isolates collected from different regions of the United States.[4] The multidrug-resistant (MDR) isolates comprised 56% of the resistant isolates and more than half of these were resistant to amoxicillin, amoxicillin-clavulanate, and enrofloxacin.

P aeruginosa

Infections caused by *P aeruginosa* present a special problem because so few drugs are active against this organism. *P aeruginosa* has an ability to develop resistance via its large genome and multiple mechanisms that produce resistance to the most commonly used antibiotics. Of the β-lactam antibiotics, a few are designated as anti-*Pseudomonas* antibiotics. Although extended-spectrum cephalosporins (second-generation or third-generation cephalosporin) usually are active against enteric gram-negative bacteria, they are not active against *P aeruginosa*. Ceftazidime, an injectable third-generation cephalosporin, is an exception because it has consistently shown activity against *P aeruginosa*.

In one published study, the in vivo activity was examined in 23 strains of *Pseudomonas*: 19 *P aeruginosa*, 3 *Pseudomonas fluorescens* and 1 *Pseudomonas* spp. The most effective antibiotics were tobramycin (100% susceptible), marbofloxacin (91.3%), and ceftazidime (91.3%). Ticarcillin and gentamicin showed good activity (86% and 65.2% respectively). Lower susceptibility was found with enrofloxacin (52.1%).[5] Isolates of *P aeruginosa* from otitis media showed that 97% were susceptible to ceftazidime, and 81% to carbenicillin.[6] Fewer were susceptible to enrofloxacin (51%) and gentamicin (68%). In a study that isolated *P aeruginosa* from the skin and ears of dogs, the pattern of resistance was similar.[7] There were no trends identified, and most isolates were susceptible to ciprofloxacin, piperacillin, ticarcillin, amikacin, and gentamicin (enrofloxacin was not tested). However, isolates from the ears tended to be more resistant than isolates from the skin, with lower susceptibility to topical drugs such as gentamicin.

Staphylococcus Species

Staphylococcus isolated from small animals is most likely to be *Staphylococcus pseudintermedius* rather than *Staphylococcus aureus*. (Previously identified *Staphylococcus intermedius* probably have been misidentified and are now referred to as *S pseudintermedius* by most laboratories.) When infection is caused by a typical wild-type strain, *S pseudintermedius* has a predictable susceptibility to β-lactamase–resistant β-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). *Staphylococcus* is also susceptible to oxacillin and dicloxacillin (even though these are not used commonly in small animal medicine). Previous reports of studies on *S pseudintermedius* have shown that, despite frequent use in small animals of the drugs mentioned earlier, the distribution of wild-type strains has remained consistent.[8,9] However, methicillin-resistant *Staphylococcus* species, especially *S pseudintermedius*, are being isolated with increased frequency from animals with skin infections.[10–12] These infections are not confined to dermatology. Orthopedic surgeons have also encountered these strains as a cause of postsurgical orthopedic infections.

Resistant mechanisms

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 multidrug resistant. 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.[13–17] Methicillin has replaced oxacillin for testing in laboratories and resistance to oxacillin is equivalent to methicillin resistance. If the pathogen is *S aureus*, the term methicillin-resistant *S aureus* (MRSA) can be applied. However, *S aureus* is an infrequent pathogen in dogs, and is only occasionally found in cats. Bacteria from dogs and cats are most likely *S pseudintermedius* and these strains are referred to as methicillin-resistant *S pseudintermedius* (MRSP).[18,19] Other *Staphylococcus* species also have been identified among veterinary isolates, including coagulase-negative *Staphylococcus*.

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 does not overcome methicillin resistance. However, these bacteria often carry coresistance to many other non–β-lactam drugs, including lincosamides (clindamycin, lincomycin), fluroquinolones, macrolides (erythromycin), tetracyclines, and trimethoprim-sulfonamides. In the report by Bemis and colleagues,[17] more than 90% of the methicillin-resistant isolates of *S pseudintermedius* also were resistant to more than 4 other drugs. The cause of the increased frequency of resistance has not been identified with certainty. Use of fluoroquinolones and cephalosporins in people has been linked to emergence of methicillin-resistant *S aureus*.[20–22]

Resistant Enterococcus

Enterococci are gram-positive cocci that have emerged as important causes of infections, especially those that are nosocomial. The most common species identified are *Enterococcus faecalis* and *Enterococcus faecium*. *E faecalis* is more common, but *E faecium* is usually the more resistant. Wild-type strains of enterococci may still be

susceptible to penicillin G and ampicillin, or amoxicillin, which is ordinarily the preferred first choice. However, the enterococci have an inherent resistance to cephalosporins and fluoroquinolones. These strains also are usually resistant to trimethoprim-sulfonamide combinations, clindamycin, and macrolides (erythromycin). Susceptibility test results for cephalosporins, β-lactamase–resistant penicillins (eg, oxacillin), trimethoprim-sulfonamide combinations, and clindamycin can give misleading results.[1] Even if isolates are shown to be susceptible to a fluoroquinolone, this class of drugs may not be a good alternative for treatment.

In human medicine, frequent use of fluoroquinolones and cephalosporins (both of which have poor activity against enterococci) has been attributed to emergence of a higher rate of enterococcal infections.[22] Evidence to document this trend is limited in veterinary medicine, but one study from a veterinary teaching hospital indicated an increased rate of enterococcal urinary tract infections.[23]

Isolation of *Enterococcus* species from a site does not always indicate that treatment is needed. If there is no evidence of clinical signs, such as asymptomatic bacteriuria, treatment may be withheld and the patient simply monitored. The low pathogenicity of *Enterococcus* may not justify the risks and expense of antibiotic treatment. When enterococci are present in wound infections, lower urinary tract, peritoneal infections, and body cavity infections (eg, peritonitis), the organism may exist with other bacteria such as gram-negative bacilli or anaerobic bacteria. In these cases, there is evidence that treatment should be aimed at the anaerobe and/or gram-negative bacilli and not directed at the *Enterococcus*. Treatment cures are possible if the other organisms are eliminated without specific therapy for *Enterococcus*.[24]

If treatment is needed, selection of the appropriate agent for *Enterococcus* is frustrating because there are so few drug choices. If possible, the clinician should be guided by a valid culture and susceptibility test performed using the standards listed by the CLSI.[1] If the *Enterococcus* isolated is sensitive to a penicillin, amoxicillin or ampicillin should be administered at the high -end of the dose range. When possible, combine an aminoglycoside with a β-lactam antibiotic for treating serious infections. One of the carbapenems (imipenem-cilastatin) or an extended-spectrum penicillin (eg, piperacillin) can occasionally be considered for treatment of *E faecalis* (but not *E faecium*).

For resistant strains, selecting the appropriate antibiotic is difficult because of the unpredictable nature of these strains. As mentioned later, sometimes the only active drug is chloramphenicol, a glycopeptide (vancomycin), or the oxazolidinone linezolid. Dosage regimens and problems associated with these agents have been discussed in other sources.[25–27]

DRUG CHOICES FOR RESISTANT GRAM-NEGATIVE INFECTIONS

A susceptibility report may show that the only antimicrobials to which some gram-negative bacilli, including *P aeruginosa*, are susceptible are extended-spectrum cephalosporins, carbapenems (penems), selected penicillin derivatives, amikacin, or tobramycin.

Cephalosporins

When injectable cephalosporins are considered for resistant infections in small animals, those most often used are cefotaxime and ceftazidime, although individual veterinary hospitals have used others in this group. Ceftriaxone is a commonly used third-generation cephalosporin in people. It has high protein binding in people (95%), and a long half-life (8 hours) that allows once-daily convenient dosing. However, the protein binding in dogs is lower (25%) and the short half-life (approximately

1 hour) does not confer any advantage compared with other drugs in this group. Ceftiofur is popular for use in large animals, but is not suitable for resistant infections in small animals. Its only approval in small animals is for urinary tract infections in dogs. Effective concentrations are attained only in urine, and high doses can produce adverse effects in dogs.

In general, the third-generation cephalosporins are expensive, and must be injected. These drugs are usually given via the intravenous (IV) route, although subcutaneous (SC), and intramuscular (IM) routes have been used. As with the penicillins, frequent administration is necessary (for example, every 6–8 hours in animals with normal kidney function) because of their time-dependent activity and short half-lives. Dosage regimens have been published in other sources.[25,26] Of the cephalosporins, only the third-generation cephalosporins, ceftazidime (Fortaz, Tazidime), cefoperazone (Cefobid), or cefepime (Maxipime), a fourth-generation cephalosporin, have predictable activity against *P aeruginosa*. Ceftazidime has greater activity than cefoperazone and is the one used most often in veterinary medicine. Cefoperazone is no longer marketed.

Cefpodoxime and Cefovecin

Cefpodoxime is more active than many other third-generation cephalosporins against *Staphylococcus*, and pharmacokinetic properties allow once-daily dosing.[28] However, it is not active against *P aeruginosa*, *Enterococcus*, or methicillin-resistant *Staphylococcus*. Examination of wild-type distributions[29] also indicates that it is not a true third-generation cephalosporin in terms of activity against Enterobacteriaceae (for example *E coli*). The minimum inhibition concentration (MIC) for cefpodoxime is 8-fold higher than that for cefotaxime and 4-fold higher than that for ceftazidime against wild-type strains of *E coli* (wild-type cutoff values).

In the spring of 2008, cefovecin (Convenia) was registered by the US Food and Drug Administration (FDA) Center for Veterinary Medicine for use in dogs and cats for treatment of routine skin infections, and previously had been approved in other countries for routine skin infections and urinary tract infections. There have been pharmacokinetic studies published for dogs and cats,[30,31] pharmacodynamic studies published,[32] and clinical efficacy studies in dogs and cats.[33–36] In the clinical studies, cefovecin was compared with another active antimicrobial (cefadroxil, cephalexin, or amoxicillin-clavulanate) and was noninferior to these other drugs.

There are currently no CLSI-approved standards for susceptibility testing established for cefovecin.[1] Based on the distribution of organisms reported,[32] less than or equal to 2.0 μg/mL should be considered for a susceptible breakpoint. It has acceptable activity against wild-type strains of *Staphylococcus* species and gram-negative bacteria of the Enterobacteriaceae (eg, *E coli*, *Klebsiella*). However, activity against *P aeruginosa* is poor and it is not effective against methicillin-resistant staphylococci.

Even though cefovecin is classified as a third-generation cephalosporin based on structure, it is not as active against gram-negative bacteria as the other third-generation cephalosporins. It should not be regarded as a drug to use for bacteria that have already shown resistance to other agents. Although it had greater activity against gram-negative bacteria, as demonstrated by the MIC_{90} (MIC required to inhibit the growth of 90% of organisms) values of 1 μg/mL, compared with 16 μg/mL for cephalexin and cefadroxil,[36] other third-generation cephalosporins (eg, ceftazidime, cefotaxime) are more active and have lower MIC values. Moreover, the free (protein unbound) plasma concentrations of cefovecin are not sustained highly enough throughout the dose interval to be considered for treatment of systemic infections against gram-negative bacilli.

Based on these observations, although cefovecin and cefpodoxime are technically considered third-generation cephalosporins, the activities of cephalosporins within these arbitrary generations are not always similar. Cefovecin and cefpodoxime are not as active against gram-negative bacteria as injectable third-generation cephalosporins used in human medicine, such as ceftazidime or cefotaxime.

Carbapenems

The β-lactam antibiotics with greatest activity against *P 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 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 *E faecium*. The high activity of imipenem is attributed to its stability against most of the β-lactamases (including extended spectrum β-lactamase) and ability to penetrate porin channels that usually exclude other drugs.[37] 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 before administration. Meropenem, a more recent carbapenem (some experts consider it a second-generation penem) and has antibacterial activity greater than imipenem against some isolates. One important advantage compared with imipenem is that it is more soluble and can be administered in a smaller 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,[38] the recommended dose for Enterobacteriaceae and other sensitive organisms is 8.5 mg/kg SC every 12 hours, or 24 mg/kg IV every 12 hours. For infections caused by *P aeruginosa* or other similar organisms that may have MIC values as high as 1.0 μg/mL, the dose is 12 mg/kg every 8 hours, SC, or 25 mg/kg every 8 hours, IV. For susceptible 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.

Penicillins

Penicillin derivatives with activity against *P aeruginosa* and the Enterobacteriaceae include the ureidopenicillins (mezlocillin, azlocillin, piperacillin) and the carboxylic derivatives of penicillin (carbenicillin, ticarcillin). These derivatives are available as sodium salts for injection; there are no orally effective formulations in this class, except indanyl carbenicillin (Geocillin, Geopen), which is poorly absorbed and not useful for systemic infections. These drugs are more expensive than the more commonly used penicillins, and must be administered frequently (eg, at least 4 times daily in patients with normal kidney function) to be effective. Dosage regimens for these drugs have been published in other sources.[25,26] Ticarcillin is usually administered in combination with the β-lactamase inhibitor clavulanic acid (Timentin). Because these drugs degrade quickly after reconstitution, observe the storage recommendations on the package insert to preserve the drug's potency.

Fluoroquinolones

Once a resistant strain of the Enterobacteriaceae (eg, *E coli*, *Klebsiella pneumoniae*) has been identified, the fluoroquinolones are rarely an available choice for treatment.[39] These strains are usually multidrug resistant and susceptibility to fluoroquinolones is unlikely. In addition, fluoroquinolone activity may be especially unpredictable if the patient has previously been treated with this class of agents. Previous exposure to fluoroquinolones may select for resistant strains of *E coli* in dogs that can persist long after drug treatment has been discontinued.[40]

In some cases, a fluoroquinolone may be active against *P aeruginosa*. When administering a fluoroquinolone to treat *P aeruginosa*, the high end of the dose range is suggested because even among wild-type strains the MIC values are higher than for other gram-negative bacteria. Of the currently available fluoroquinolones (human or veterinary), ciprofloxacin is the most active against *P aeruginosa*, followed by marbofloxacin, enrofloxacin, difloxacin, and orbifloxacin.[41,42] Note that this ranking applies to in vitro activity (comparison of MIC values) and does not attempt to predict the comparative efficacy of these drugs. Ciprofloxacin oral absorption can be unpredictable in dogs and there is no assurance that effective concentrations will be achieved after oral administration.[43] Ciprofloxacin is poorly absorbed from oral administration in cats and is not expected to attain effective concentrations.[44]

Aminoglycosides

Aminoglycosides are active against most wild-type strains of *P aeruginosa*. Against resistant isolates, amikacin and tobramycin are more active than gentamicin, and resistance is less likely to these drugs.[7] When availability of amikacin has been limited, veterinarians have used tobramycin as an alternative. Aminoglycosides are valuable for treating gram-negative bacilli that are resistant to other drugs. They are rapidly bactericidal, less expensive than the injectable drugs listed earlier, 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 can be administered once daily IV, IM, or SC.

There are 3 disadvantages to systemic use of aminoglycosides[45]: (1) when treatment must extend for 2 weeks or longer, the risk of kidney injury is greater with longer duration of treatment. (2) They must be injected (except for topical uses), which some pet owners are reluctant to perform. (3) Activity of aminoglycosides is diminished in the presence of pus and cellular debris,[46] which may decrease their usefulness for the treatment of wound and ear infections that are characterized by this environment, such as infections caused by *P aeruginosa*. Strategies to decrease the risk of drug-induced kidney injury from aminoglycosides are discussed later in this article.

DRUG CHOICES FOR METHICILLIN-RESISTANT *STAPHYLOCOCCUS* AND RESISTANT *ENTEROCOCCUS* SPECIES

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. Chloramphenicol, tetracyclines, aminoglycosides (gentamicin, amikacin), and rifampin are drugs to consider for these infections if a susceptibility test can confirm activity. These drugs are discussed in more detail elswhere[27] and briefly later in this article. Unlike the human strains of community-acquired *S aureus*, the veterinary strains of MRSP are usually not susceptible to trimethoprim-sulfonamides, clindamycin, or fluoroquinolones.[17,47] However, a susceptibility test should always be used to confirm whether or not these drugs may have activity against isolates from animals. The use

of these medications in veterinary dermatology has been discussed previously.[48–50] Most staphylococci are also susceptible to nitrofurantoin, but this drug is used only for urinary tract infections. Topical drugs also should be considered for treatment of localized infections. These drugs (eg, mupirocin or fusidic acid) are available in topical ointments and have been used in dogs and cats.

Rifampin (Rifampicin)

Rifampin, also known in some countries as rifampicin, is an old 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*. Small animal veterinarians are now being introduced to this antibiotic because of its activity against methicillin-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 United States Pharmacopeia official name, and rifampicin is the International Nonproprietary Name and British Approved Name; the names are synonymous. Rifamycin and rifabutin are structurally similar antibiotics(they are in the group of rifamycins) but they 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 most animal species studied. The intracellular penetration has made this drug valuable for treating intracellular bacteria in people and animals, including *Mycobacterium* and *R equi*. Rifampin is active against most strains of MRSP,[47] although resistance among canine isolates has been identified.[51] Rifampin has been effective for treatment of canine pyoderma caused by *S pseudintermedius* at a dose of 5 mg/kg once daily for 10 days.[52] A dose of 10 mg/kg per day, usually split into 2 doses 12 hours apart, has been recommended,[26,27] although some veterinary formularies have recommend a much higher dose.

Resistance occurs through mutations and clonal spread of a resistant strain. To reduce the rate of mutation, combination therapy with other agents has usually been recommended in human guidelines,[53] as was the recommendation from a veterinary study.[51] However, experimental infections caused by *Staphylococcus* have been successfully treated with rifampin monotherapy.[54] In a review of the evidence from clinical trials of eradication of *S aureus* in humans, rifampin was also an effective agent for eradication of *S aureus*, whether administered as monotherapy or as a combination.[53] Addition of a second antibiotic did not seem to confer additional effectiveness to rifampin monotherapy for eradication of methicillin-resistant *Staphylococcus*. As the investigators 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."

Interactions and adverse effects

Rifampin is a strong inducer of drug metabolizing enzymes. According to one article, "The list of drugs that interact with rifampin is remarkably long."[55] Induction can significantly increase the metabolism and clearance of other coadministered drugs that are affected by these proteins. The consequence of induction is diminished effect of the coadministered drug and it may require a higher dose or more frequent administration. For example, rifampin coadministration significantly affects the exposure to prednisolone.[56] In people, 4 weeks are required for full recovery of the rifampin effect after discontinuation.[54,55] 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 gastrointestinal disturbance. In dogs, hepatotoxicosis is the most common adverse reaction and 20% to 26% of dogs receiving 5 to 10 mg/kg develop increases in liver enzymes, and some develop hepatitis. Dogs seem to be more susceptible to liver injury than humans. To avoid adverse effects, it is recommended not to exceed a dose of 10 mg/kg per day and periodically monitor liver enzymes. 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)

Some MRSP are susceptible to tetracyclines. Because the choice of oral tetracyclines is limited for small animals, either doxycycline or minocycline should be used. Both are at least as active, and perhaps more active in vitro, against *Staphylococcus* species.

Doxycycline

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.[57]

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. Its oral absorption is not affected by administration of sucralfate, compared to other tetracyclines. It has been mixed with chocolate milk for administration to children with no interference with absorption.

An adverse reaction associated with doxycycline hyclate is injury to the esophagus from a broken tablet or incompletely dissolved capsule. This reaction has been documented in cats and is probably the result of the hydrochloride (HCl) contact with the esophageal mucosal owing to slow transit through the esophagus. This problem has been primarily associated with doxycycline hyclate (the form most common in the United States), rather than doxycycline monohydrate.

This reaction can be alleviated by administration of oral doxycycline hyclate with a water flush or immediate feeding to ensure that the medication passes to the stomach.

Minocycline

Minocycline can be considered as an alternative if doxycycline is not available. Minocycline is at least as active against bacteria as other tetracyclines. There has been not been as much clinical experience with minocycline as with doxycycline; however, it may be acceptable when other alternatives are not available.

Only limited susceptibility data for minocycline are available, but it is likely that some isolates of MRSP may be susceptible to minocycline even though they are resistant to other tetracyclines. It depends on whether or not the bacteria carries the tet(M) resistance or just the tet(K) resistance. *Staphylococcus* strains that are tetracycline resistant because of efflux mediated by *tet*(K) may still be susceptible to minocycline; however, resistance caused by the ribosomal protection mechanism *tet*(M) produces cross-resistance to both doxycycline and minocycline. Published data so far on activity of minocycline against resistant strains from animals[58] and some other preliminary data are encouraging.

In humans, minocycline is rapidly and almost completely absorbed after oral administration. In people, it is 75% protein bound, has a volume of distribution (V_d) of 1.17 L/kg and has a half-life ($t_{1/2}$) of 15 to 19 hours. Between 5% and 12% of the minocycline dose is recovered in urine. Details of the oral pharmacokinetics have not been reported for dogs. Protein binding is reported to be 75% in dogs,[59] which is lower than for doxycycline, but this value was from an unreferenced source, and more recent studies indicate that protein binding in dogs may be only 50–60%. From the published study of IV minocycline in dogs,[60] it had a terminal half-life of approximately 7 hours, which is less than half of the value reported for people. The V_d was greater than 2 L/kg in dogs, which is almost twice that of people. Both of these values suggest that extrapolation of doses from people is likely to be ineffective.

The extent of oral absorption in dogs or cats is not known. In people it is almost complete. However, if oral absorption is calculated based on area-under-the-curve (AUC) values provided in a previous study,[61] it suggests a much lower oral absorption rate in dogs than in people: only 20%. Only 2.2% of the oral dose was excreted in the urine. Minocycline seems to be safe in dogs. In the previously cited study,[61] dogs tolerated 30 mg/kg per day for 30 days, and did not see adverse effects until doses were increased to 40 mg/kg. However, there are anecdotal accounts of gastrointestinal upset from minocycline in dogs at therapeutic doses.

Because of the shortage of data on minocycline, the most effective dose is not known. But if 1 the V_d, protein binding, half-life, clearance, and AUC/MIC target are considered, an approximate dose is 5–10 mg/kg every 12 hours.

For either doxycycline or minocycline, the current CLSI breakpoint to determine susceptibility is not recommended.[1] The doxycycline breakpoint for humans is less than or equal to 4 μg/mL, which is probably too high for dogs. It is likely much lower, and less than or equal to 0.12 μg/mL is more reasonable based on MIC distributions and pharmacokinetic/pharmacodynamic (PK/PD) data. The equivalent breakpoint for susceptible bacteria if tetracycline is used for testing is less than or equal to 0.5 μg/mL. It is difficult to attain the AUC/MIC target using a breakpoint of 4 μg/mL; a lower breakpoint is recommended. CLSI may consider a veterinary-specific breakpoint at a later time.

Chloramphenicol

Chloramphenicol was popular decades ago, but its use diminished in the 1970s and 1980s because other active and safer drugs became available. The small animal formulation is approved by the FDA (Chloromycetin) but is not actively marketed. Chloramphenicol has the disadvantage of a narrow margin of safety in dogs and cats, and the necessity of frequent administration in dogs to maintain adequate concentrations (3 or 4 times daily oral administration). These disadvantages still exist, but the activity of chloramphenicol against bacteria (eg, staphylococci and enterococci) that are resistant to other oral drugs has created increased use of chloramphenicol in recent years. Florfenicol (Nuflor), an injectable alternative for cattle and pigs, is cleared so rapidly in dogs that frequent high doses are necessary. There is no oral formulation of florfenicol for dogs and effective clinical doses have not been established.

Chloramphenicol has FDA approval 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.

Dose recommendations

Plasma concentrations of chloramphenicol were published in several studies and summarized in a review.[27] Using Monte Carlo simulations and available pharmacokinetic parameters, a dose of 50 mg/kg by mouth to dogs, every 8 hours attains antibacterial concentrations greater than the MIC value of 8 μg/mL in most animals. There is some evidence that chloramphenicol may be more bactericidal against *Staphylococcus* than previously thought.

Adverse effects and interactions

Significant disadvantages of chloramphenicol are adverse effects and drug interactions. As cited earlier, chloramphenicol has a narrow margin of safety. The recommend dose of 50 mg/kg every 8 hours in dogs frequently produces gastrointestinal problems. High doses easily produce toxicity in dogs.[62] 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 is possible from exposure to people, but has not been described in animals. The incidence of aplastic anemia 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 human exposure does not occur at home.

Chloramphenicol is notorious for producing drug interactions. Chloramphenicol is an inhibitor of cytochrome P450 CYP2B11, and possibly other enzymes, in dogs.[63,64] Therefore, chloramphenicol can decrease the clearance of other drugs that are metabolized by the same metabolic enzymes. Chloramphenicol inhibits the metabolism of opiates, barbiturates, propofol, phenytoin, salicylate, and perhaps other drugs.[64–67]

A previously unrecognized problem is the association between chloramphenicol administration and neurologic problems in dogs. In some dogs (some anecdotal accounts indicate that large breeds are more susceptible) reversible neurologic deficits are possible, which manifest as paresis, ataxia, and hind limb dysfunction. The mechanism for this reaction is unknown.

Aminoglycosides (Gentamicin, Amikacin)

Aminoglycosides (specifically amikacin and gentamicin) have consistent in vitro activity against *Staphylococcus*, including methicillin-resistant strains of *S pseudintermedius*. The disadvantages of aminoglycosides were discussed earlier in this article. Because oral absorption is not possible, these agents must be administered by injection and there is a potential for kidney injury in animals from prolonged use. The risk of kidney injury is higher if animals have prior evidence of kidney disease.[45]

Aminoglycosides are rapidly bactericidal and can be administered once daily.[68] In hospital, the route is usually IV, but dog and cat owners have been trained to administer SC or IM injections at home. Because these are water-soluble formulations, they are well absorbed from SC and IM injection sites, although these routes may produce pain in some patients. Gentamicin also is a component of many topical formulations used for skin infections.

For gentamicin, the current CLSI breakpoint for susceptible bacteria[1] is less than or equal to 2 μg/mL for gram-negative bacteria (assuming a dose of 10 mg/kg every 24 hours), but these values are probably appropriate for *Staphylococcus* species as well. There is no veterinary-specific breakpoint for amikacin. The human CLSI susceptibility breakpoint for amikacin is less than or equal to 16 μg/mL,[1] but most veterinary

isolates are probably less than or equal to 4 μg/mL. Activity of aminoglycosides is diminished in the presence of pus and cellular debris,[46] which may be important for some skin infections. These conditions may decrease the usefulness for the treatment of wound and ear infections.

Although aminoglycosides have in vitro activity against *Staphylococcus* and *Enterococcus*, their clinical efficacy as single agents for treating infections caused by these organisms in animals has not been reported. These drugs are usually considered excellent bactericidal drugs for gram-negative bacilli, but clinical efficacy for gram-positive cocci is less certain. In addition to their effect on bacterial ribosomes, an additional (and perhaps more important) mechanism is that these agents act to disrupt the cell surface biofilm, particularly on gram-negative bacteria, to produce disruption, loss of cell wall integrity, and a rapid bactericidal effect. This property is not as prominent for gram-positive bacteria and these drugs are not as active against gram-positive bacteria unless administered with a cell wall disrupting agent such as vancomycin or a β-lactam antibiotic.

Adverse effects

The most serious toxic effect associated with aminoglycoside therapy is kidney injury.[45] Toxicity initially affects the renal proximal tubules because of active uptake in these cells. The entire nephron can eventually be affected. Animals that are dehydrated, have electrolyte imbalances (for example low Na^+ or K^+), are septicemic, or have existing renal disease are at a higher risk for toxicity than healthy animals. Kidney injury is attributed to persistent drug levels (especially high trough concentrations) throughout the dose interval. Therefore, extended once-a-day dosing intervals decrease risk of kidney injury.[68]

Glycopeptides (Vancomycin)

Of the glycopeptides, vancomycin is the only one used in veterinary medicine. Although vancomycin is an old drug, it is unfamiliar to most veterinarians. It is difficult to administer to small animals because of the need to administer IV and the requirement for a slow infusion. Despite is long history of use in people, there are uncertainties and better alternatives are being sought.[69] Resistance to vancomycin among *S aureus* is rare, but MIC values may be shifting higher. Resistance among *S pseudintermedius* has not been reported. Vancomycin-resistant enterococci are an important problem in human medicine but are rare in veterinary medicine.

Dosing regimens

Vancomycin is 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. IM administration is painful and irritating to tissues. The usual dosage for small animals is 15 mg/kg every 8 hours, IV, via slow infusion. Therapeutic drug monitoring can be performed to ensure that trough concentrations are maintained at more than 10 μg/mL for skin and soft tissue infections.

Adverse effects

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 were reported. Newer formulations are safer because impurities have been removed.

Some New 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 for people, but there has not been a similar response for treating resistant infections in animals. These drugs are generally expensive, and most of them must be administered by the IV 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 glycopeptide; 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. There are no veterinary drugs in this class. It is used in people to treat methicillin-resistant *Staphylococcus* and vancomycin-resistant gram-positive infections caused by enterococci and streptococci. It has excellent activity against staphylococci and enterococci. Resistance has been documented,[70] 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.

Pharmacokinetics and dosing

Linezolid is absorbed orally and also can be administered intravenously. Oral absorption is practically 100% in all animals tested,[71] and is not affected by food. Linezolid is metabolized similarly across species[71] and pharmacokinetic parameters scale allometrically across species, allowing accurate prediction of doses for both dogs and cats of approximately 10 mg/kg twice daily.[72]

Clinical use in animals

Because of the high expense, linezolid has been used infrequently in veterinary medicine, and probably will remain a rarely used medication. Its use at this time has only been reported in unpublished anecdotal canine and feline cases, which have responded with good outcomes.

Adverse effects

Toxicokinetic studies in dogs at high doses showed that linezolid was well tolerated and did not accumulate.[71] Linezolid is a mild, reversible inhibitor on monoamine oxidases A and B. In the 10 years of clinical use of linezolid in people, these theoretic 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.

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