ANTIBIOTICS

Fluoroquinolones

The fluoroquinolone class of antibiotics work via inhibition of DNA gyrase (topoisomerase II). Resistance is mediated through chromosomal mutations in DNA gyrase which confers cross-resistance to other FQs. FQs distribute well to tissues and intracellularly. Elimination is via the kidney, and these drugs are often highly effective for treating resistant UTIs. The spectrum of activity includes Gram-negative bacteria and staphylococci.

Enrofloxacin, and to a lesser extent marbofloxacin and orbifloxacin, continue to be used in horses. Ciprofloxacin pharmacokinetics were investigated following IV and oral administration to adult horses. This study confirmed the previously reported low oral bioavailability of the drug (avg 10.5%), and it also elucidated numerous adverse effects associated with both oral and IV administration, including mild transient diarrhea to severe colitis, endotoxemia and laminitis necessitating euthanasia of three out of the 8 study horses. Other adverse effects associated with IV administration were agitation and excitement followed by lethargy, sweating, muscle fasciculation, increased flehmen response, lip smacking, periorbital edema, patchy edema involving the face, neck and/or cranial thorax, and transient loss of appetite. The conclusions of this study were that the high incidences of adverse events preclude oral and rapid IV administration of ciprofloxacin. Levofloxacin pharmacokinetics have also been studied in stallions. Levofloxacin is the active enantiomer of ofloxacin, and has increased activity against topoisomerase IV. Bioavailability after IM administration approached 100% and IV or IM administration produced plasma concentrations expected to be therapeutic for bacteria with MICs ≤ 0.1 µg/mL following a dose of 4 mg/kg. Danofloxacin at 5 mg/kg IV or IM may also be considered as a potential therapeutic for MICs ≤ 0.25 µg/mL.

Macrolides and Derivatives

The macrolide antibiotics are considered bacteriostatic, and work through inhibition of protein synthesis at the level of the 50s ribosomal subunit. Due to their high intracellular concentrations, these drugs are most frequently used for the treatment of intracellular pathogens such as Rhodococcus equi and Lawsonia intracellularis. Erythromycin is the prototypical macrolide, however, it has many disadvantages, including adverse GI effects, poor bioavailability, and a short half-life. Newer drugs have been developed that have better pharmacokinetic properties, improved spectrum of activity, and are better tolerated. Clarithromycin exhibits a broader spectrum of activity, better tolerability and higher intracellular accumulation than erythromycin. Azithromycin has a similar Gram-positive spectrum as erythromycin, but it has some activity against anaerobes and other intracellular bacteria, better oral absorption, and persistence in the tissues and cells.

Tilmicosin, a cattle and swine antibiotic, is not advisable to use in the horse due to negligible oral absorption, severe injection site reactions following subcutaneous administration, and cardiotoxicity after intravenous administration. Tulathromycin, another cattle and swine antibiotic, has also been studied in foals. Although the pharmacokinetics are favorable, with a
long half-life, large volume of distribution, and accumulation in BAL cells, this drug has been determined not to be effective in the case of *R. equi* pneumonia, due to the inherent resistance of *R. equi* to the drug (MIC$_{90}$ > 64 µg/mL).

The pharmacokinetics of clarithromycin have been investigated in foals and a dose of 7.5 mg/kg orally q12h is suggested for the treatment of *R. equi* pneumonia. Based on pharmacokinetic data and anecdotal clinical experience, veterinarians have used azithromycin in foals at a dose of 10 mg/kg once daily initially, followed by 10 mg/kg orally every other day after clinical improvement is observed. Clinical experience with azithromycin and clarithromycin in the field indicates that they are safe for use in foals for the treatment of *R. equi* or *L. intracellularis* infections. However, given the chronic nature of these diseases and the need for extended treatment, another drug, gamithromycin, has recently been evaluated. A single dose of gamithromycin (6.6 mg/kg IM) maintained PELF concentrations above the MIC$_{90}$ for *S. zooepidemicus* and phagocytic cell concentrations above the MIC$_{90}$ for *R. equi* for approximately 7 days. Clinical efficacy and safety of this drug have not been reported, however it has recently been approved for use in cattle in the United States. Due to the increase in resistance of *R. equi* to macrolide antibiotics over the last 10 years, another drug, telithromycin, has been studied.

Typically, macrolide antibiotics are not used in adult horses, due to the risk of antibiotic associated colitis. However, azithromycin has been used clinically by the author in a limited number of cases with no severe adverse effects, and the pharmacokinetics and safety have been study in the adult horse. Bioavailability was similar to foals, however a dose of 10 mg/kg PO q24h produced mild decreases in appetite and alterations in fecal consistency in some horses. Therefore, the safety of this compound in this age of horse needs further investigation.

**Rifampin**

Rifampin inhibits DNA-dependent RNA polymerase in susceptible organisms, suppressing RNA synthesis. It has no effect on the mammalian enzyme. Its action is bacteriostatic or bactericidal depending on the susceptibility of the bacteria and the concentration of the drug. Bacterial resistance to rifampin develops rapidly, therefore it is usually administered with another antimicrobial. However, recent evidence suggests that co-administration of rifampin with other macrolide antibiotics may result in the decreased bioavailability of the macrolide. Both tulathromycin and clarithromycin have been shown to have a significantly reduced bioavailability.

**β-lactam Antibiotics**

The β-lactam antibiotics include the penicillins, cephalosporins and carbapenems. They have excellent activity against most Gram-positive bacteria, and very few associated side effects. They are considered bactericidal and time-dependent. Post-antibiotic effects have been associated with some drugs in this class. The mechanism of action involves penetration of the outer cell wall and binding to penicillin binding proteins (PBP). This interferes with cell wall synthesis and opens channels through the cell wall to create pores that allow fluid into the cell, causing cell swelling and death. In general, the beta-lactam antibiotics have low plasma protein binding, distribute well to the extracellular fluid in most tissues, and are excreted renally. With a few exceptions, they have a very short half-life and require frequent dosing. Beta-lactams do not distribute well to protected sites, such as the CNS, the eye or the prostate.

The cephalosporin antibiotics have many advantages in animals, including a broad spectrum of activity and a good safety profile. Oral absorption of first-generation cephalosporins is somewhat limited, but this route can be used in some cases, as with cephalexin. Perhaps the
most frequently used cephalosporin in horses is ceftiofur. Ceftiofur was approved for use in horses for treatment of respiratory tract infections caused by *Streptococcus equi* subsp. *zooepidemicus* at a dose of 2.2 to 4.4 mg/kg q24h IM. Higher doses or more frequent intervals have been recommended for treating gram-negative organisms (e.g., Klebsiella, Enterobacter, Salmonella). In septic neonatal foals, doses as high as 10 mg/kg IV q6h have been used. However, more recent studies in foals have shown lower doses (5 mg/kg IV, SC q12h) are sufficient for the treatment of most bacteria cultured from septic neonates (MIC<sub>90</sub> < 0.5 µg/mL). Constant rate infusion of ceftiofur has also been shown to be safe in foals at doses up to 20 mg/kg/day. This dose rate is adequate for the treatment of bacteria with MICs up to 4 µg/mL. Toxicity studies have shown that horses tolerate ceftiofur doses up to 11 mg/kg/day IM, with pain at the injection site and decreased feed consumption as the most common adverse effect at the highest dose.

A new formulation of ceftiofur has been approved for use in horses (ceftiofur crystalline free acid (CCFA), Excede®). This formulation is designed to provide 10 days worth of therapeutic concentrations against streptococci (MIC < 0.2 µg/mL) following a 2 dose regimen (6.6 mg/kg IM, repeated 96 hours later). The main adverse effect associated with this formulation has been injection site reactions, which can be minimized by splitting the dose into two different injection sites. Prolonged dosing regimens for treatment of streptococci are 6.6 mg/kg IM on day 1 and 4, then every 7 days after. For more resistant bacteria (MIC ≤ 1 µg/mL), the recommended dosing regimen is 6.6 mg/kg IM every 4 days. All of the above regimens are for adult horses, as the pharmacokinetics differs in foals. Administration at a dose of 6.6 mg/kg body weight SC every 72 h would provide protection against bacteria isolated from neonatal foals, based upon an MIC of 0.5 µg/mL, and SC administration resulted in minimal injection site inflammation. Weanling age foals (4-6 months old) also exhibit different pharmacokinetics, including higher peak plasma concentrations and area under the curve compared to adults, however these differences were not significant enough to necessitate a difference in dosing regimen. Therefore, administration of 6.6 mg/kg IM in weanling foals provided plasma and PELF concentrations above the therapeutic target of 0.2 µg/mL for at least 4 days and would be expected to be an effective treatment for pneumonia caused by *Streptococcus equi* subsp. *zooepidemicus* at doses similar to the adult label.

An ester formulation of cefpodoxime, cefpodoxime proxetil, has been examined for use in horses. Cefpodoxime has higher activity against Gram-negative bacteria than first-generation cephalosporins and is more active than many other third-generation cephalosporins against *Staphylococcus*. However, it is not active against *Pseudomonas aeruginosa*, enterococci, or MRSA. In a study in horses and foals, oral absorption was good enough that a dose of 10 mg/kg q6-12h produced plasma concentrations that would potentially treat infections in horses.

The carbapenems are the newest class of β-lactam antimicrobials. They have an extended spectrum of activity, including Gram-negatives, and are associated with more of a post-antibiotic effect. Clinical use in horses is limited due to cost, however imipenem has been used in foals at a dose of 5 mg/kg IV infused over 20 minutes q6-8h. The author has used meropenem in adult horses. Due to its short half-life, a constant rate infusion of 10 µg/kg/min (15 mg/kg/day) is recommended.

**Aminoglycosides**

The aminoglycosides include gentamicin, tobramycin, and amikacin. Among these, gentamicin and amikacin are used most often in horses, with amikacin often preferred in
neonates. Aminoglycosides are considered the drug of choice for severe gram-negative infections. They also have activity against staphylococci. Their primary mechanism of action includes binding to the 30S ribosomal subunit causing the formation of nonfunctional proteins. Aminoglycosides have high water solubility, low protein binding and poor oral absorption. They distribute well to the extracellular fluid, but do not penetrate intracellularly or into the CNS, eye or prostate. Aminoglycosides have a long post-antibiotic effect, allowing for once daily dosing which is important in preventing toxicity. These drugs are excreted via glomerular filtration; they are also reabsorbed/sequestered in the proximal tubular epithelium.

A study investigating the disposition of amikacin in adult horses showed that a daily dose of 10 mg/kg IV distributed well into extracellular fluids, including peritoneal fluid, synovial fluid and interstitial fluid, and would be expected to be therapeutic against bacteria with an MIC of \( \leq 4 \) \( \mu \)g/mL. This dose is much lower than that recommended for foals (20-25 mg/kg), mainly due to differences in total body water content resulting in a larger volume of distribution in foals. Similarly, doses of gentamicin vary between adult horses (4-6.6 mg/kg/day) and foals (8-12 mg/kg/day). Recent shortages in drug availability of amikacin have led to an increased use of tobramycin in horses. A daily dosing regimen of 4 mg/kg IV has been found to be effective. The author has also administered the drug intramuscularly and intra-articularly with no adverse effects.

Tetracyclines

Tetracyclines are considered broad spectrum and have activity against gram-positive and gram-negative bacteria, Chlamydia, rickettsia, spirochetes mycoplasma, and some protozoa. Of this group, doxycycline is the most active. The mechanism of action involves binding to the 30S ribosomal subunit and blocking protein synthesis. This binding is reversible, making tetracyclines bacteriostatic. Resistance is widespread among staphyclococci, streptococci, *Pseudomonas* sp, and Enterobacteraceae. Enterococci are not susceptible to tetracyclines. Resistance is plasmid-mediated, and relates to a failure of the active transport system necessary to penetrate the bacterial cell.

Oral absorption of the tetracyclines can be erratic, since these drugs are excellent chelators, and cations in the stomach can bind the drugs and prevent oral absorption. Tetracyclines distribute well to most tissues, with the exception of the CNS and the eye, and are mainly eliminated by the kidneys. Doxycycline is an exception, in that a significant amount of excretion is through the intestine. Tetracyclines accumulate within cells, making them ideal for intracellular infections. They are considered the first choice antibiotic for infections caused by *Neorickettsia risticii*, *Anaplasma phagocytophilum*, and *Lawsonia intracellularis*.

Recent work on tetracyclines has focused on the pharmacokinetics of oral doxycycline in foals. Oral absorption is presumed to be higher in foals based on a higher \( C_{\text{max}} \) and AUC compared to adult horses. Oral administration at a dosage of 10 mg/kg every 12 h would maintain serum, PELF, and BAL cell activity above the minimum inhibitory concentrations of *Rhodococcus equi*, beta-hemolytic streptococci, and other susceptible bacterial pathogens (MIC \(< 3 \) \( \mu \)g/mL) for the entire dosing interval. Other areas of research have focused on the use of these drugs as antiinflammatory agents. Doxycycline has been shown to accumulate in synovial fluid, suggesting a possible role for the treatment of osteoarthritis. Doxycycline concentrations have also been detected in the preocular tear film, suggesting that it may be useful for the treatment of ulcerative keratomalacia. Minocycline may have more anti-inflammatory activity, and has been proposed as a treatment at a dose of 4.4 mg/kg PO q12h.
**Nitrofurantoin**

Nitrofurans are bacteriostatic antibiotics that block oxidative decarboxylation of pyruvate to acetyl coenzyme A, depriving susceptible bacteria of energy producing pathways. The spectrum of activity includes mainly gram-negative bacteria, but they are also effective against some gram-positive bacteria and protozoa. It concentrates in mammary secretions and urine, making it a possible treatment for susceptible bacteria causing mastitis or lower urinary tract infections. Dosing recommendations are 4.5 mg/kg PO as a loading dose followed by 2.25 mg/kg PO q8h.

**ANTIFUNGALS**

The azole antifungal drugs have a high safety profile, a broad spectrum of activity and are available in topical, oral and intravenous formulations. All azoles exert their antifungal effect on the cell membrane of the fungus by inhibiting synthesis of the primary sterol of the fungal cell membrane, ergosterol. The potency of each azole drug is related to its affinity for binding the P-450 enzyme. The selective toxicity of each compound is directly dependent upon its specificity for binding fungal P-450 more readily than mammalian P-450. The inhibition of mammalian P-450 enzymes is also responsible for the numerous drug-drug interactions found with theazole antifungals which is greatest with ketoconazole, followed by itraconazole, voriconazole and fluconazole. Azole antifungals have the ability to inhibit P-glycoprotein pumps and therefore increase the oral absorption and tissue distribution of drugs within the body, particularly into protected sites, such as the blood-brain-barrier and the blood-retinal-barrier. The ability to inhibit P-glycoprotein is greatest with itraconazole, followed by ketoconazole, voriconazole and fluconazole.

**Itraconazole**

Itraconazole oral capsules require an acid environment for dissolution and therefore absorption is often highly variable. There is also an oral solution licensed for use in humans that contains 10 mg/mL of itraconazole complexed with hydroxypropyl-β-cyclodextrin, to increase the solubility. This product has been demonstrated to have higher, less variable absorption in horses. Because of its low and highly pH dependent solubility, compounded formulations of itraconazole are often not stable and not well absorbed, therefore their use is not recommended. Itraconazole is highly (99.8%) protein bound (95% to albumin and 5% to red blood cells); however, due to its lipophilicity and even higher affinity for tissue proteins, it is extensively distributed throughout the body. Although it does not reach high concentrations in the CSF compared to fluconazole, itraconazole was found to be effective in treating meningeal cryptococcosis in both mouse and guinea pig models. Itraconazole has been reported to be effective in horses for the treatment of mycotic rhinitis, osteomyelitis, and guttural pouch mycosis. The oral solution at a dose of 5 mg/kg q24h should be sufficient for treatment. The oral capsules have a lower bioavailability and higher doses or more frequent dosing intervals are recommended. No adverse effects of itraconazole therapy in the horse have been reported. In other species, elevated hepatic enzymes have been reported. In humans, there is a link between itraconazole use and the development of congestive heart failure.
**Voriconazole**

The newest triazole to be investigated in animals is voriconazole. It has a broad spectrum of activity including *Aspergillus* and *Fusarium* spp. It has excellent oral bioavailability and tissue distribution. Recently, the pharmacokinetics of voriconazole have been studied following single dose administration in the horse. It has a long half-life (13.11 hrs) following oral administration, as well as good distribution into the aqueous humor. The oral dose used in that study was 4 mg/kg, however plasma concentrations were higher than necessary for the treatment of most common veterinary pathogens, with the exception of *Fusarium* sp. A subsequent study showed that, voriconazole concentrations in urine, aqueous humor and synovial, peritoneal and cerebrospinal fluids higher than the therapeutic target of 0.5 µg/mL can be achieved by the use of 4 mg/kg administered orally once daily.

**Terbinafine**

Terbinafine is a selective inhibitor of fungal squalene epoxidase, thereby increasing the extracellular concentration of squalene to levels toxic to fungal cells and inhibiting cell wall function because of decreased synthesis of ergosterol. It has activity against many dermatophytes, as well as some *Aspergillus* sp. The pharmacokinetics of this drug have been studied in horses. Although absorption is low, therapeutic concentrations against some fungi that affect horses were reached in the plasma following a dose of 20-30 mg/kg PO. The author has used this drug in clinical cases for up to 14 days with no reported adverse effects.

**ANTIVIRALS**

**Nucleoside Analogs**

Acyclovir is an acyclic guanosine derivative that has been used clinically in the horse for the treatment of equine herpesvirus type 1 (EHV-1). Oral absorption in horses is low and variable. Based on the results of simulated multiple IV doses, twice-daily (q12h) IV infusions of acyclovir (10 mg/kg) would result in therapeutic plasma concentrations. In order to increase the absorption of the nucleoside analogs, they are often administered as a prodrug like valacyclovir and famciclovir. The pharmacokinetics of these drugs have been evaluated as a potential therapy for EHV-1 induced neurologic disease. Valacyclovir is well absorbed in horses. Several treatment regimens have been reported, including 27 mg/kg PO q8h for 2 days followed by 18 mg/kg PO q12h or 40 mg/kg PO q8h. Administration of 40 mg/kg PO q8h for 4 days resulted in therapeutic plasma concentrations of acyclovir in the plasma, however concentrations in the nasal mucus and CSF were below the reported EC50 for EHV-1. Clinical experience with valacyclovir has shown that it can reduce fever and neurologic signs if started within 2 days of infection. If treatment is delayed beyond this, the drug ganciclovir (2.5 mg/kg IV q8h for 1 day, then q12h for 1 week) can be used with greater expected efficacy. Oral dosing of famciclovir resulted in plasma concentrations of penciclovir expected to be therapeutic against EHV-1, using a dose of 20 mg/kg famciclovir. Clinical experience with this drug is currently limited, and multiple dose pharmacokinetics have not been published.