

Current Concepts in Antimicrobial Therapy for Horses

Mark G. Papich, DVM, MS, Diplomate ACVCP

Author's address: College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina 27606. © 2001 AAEP.

1. Introduction

Antibiotic therapy for horses has always been challenging because there are many drugs that are not practical to administer to horses; they may not absorb some oral medications; and many drugs are very expensive because of the horse's size. Horses are also prone to adverse reactions that limit the use of some drugs, for example, oral lincosamides may disrupt the intestinal bacteria and cause enteritis, aminoglycosides can injure the kidneys, and fluoroquinolones should not be administered to young horses because of a risk of injury to the developing articular cartilage. Despite these drawbacks, it is essential that horses with serious infections receive appropriate therapy to prevent a chronic or life-threatening condition. Drug-resistant bacterial infections are an emerging problem and the use of highly active drugs has become more important than ever before. Yet, the rational use of these drugs is essential to prevent the development of further resistance.

Foals, especially, need highly active drugs because they may be immunocompromised at the time of treatment. Drug treatment for foals produces additional challenges because of differences in drug disposition in foals vs. adults. An indepth discussion of these differences would be the subject of a

separate paper and can be reviewed elsewhere.^{1,2} But, certain differences in oral absorption, volumes of distribution, metabolism, and clearance between foals and adults must be considered when selecting antibacterial dosage regimens for foals.

In order to assist veterinarians in prescribing effective antibiotics to their equine patients, there have been several advances that have provided veterinary medicine with effective drugs and the tools (specifically, pharmacokinetic and pharmacodynamic information) to guide dosing. The most appropriate drug selection has been facilitated by new approaches to bacterial identification and susceptibility testing. This article will review some of the concepts that guide antibiotic therapy for equine patients and provide important strategies for effective dosing.

2. Bacterial Susceptibility

If the bacteria is accurately identified, antibiotic selection is simplified because the susceptibility pattern of many organisms is predictable. For example, if the bacteria is likely to be *Pasteurella*, *Streptococcus*, or *Actinomyces*, susceptibility is expected to penicillin or an aminopenicillin such as ampicillin, or a trimethoprim-sulfonamide.

NOTES

IN DEPTH: CURRENT CONCEPTS IN SELECTION AND USE OF ANTIMICROBIALS

Staphylococcus sp. isolated from horses is likely to be coagulase-positive and may be β -lactamase positive. The β -lactamase will inactivate penicillins, aminopenicillins (ampicillin), and some of the extended-spectrum penicillins such as ticarcillin. However, the addition of a β -lactamase inhibitor, as with the addition of sulbactam to ampicillin in the product Unasyn^a will increase the activity to include β -lactamase-producing strains of staphylococci.

Staphylococcus also has a predictable susceptibility to β -lactamase resistant β -lactam antibiotics such as a cephalosporin (cefadroxil and cefazolin, for example). *Staphylococcus* also is susceptible to oxacillin and dicloxacillin but these are not used commonly in horses. Most staphylococci are sensitive to fluoroquinolones (e.g., enrofloxacin^b) and aminoglycosides (e.g., gentamicin^c). The majority of staphylococci are sensitive to lincosamides (clindamycin, lincomycin), chloramphenicol, trimethoprim-sulfonamides, or erythromycin, but resistance is possible.

If the bacteria are anaerobic, predictable susceptibility patterns also are available. In horses, anaerobic bacteria causing infection include *Clostridium*, *Fusobacterium*, *Peptostreptococcus*, and *Bacteroides* sp.³ These usually are sensitive to a penicillin, chloramphenicol, metronidazole, clindamycin, amoxicillin-clavulanic acid, or one of the second-generation cephalosporins such as cefotetan or ceftiofur. If the anaerobe is from the *Bacteroides fragilis* group, resistance may be more of a problem because these organisms can produce a β -lactamase that inactivates 1st generation cephalosporins, penicillins, and ampicillin/amoxicillin. The incidence of resistant strains of *Bacteroides* has increased in recent years,⁴ and some are now resistant to clindamycin. Since many anaerobic infections in horses may be caused by *B. fragilis*, which can be resistant to β -lactam antibiotics (penicillins, ampicillin),⁵ metronidazole can be selected, which is consistently active against anaerobes, including *B. fragilis*. The activity of 1st-generation cephalosporins, trimethoprim-sulfonamides/ormetoprim-sulfonamides, or fluoroquinolones for an anaerobic infection is unpredictable. None of the aminoglycosides (gentamicin, amikacin) are active against anaerobic bacteria.

Problem, or Resistant Bacteria

If the organism is *Pseudomonas aeruginosa*, *Enterobacter*, *Klebsiella*, *Escherichia coli*, or *Proteus*, resistance to many common antibiotics is possible and a susceptibility test is advised. Many *E. coli* isolated are now resistant to the commonly used antibiotics such as penicillins, aminopenicillins, 1st-generation cephalosporins, and tetracyclines. Based on susceptibility data, we usually expect the gram-negative enteric bacteria to be susceptible to fluoroquinolones and aminoglycosides. However, as documented in small animals, resistance to fluoroquinolones (e.g., enrofloxacin^b) has been observed, and may be in-

creasing.^{6,7} Resistance to gentamicin among equine pathogens has been documented in veterinary teaching hospitals,⁸ and amikacin is the most active of the aminoglycosides against gram-negative bacteria in horses, including *Pseudomonas aeruginosa*. An extended-spectrum cephalosporin (2nd- or 3rd-generation cephalosporin) usually is active against enteric-gram negative bacteria, but will not be active against *Pseudomonas aeruginosa*. There is inherent resistance for *Pseudomonas aeruginosa* to many drugs, but it may be susceptible to fluoroquinolones, aminoglycosides, or an extended-spectrum penicillin such as ticarcillin or piperacillin. If one uses a fluoroquinolone to treat *Pseudomonas aeruginosa*, a large dose is necessary because the minimum inhibitory concentrations (MIC) of susceptible bacteria are higher than other gram-negative organisms. However, the high doses recommended for treating *Pseudomonas* in dogs have not been tested for safety in clinical studies in horses. Of the currently available fluoroquinolones, (human or veterinary drugs) ciprofloxacin is the most active against *Pseudomonas aeruginosa*, but it is not absorbed well after oral absorption in horses.⁹

The extended-spectrum cephalosporins (2nd-, 3rd-, and 4th-generation cephalosporins) have been used for some of the refractory gram-negative infections. They have higher activity against gram-negative bacteria than 1st-generation cephalosporins such as cefazolin. Ceftazidime has the highest activity against *Pseudomonas aeruginosa*. Since the extended-spectrum cephalosporins are expensive, drugs such as cefotaxime and ceftazidime have been used only to a small extent in horses. However, one of the veterinary drugs, ceftiofur^d (50 mg/mL) has been frequently used in horses. Ceftiofur is metabolized quickly to an active metabolite, desfuroylceftiofur (and other metabolites). The metabolite has activity that resembles a 3rd-generation cephalosporin in vitro. Ceftiofur was approved for use in horses for treatment of respiratory tract infections at a dose of 2.2–4.4 mg/kg q 24 h IM. Higher doses have been recommended for treating gram-negative organisms (e.g., *Klebsiella*, *Enterobacter*, and *Salmonella*). Studies in foals indicated that a dose of 2.2–6.6 mg/kg could be given to foals q 12 h IM for treatment of neonatal sepsis. Toxicity studies have shown that horses tolerate doses up to 11 mg/kg q 24 h IM, with pain at the injection site and decreased feed consumption being the most commonly observed adverse effect at the highest dose.

3. Bacterial Susceptibility Testing

When bacterial resistance is likely, a susceptibility test is recommended. Bacterial susceptibility to drugs has traditionally been tested with the agar-disk-diffusion test (ADD), also known as the Kirby-Bauer test. With this test, paper disks impregnated with the drug are placed on an agar plate and the drug diffuses into the agar. Activity of the drug against the bacteria correlates with the zone of inhibition

IN DEPTH: CURRENT CONCEPTS IN SELECTION AND USE OF ANTIMICROBIALS

around the disk. The test must be performed according to strict procedural guidelines and variables such as inoculation size, depth of agar, and so on, must be well controlled.¹⁰ The precise incubation time (usually 18–24 h), selection and preparation of the agar, and interfering compounds should be known. The ADD test results are only qualitative (that is, it determines only resistance vs. sensitivity) rather than providing quantitative information. If this test is performed using standardized procedures, it is valuable, even though it may sometimes overestimate the degree of susceptibility.

MIC Determination

It is more common for laboratories to directly measure the minimum inhibitory concentration (MIC) of an organism with an antimicrobial dilution test. The test is performed by inoculating the wells of a plate with the bacterial culture. Dilutions of antibiotics are arranged across the rows of the plate. The MIC can be directly determined by observing the exact concentration required to inhibit bacterial growth. In some laboratories other methods to measure the MIC are being used such as the E-test (epsilometer test).^e The E-test is a quantitative technique that identifies the MIC via direct measurement of bacterial growth along a concentration gradient of the antibiotic contained in a test strip.

When the MIC is measured, resistance and susceptibility are determined by comparing the organism's MIC to the drug's breakpoint as established by the National Committee for Clinical Laboratory Standards (NCCLS).¹¹ If bacteria have an MIC \leq the "susceptible" breakpoint, treatment with this drug should produce a cure unless there are other factors independent of the drug's activity. MIC \geq the "resistant" breakpoint indicates that the organism is resistant regardless of the dose administered or location of the infection. An MIC in the intermediate range (or the "F category", which has been used for enrofloxacin) means that the organism is resistant to the drug unless dosing modifications are used, or unless the drug concentrates at the site of infection as with topical treatment or in lower urinary tract infections. MIC tests are more quantitative than an ADD test, but must be performed according to strict guidelines.¹⁰ In some cases, even when the breakpoint is below the susceptible range, the organism is resistant *in vivo*. Examples include cephalosporins for treating oxacillin-resistant staphylococci, and ampicillin for treating β -lactamase producing staphylococci.

4. Penetration to the Site of Infection

For most tissues, antibiotic drug concentrations in the serum or plasma approximate the drug concentration in the extracellular space (interstitial fluid). This is because there is no barrier that impedes drug diffusion from the vascular compartment to extracellular tissue fluid.¹² Pores (fenestrations)

or microchannels in the endothelium of capillaries are large enough to allow drug molecules to penetrate unless the drug is highly protein bound in the blood.¹³ However, there are no antibiotics that have such high plasma drug protein binding to affect drug distribution enough to be clinically relevant. Tissues lacking pores or channels may inhibit penetration of some drugs (discussed below).

Diffusion into Tissues Determined by Blood Flow

Diffusion of most antibiotics from plasma to tissues is determined by tissue blood flow, rather than drug lipid solubility. This has been called *perfusion-rate limited* drug diffusion. If adequate drug concentrations can be achieved in plasma, it is unlikely that a barrier in the tissue will prevent drug diffusion to the site of infection as long as the tissue has an adequate blood supply. For example, gentamicin reached concentrations in lymph fluid of horses that closely paralleled plasma concentrations.¹⁴ Ticarcillin diffused into mare's tissues adequately when one accounts for the percentage of tissue occupied by extracellular water.¹⁵ Although gentamicin and ticarcillin are not very lipophilic, they were able to diffuse from the plasma to the extracellular fluid of these tissues easily. Rapid equilibration between the extracellular fluid and plasma was possible because of high surface area:volume ratio (high SA:V). That is, the surface area of the capillaries is high relative to the volume into which the drug diffuses. Tissue concentrations in homogenized tissues reflect the total tissue content (intra- and extracellular drug concentration) rather than the drug concentration in interstitial fluid.

Drug diffusion into an abscess or cavitated lesion may be delayed because the volume into which the drug must diffuse is higher resulting in a lower SA:V ratio, lower drug concentrations, and slower equilibrium between plasma and tissue. The observed slow equilibrium or a low peak drug concentration in this case is more a factor of the geometry of the tissue (low SA:V ratio), rather than a physical barrier to diffusion. For an abscess or granulation tissue, penetration by antibiotics also is impaired because drug penetration relies on simple diffusion and the site of infection may lack an adequate blood supply.

Even in tissues once thought to present a barrier to drug diffusion, adequate drug penetration is possible. For example, it is a common misconception that, in horses, drug penetration into synovial fluid of joints is impaired. However, as demonstrated by Bowman et al¹⁶ there was adequate penetration of ampicillin and gentamicin from the vascular compartment to synovial fluid in horses, except that equilibrium is delayed because of the synovial volume (low SA:V ratio). The ability of plasma concentrations to predict synovial fluid concentrations was also shown by Ensink and colleagues²⁸ and Anderson and colleagues.¹⁴ In these studies of gentamicin and ampicillin there was delayed equilib-

IN DEPTH: CURRENT CONCEPTS IN SELECTION AND USE OF ANTIMICROBIALS

rium caused by the lower SA:V ratio in joints, but after equilibrium was achieved, synovial fluid concentrations either paralleled plasma drug concentrations or declined more slowly. That these drugs penetrated joints is an important observation, since ampicillin and gentamicin are incapable of diffusing readily through lipid membranes and rely on diffusion through capillary pores. Beta-lactam antibiotics and aminoglycosides penetrated inflamed joints more rapidly and achieved higher concentrations than healthy joints,¹⁷ most likely from increased blood flow to the joint. However, chronic inflammation penetration could be impeded by presence of pus and fibrosis.

When the SA:V ratio is small, and the drug's elimination from the plasma is rapid, there may not be sufficient time for some drugs to adequately diffuse into infected sites. For example, in horses it was shown that cefapirin diffused poorly into infected tissue chambers, because (a) these tissue chambers had a different geometry (lower SA:V ratio) than the tissue compartment predicted by a pharmacokinetic model, and (b) cefapirin was rapidly eliminated from plasma with a half-life of 19 min, which didn't allow enough time for equilibrium between the tissue cage and serum.¹⁸

Diffusion into Tissues Determined by Lipid Solubility

In some tissues a lipid membrane (such as tight junctions in capillaries) presents a barrier to drug diffusion. This has been called *permeability-rate limited* drug diffusion. In these instances, a drug must be sufficiently lipid-soluble, or be actively carried across the membrane in order to reach effective concentrations in tissues. These tissues include: the central nervous system, eye, and prostate. There also is a barrier between plasma and bronchial epithelium (blood:bronchus barrier).¹⁹ This restricts penetration of some drugs in the bronchial secretions and epithelial fluid of the airways. However, disposition into lung tissue not separated by the blood:bronchus barrier is not impaired.

Lipophilic drugs (e.g., macrolides, fluoroquinolones, tetracyclines, trimethoprim, or chloramphenicol) may be more likely to diffuse through lipid membranes to treat infections in these tissues. Depending on the susceptibility of the organism these drugs have been used to treat infections of the central nervous system, respiratory tract, and eye.

Intracellular Drug Penetration

Most bacterial infections are located extracellular, and a cure can be achieved with adequate drug concentrations in the extracellular (interstitial) space rather than intracellular space. One should not assume that lipophilic drugs that penetrate intracellularly have an advantage over less lipophilic drugs when the infecting organism is in the extracellular space.^{12,13} Intracellular infections present a different problem, however. For drugs to reach intracellular sites, they must be carried into the cell

or diffuse passively. One of the most important equine intracellular organisms is *Rhodococcus equi*. Drugs traditionally used for treatment of *Rhodococcus* in foals include erythromycin or rifampin because these drugs are known for their ability to achieve high concentrations intracellularly.²⁰

Other intracellular organisms include *Chlamydia*, *Rickettsia*, and *Mycobacteria*. Staphylococci may, in some cases, become resistant to treatment because of intracellular survival.

Examples of drugs that accumulate in leukocytes, fibroblasts, macrophages, and other cells are fluoroquinolones, lincosamides (clindamycin, lincomycin), macrolides (erythromycin, clarithromycin), and the azalides (azithromycin).²¹ β -lactam antibiotics and aminoglycosides do not reach effective concentrations within cells. The erythromycin derivative azithromycin^e achieves particularly high concentrations of active drug intracellularly. In studies in horses²² the oral absorption of azithromycin in foals was 33% and the concentrations achieved in phagocytes were 200 times the corresponding plasma concentrations. Therefore, this drug may have potential for treating intracellular infections such as *Rhodococcus* in foals.

5. Local Factors that Affect Antibiotic Effectiveness

Local tissue factors may decrease antimicrobial effectiveness. For example, pus and necrotic debris may bind and inactivate vancomycin or aminoglycoside antibiotics (gentamicin or amikacin), causing them to be ineffective. Cellular material also can decrease the activity of topical agents such as polymyxin B. Foreign material in a wound, such as material surgically implanted, can protect bacteria from antibiotics and phagocytosis by forming a biofilm (glyco-calyx) at the site of infection.²³ Cations can adversely affect the activity of antimicrobials at the site of infection. Two important drug groups diminished in activity by cations such as Mg^{+2} , Al^{+3} , and Ca^{+2} at the site of infection are fluoroquinolones and aminoglycosides. (Cations such as magnesium, iron, and aluminum also can inhibit oral absorption of fluoroquinolones.)

The acidic environment of infected tissue may decrease the effectiveness of clindamycin, erythromycin, fluoroquinolones, and aminoglycosides. Penicillins and tetracycline activity is not affected as much by tissue pH, but hemoglobin at the site of infection will decrease the activity of these drugs. An anaerobic environment decreases the effectiveness of aminoglycosides because oxygen is necessary for drug penetration into bacteria.

As mentioned previously, an adequate blood flow is necessary to deliver an antibiotic to the site of infection. Effective antibacterial drug concentrations may not be attained in tissues that are poorly vascularized (e.g., extremities during shock, sequestered bone fragments, and endocardial valves).

6. Drug Absorption: Getting the Drug to the Site of Action

Injectable Drugs

Many injectable solutions can be administered intravenously, which delivers high concentrations to tissues rapidly. Intramuscular administration also is suitable for many drugs, although pain and muscle injury from injection can be important drawbacks. The absorption rate from an IM injection usually is sufficient to achieve high concentrations rapidly and absorption ordinarily is complete. For some drugs slow release of the drug from the IM injection may effectively prolong the dosing interval.^{24,25} Uboh and colleagues²⁶ showed that after IM administration of penicillin G potassium, the plasma penicillin concentrations 24 hr after drug administration were similar to concentrations after IM administration of procaine penicillin. Prior to that report it was assumed that the sole reason for prolonged absorption of penicillin from procaine penicillin G was the complexation with procaine and slow release from the injection site.²⁵ However, it appears that injection of soluble salts (penicillin potassium) IM also will produce prolonged plasma concentrations.²⁶ The long half-life from IM injection of these solutions is probably caused by disruption of blood flow at the injection site after IM administration and slower uptake into the circulation. Because the rate of absorption determines the terminal half-life in these instances (it would be incorrect to refer to the terminal slope of the plasma-concentration vs. time curve as an "elimination curve"), half-life is prolonged. This is referred to as the "flip-flop effect" by pharmacokineticists. Systemic availability (%F) may be falsely overestimated in studies conducted in which the flip-flop effect is observed.

As in cattle,²⁷ the site of IM injection also affects drug absorption. In studies in which different IM sites were compared, injections in the neck muscle of horses showed faster and more complete drug absorption compared to injections in the gluteal or hamstring muscles (semitendinosus).²⁵

Oral Absorption

Oral absorption is low for many drugs in horses. Drugs such as aminopenicillins (ampicillin, amoxicillin), cephalosporins, and macrolide antibiotics are not absorbed as rapidly or to as great an extent compared to administration of these drugs in small animals or humans. This limits the use of the oral route of administration for many drugs in horses. For example, oral amoxicillin is absorbed well enough in humans, dogs, and cats to be a useful and practical route of administration. But systemic availability of oral amoxicillin in adult horses is only 2–10%.^{24,28,29} Even though oral absorption is poor for these drugs in adult horse, there may be an advantage for oral administration in foals because they appear to exhibit higher oral absorption.

For example, compared to the poor oral absorption of amoxicillin cited above for adult horses, oral absorption of amoxicillin in foals is somewhat better, at 36–42%.³⁰ Cefadroxil also showed relatively good oral absorption in foals with a mean systemic availability (%F) of 58% and longer terminal half-life compared to IV,³¹ but oral absorption was poor and inconsistent in adult horses.³²

Modification of some drugs has improved oral absorption in horses. The ester prodrugs of ampicillin, such as bacampicillin and pivampicillin, produce higher systemic availability in horses after oral administration of 35–45%.³³ However, these prodrugs are no longer available as commercial products in the U.S. Esters and salts of erythromycin also have improved oral absorption in horses. Erythromycin base administered to horses is rapidly degraded into inactive metabolites in the equine stomach and intestine and systemic availability of erythromycin is poor.³⁴ However, if erythromycin is administered as an ester prodrug such as erythromycin estolate, it is absorbed as the intact ester and converted to the active drug after absorption.³⁵ Oral absorption is also improved if erythromycin is administered as a phosphate salt, whereby it resists degradation in the stomach and intestine and is absorbed as active erythromycin.³⁵

Clinicians should be aware of the interactions that are possible from oral administration of some drugs. Feeding inhibited the oral absorption of microencapsulated erythromycin in horses compared to administration to fasted animals. Oral administration of drugs that contain cations (Fe^{+3} , Al^{+3}) will significantly inhibit oral absorption of fluoroquinolones (e.g., enrofloxacin^b). Compounds that may contain these cations are antacids, sucralfate (Carafate), iron supplements, and molasses.

Local Drug Administration

Direct drug administration has been used to provide high concentrations of drugs in bones and joints of horses, and decrease reliance on high systemic doses. Intra-articular administration of gentamicin to horses produces high synovial drug concentrations.³⁶ Because of the low SA:V ratio in joints and delayed equilibrium, drug clearance from joint fluid after this administration is slower than from the plasma and may provide effective concentrations for at least 24 hr. High concentrations in the limbs can also be achieved via regional limb perfusion. In this technique, an infected limb is perfused with an antibiotic and the drug concentration kept high from a temporary tourniquet applied to the limb proximal to the site of drug administration. This technique has been described in available references.³⁷ Regional limb perfusion of equine limbs allows high concentrations to be achieved in bone and joints of limbs without high doses and systemic exposure to the drug.

7. Pharmacokinetic-Pharmacodynamic (PK-PD)

Optimization of Doses

To achieve a cure, the drug concentration in plasma, serum, or tissue fluid should be maintained above the MIC, or some multiple of the MIC, for at least a portion of the dose interval. Antibacterial dosage regimens are based on this assumption, but drugs vary with respect to the magnitude of the peak concentration and the time above the MIC that is needed for a clinical cure. Pharmacokinetic-pharmacodynamic (PK-PD) relationships of antibiotics attempt to describe how these factors can correlate with clinical outcome.^{38,39} Shown on Figure 1 are some terms used to describe the shape of the plasma concentration vs. time profile. The C_{MAX} is simply the maximum plasma concentration attained during a dosing interval. The C_{MAX} is related to the MIC by the $C_{MAX}:MIC$ ratio. The AUC is the total area-under-the-curve. The AUC for a 24-hr period is related to the MIC value by the AUC:MIC ratio. Also shown in Figure 1 is the relationship of time to MIC measured in hr ($T > MIC$).

Antibiotics can be bactericidal, bacteriostatic, or both, depending on the drug and the organism. For a drug that is bactericidal, its action may be either concentration-dependent or time-dependent. If concentration-dependent, one should administer a high enough dose to maximize the $C_{MAX}:MIC$ ratio. If time-dependent, the drug should be administered frequently enough to maximize the $T > MIC$. For bacteriostatic drugs, the drug concentration should be kept above the MIC at the site of action for as long as possible during the dosing interval. Examples of how these relationships affect drug regimens are described in the following sections.

Aminoglycosides

Aminoglycosides (e.g., gentamicin, or amikacin) are concentration-dependent bactericidal drugs, there-

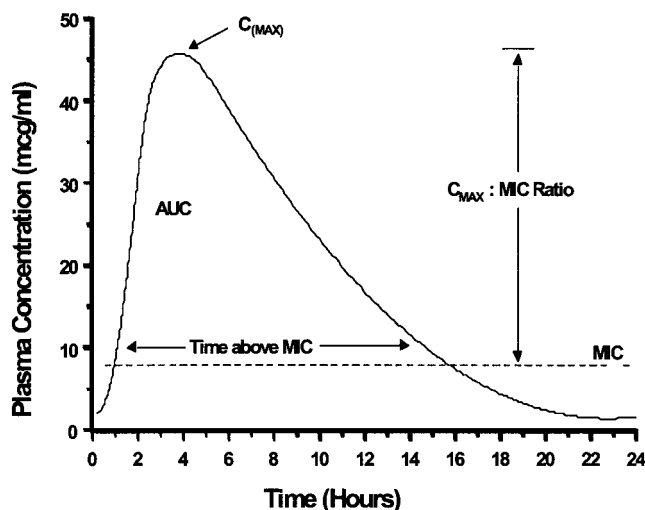


Fig. 1. Plasma concentration vs time profile and MIC. Relationship between MIC and pharmacokinetic terms are shown.

fore the higher the drug concentration, the greater the bactericidal effect. An optimal bactericidal effect occurs if a high enough dose is administered to produce a peak of 8–10 times the MIC. This can be accomplished by administering a single dose once daily. This regimen is at least as effective, and perhaps less nephrotoxic, than lower doses administered more frequently.⁴⁰ Our current regimens in animals employ this strategy. The single daily dose is based on the drug's volume of distribution (VD): $Dose = C_{MAX} \times VD$. A once-daily dose for gentamicin in adult horses determined from a clinical study is 4 to 6.8 mg/kg.⁴¹ This article also reviewed previous studies that have examined once-daily treatment using gentamicin in horses. In adult horses an appropriate dose for amikacin is 7.25 to 14.5 mg/kg q 24 h. However, for foals, because of a higher volume of distribution, the dose of amikacin should be increased to 20–25 mg/kg q 24 h.⁴² The efficacy of these regimens has not been tested for conditions encountered in veterinary medicine, but the relationships are supported by studies in experimental animals. These regimens assume some competency of the immune system. If the animal is severely immunocompromised, one may consider a more frequent interval for administration or combinations with β -lactam antibiotics.

Fluoroquinolones

As reviewed by Hyatt et al,³⁸ Dudley,⁴³ and recently by Wright et al⁴⁴ and Papich and Riviere,⁴⁵ investigators have shown that either the peak plasma concentration above bacterial MIC, also known as the $C_{MAX}:MIC$ ratio, or the total AUC above the MIC (also known as the AUC:MIC ratio), may predict clinical cure in studies of laboratory animals, and in a limited number of human clinical studies. There are no published studies involving horses (or dogs and cats for that matter) to indicate which of these parameters is a predictor of clinical cure, or what the respective target ratios might be. However, in other studies cited in these references, a $C_{MAX}:MIC$ of 8–10, or a AUC:MIC of greater than 125, has been associated with a cure. The AUC:MIC ratio of >125 that has been cited refers to administration to human patients that were critically ill. In other patients, the ratio to achieve a cure may not need to be that high. In the review by Wright et al,⁴⁴ evidence was presented that AUC:MIC ratios as low as 30–55 are associated with a clinical cure. This difference may reflect the severity of illness among these investigations, but also may be organism specific. With clinical doses used for many infections in veterinary medicine, the AUC:MIC ratios are often lower than 125 and clinical cures are still reported. An examination of the current use of the fluoroquinolones in veterinary medicine⁴⁵ suggests that, in immunocompetent animals, AUC:MIC ratios of 50–60 are likely to be effective.

IN DEPTH: CURRENT CONCEPTS IN SELECTION AND USE OF ANTIMICROBIALS

Table 1. Table of Approximate Doses for Antibiotics Mentioned

Drug	Brand Name	Dosing Information
Amikacin	Amiglyde-V	Adult: 10 mg/kg IM, IV, q 24 h Foals: 20–25 mg/kg, IM, IV, q 24 h
Ampicillin	Amp-Equine, and generic	6.6 mg/kg to 10–20 mg/kg every 6–8 h IM, IV. Doses up to 25 to 40 mg/kg every 6 to 8 h have been used for refractory infections.
Amoxicillin	Amoxitabs	10–20 mg/kg, IM, not absorbed well orally, except foals.
Azithromycin	Zithromax	For <i>Rhodococcus equi</i> : 10 mg/kg orally, q 24 h for first week, then every 48 h thereafter. This is a suggested dose only, it has not been tested for efficacy.
Cefadroxil	Cefa-Tabs	30 mg/kg q 12 h, oral Oral absorption is adequate only in young foals, not adults.
Cefazolin	Ancef, Kefzol	25 mg/kg IM, q 6–8 h
Cefepime	Maxipime	Foals: 11 mg/kg IV, q 8 h
Cefoxitin	Mefoxin	20 mg/kg q 4–6 h, IV, IM
Cefotaxime	Claforan	Foals: 40 mg/kg, q 6 h, IV
Ceftiofur	Naxcel	2.2 mg/kg, IM, q 12 h up to 11 mg/kg/day IM
Cephapirin	Cefadyl, and generic	20–30 mg/kg q 4–8 h, IM, IV
Chloramphenicol	Chloromycetin, and generic	35–50 mg/kg, PO q 6–8 h
Doxycycline	Vibramycin, and generic	10 mg/kg q 12 h, PO Do not administer IV.
Enrofloxacin	Baytril and Baytril-100	5 mg/kg q 24 h, IV, IM; 7.5–10 mg/kg q 24 h, PO.
Erythromycin	Generic	Note: plain tablets are poorly absorbed in horses. Use either erythromycin estolate, or erythromycin phosphate Erythromycin estolate: For treating <i>Rhodococcus</i> : 25 mg/kg q 6 h, PO Erythromycin phosphate or Erythromycin estolate: 37.5 mg/kg q 12 h or 25 mg/kg q 8 h PO Erythromycin gluceptate injection: Foals 5 mg/kg q 4–6 h IV
Florfenicol	Nuflor	Do not administer to horses until more safety data becomes available.
Gentamicin	Gentocin	Adult: 4 mg/kg IV, IM q 24 h to 6.8 mg/kg IV, IM, q 24 h Foal: (<2 weeks) 12–14 mg/kg q 24 h, IM, IV
Metronidazole	Flagyl, and generic	10 mg/kg q 12 h PO
Orbifloxacin	Orbax	2.5 mg/kg, q 24 h, PO
Oxytetracycline	LA-200 and other forms	<i>Ehrlichiosis</i> : 3.5 mg/kg q 12 h and up to 10 mg/kg q 24 h IV, IM (give IV slowly) Foals (flexural limb deformities): 44 and up to 70 mg/kg IV (2 to 3 grams per foal) with two doses given 24 h apart.
Penicillin G	Generic	Penicillin Potassium: 20,000 U/kg q 6–8 hr, IV Penicillin Sodium: 20,000 U/kg q 6–8 hr, IV Penicillin Procaine: 20,000 to 24,000 U/kg q 12–24 h, IM.
Pyrimethamine	Daraprim	1 mg/kg q 24 h, PO in combination with a sulfonamide
Rifampin	Rifadin	10 mg/kg q 24 h PO, Foals with <i>Rhodococcus</i> : 5 mg/kg q 12 h, PO with erythromycin
Sulfonamides	Generic	See Trimethoprim-Sulfonamides
Ticarillin	Ticar	44 mg/kg q 6–8 h, IV, IM Ticarillin also is used intrauterine in mares
Tilmicosin	Micotil	Do not use in horses until more safety data becomes available.
Trimethoprim-Sulfadiazine or Trimethoprim-Sulfamethoxazole	Tribrissen, Uniprim, Bactrim	25 mg/kg sulfonamide + 5 mg/kg trimethoprim (30 mg/kg total) PO, q 12–24 h

Note for Dose Table: Many of the doses listed are extra-label, or are human drugs used in an off-label or extra-label manner. Doses listed are based on best available evidence at the time of table preparation, however the author cannot assure efficacy of drugs used according to recommendations in this table. Adverse effects may be possible from drugs listed in this table, of which author was not aware at the time of table preparation. Veterinarians using these tables are encouraged to check current literature, product label, and the manufacturer's disclosure for information regarding efficacy, and any known adverse effects or contraindications not identified at the time of preparation of this table.

Current guidelines for recommend doses of fluoroquinolones attempt to achieve high $C_{MAX}:MIC$ ratios whenever possible because they have been associated with a lower incidence of development of resistance.⁴⁶ Sensitive bacteria from horses might be expected to have an MIC for enrofloxacin of 0.125

IN DEPTH: CURRENT CONCEPTS IN SELECTION AND USE OF ANTIMICROBIALS

mg/mL, or less, based on available information.⁴⁷ Pharmacokinetic studies available from horses^{45,48-50} showed that to achieve the goal of $10 \times \text{MIC}$ using enrofloxacin, IV doses of 5 mg/kg q 24 h and 7.5–10 mg/kg orally may be adequate. We have monitored plasma concentrations in many clinical equine patients after oral and injectable administration of enrofloxacin^f and confirmed that these doses are adequate to achieve targeted plasma concentrations. Studies with orbifloxacin^g have been conducted and confirmed that oral absorption of this drug is high and a dose of 2.5 mg/kg would be adequate for adult horses.^f

Beta-lactam Antibiotics

β -lactam antibiotics such as penicillins, potentiated-aminopenicillins, and cephalosporins are slowly bactericidal. Their concentration should be kept above the MIC throughout most of the dosing interval (long $T > \text{MIC}$) for the optimal bactericidal effect.⁵¹ Dosage regimens for the β -lactam antibiotics should consider these pharmacodynamic relationships. Therefore, for treating a gram-negative infection, especially a serious one, some regimens for penicillins and cephalosporins require administration 3 to 4 times per day. Some of the 3rd-generation cephalosporins have long half-lives and less frequent regimens have been used for some of these drugs (for example cefotaxime and ceftiofur). gram-positive organisms are more susceptible to β -lactam antibiotics and produce a greater bactericidal effect compared to gram-negative bacteria. Additionally, since the MICs are lower for gram-positive bacteria, and antibacterial effects occur at concentrations below the MIC (post antibiotic effect, PAE), longer dose intervals may be possible for infections caused by gram-positive compared to gram-negative bacteria.

Bacteriostatic Drugs

The drugs such as tetracyclines, macrolides (erythromycin and derivatives), sulfonamides, lincosamides (lincomycin and clindamycin), and chloramphenicol derivatives act in a bacteriostatic manner against most bacteria. However, against susceptible gram-positive bacteria, the macrolides appear to be bactericidal and can demonstrate a post-antibiotic effect. Chloramphenicol also can produce a bactericidal effect if the organism is very susceptible.

Bacteriostatic drugs are the most effective when the drug concentrations are maintained above the MIC throughout the dosing interval. In this way, they act in a time-dependent manner. Even in situations in which macrolides act in a bactericidal manner, their action is still time-dependent because the bactericidal action is slow. Most of the bacteriostatic drugs must be administered frequently or demonstrate a long half-life to achieve this goal. A property of some of these drugs is that they persist in tissues for a prolonged time, to allow infrequent

dosing intervals. The cattle drug tilmicosin^h attains drug concentrations in lungs for at least 3 days for treating susceptible *Pasteurella*. The macrolide derivative azithromycin^e (Zithromax, Pfizer) has shown tissue half-lives as long as 70–90 h in cats and dogs, permitting infrequent dosing. We have also demonstrated long persistence of azithromycin in cells of foals.²² Tissue concentrations of trimethoprim-sulfonamides persist long enough to allow once-daily dosing for many infections, although a study in equine joint infections showed that twice daily was more effective.⁵² Most published dosage regimens are designed to take these drug's pharmacodynamic action into account.

References and Footnotes

1. Wichtel MEG, Buys E, DeLuca J, Stringel G. Pharmacologic considerations in the treatment of neonatal septicemia and its complications. *Vet Clin North Am [Equine Pract]* 1999; 15:725–746.
2. Caprile KA, Short CR. Pharmacologic considerations in drug therapy in foals. *Vet Clin North Am [Equine Pract]* 1987;3:123.
3. Sweeney CR, Holcombe SJ, Barningham SC, Beech J. Aerobic and anaerobic bacterial isolates from horses with pneumonia or pleuropneumonia and antimicrobial susceptibility patterns of the aerobes. *J Am Vet Med Assoc* 1991;198:839–842.
4. Jang SS, Breher JE, Dabaco LA, Hirsh DC. Organisms isolated from dogs and cats with anaerobic infections and susceptibility to selected antimicrobial agents. *J Am Vet Med Assoc* 1997;210:1610–1614.
5. Hirsh DC, Indiveri MC, Jang SS, Biberstein EL. Changes in prevalence and susceptibility of obligate anaerobes in clinical veterinary practice. *J Am Vet Med Assoc* 1985;186:1086–1089.
6. Oluoch AO, Kim C-H, Weisiger RM, et al. Nonenteric *Escherichia coli* isolates from dogs: 674 cases (1990–1998). *J Am Vet Med Assoc* 2001;218:381–384.
7. Walker AL, Jang SS, Hirsh DC. Bacteria associated with pyothorax of dogs and cats: 98 cases (1989–1998). *J Am Vet Med Assoc* 2000;216:359–363.
8. Orsini JA, Benson CE, Spencer PA, Van Miller E. Resistance to gentamicin and amikacin of gram-negative organisms isolated from horses. *Am J Vet Res* 1989;50:923–925.
9. Dowling PM, Wilson RC, Tyler JW, Duran SH. Pharmacokinetics of ciprofloxacin in ponies. *J Vet Pharmacol Ther* 1995;18:7–12.
10. Lorian V. *Antibiotics in laboratory medicine*, 4th ed. Baltimore, MD: Williams & Wilkins, 1996.
11. Watts JL, National Committee for Clinical Laboratory Standards. *NCCLS Performance Standards for Antimicrobial Susceptibility Testing. Eleventh Informational Supplement*. NCCLS Document M100-S11. Wayne, PA: NCCLS, 1999.
12. Nix DE, Goodwin SD, Peloquin CA, et al. Antibiotic tissue penetration and its relevance: Impact of tissue penetration on infection response. *Antimicrob Agents Chemother* 1991; 35:1953–1959.
13. Ryan DM. Pharmacokinetics of antibiotics in natural and experimental superficial compartments in animals and humans. *J Antimicrob Chemother* 1993;31(Suppl D):1–16.
14. Anderson BH, Firth EC, Whittem T. The disposition of gentamicin in equine plasma, synovial fluid and lymph. *J Vet Pharmacol Ther* 1995;18:124–131.
15. Van Camp SD, Papich MG, Whitacre MD. Administration of ticarcillin in combination with clavulanic acid intravenously and intrauterinely to clinically normal estrous mares. *J Vet Pharmacol Ther* 2000;23:373–378.
16. Bowman KF, Dix LP, Riond J-L, Riviere JE. Prediction of pharmacokinetic profiles of ampicillin sodium, gentamicin sulfate, and combination ampicillin sodium-gentamicin sul-

IN DEPTH: CURRENT CONCEPTS IN SELECTION AND USE OF ANTIMICROBIALS

- fate in serum and synovia of healthy horses. *Am J Vet Res* 1986;47:1590–1595.
17. Firth EC, Klein WR, Nouws JFM, Wensing TH. Effect of induced synovial inflammation on pharmacokinetics and synovial concentrations of sodium ampicillin and kanamycin sulfate after systemic administration in ponies. *J Vet Pharmacol Ther* 1988;11:56–62.
 18. Short CR, Beadle RE, Aranas T, et al. Distribution of cephalosporin into a tissue chamber implanted subcutaneously in horses. *J Vet Pharmacol Ther* 1987;10:241–247.
 19. Baldwin DR, Honeybourne D, Wise R. Pulmonary disposition of antimicrobial agents: Methodological considerations. *Antimicrob Agents Chemother* 1992;36:1171–1175.
 20. Zertuche JML, Hillidge CJ. Therapeutic considerations for *Rhodococcus equi* pneumonia in foals. *Compen Cont Ed Pract Vet* 1987;9:965–971.
 21. Pascual A. Uptake and intracellular activity of antimicrobial agents in phagocytic cells. *Rev Med Microbiol* 1995;6:228–235.
 22. Davis JL, Gardner SY, Jones SL, et al. Azithromycin pharmacokinetics and phagocyte concentrations in foals, in *Proceedings*. Amer Coll Vet Med 2001;859.
 23. Habash M, Reid G. Microbial biofilms: Their development and significance for medical device-related infections. *J Clin Pharmacol* 1999;39:887–898.
 24. Wilson WD, Spensley MS, Baggot JD, Hietala SK. Pharmacokinetics and estimated bioavailability of amoxicillin in mares, after intravenous, intramuscular, and oral administration. *Am J Vet Res* 1988;49:1688–1693.
 25. Firth EC, Nouws JFM, Driessens F, et al. Effect of the injection site on the pharmacokinetics of procaine penicillin G in horses. *Am J Vet Res* 1986;47:2380–2383.
 26. Uboh CE, Soma LR, Luo Y, et al. Pharmacokinetics of penicillin G procaine versus penicillin G potassium and procaine hydrochloride in horses. *Am J Vet Res* 2000;61:811–815.
 27. Papich MG, Korsrud GO, Boison JO, et al. A study of the disposition of procaine penicillin G in feedlot steers following intramuscular and subcutaneous injection. *J Vet Pharmacol Ther* 1993;16:317–327.
 28. Ensink JM, Klein WR, Mevius DJ, et al. Bioavailability of oral penicillins in the horse: A comparison of pivampicillin and amoxicillin. *J Vet Pharmacol Ther* 1992;15:221–230.
 29. Ensink JM, Vulto AG, van Miert ASJPAM, et al. Oral bioavailability in vitro stability of pivampicillin, bacampicillin, talampicillin, and ampicillin in horses. *Am J Vet Res* 1996;57:1021–1024.
 30. Baggot JD. Bioavailability and disposition kinetics of amoxicillin in neonatal foals. *Equine Vet J* 1988;20:125–127.
 31. Duffee NE, Christensen JM, Craig AM. The pharmacokinetics of cefadroxil in the foal. *J Vet Pharmacol Ther* 1989;12:322–326.
 32. Wilson WD, Baggot JD, Adamson PJW, et al. Cefadroxil in the horse: Pharmacokinetics and in vitro antibacterial activity. *J Vet Pharmacol Ther* 1985;8:246–253.
 33. Sarasola P, McKellar QA. Ampicillin and its congener prodrugs in the horse. *Brit Vet J* 1994;150:173–187.
 34. Lakritz J, Wilson WD, Marsh AE, Mihalyi JE. Effects of prior feeding on pharmacokinetics and estimated bioavailability after oral administration of a single dose of microencapsulated erythromycin base in healthy foals. *Am J Vet Res* 2000;61:1011–1015.
 35. Lakritz J, Wilson WD, Marsh AE, Mihalyi JE. Pharmacokinetics of erythromycin estolate and erythromycin phosphate after intragastric administration to healthy foals. *Am J Vet Res* 2000;61:914–919.
 36. Lloyd KCK, Stover SM, Pascoe, et al. Plasma and synovial fluid concentrations of gentamicin in horses after intra-articular administration of buffered and unbuffered gentamicin. *Am J Vet Res* 1988;49:644–649.
 37. Murphey ED, Santschi EM, Papich MG. Regional intravenous perfusion of the distal limb of horses with amikacin sulfate. *J Vet Pharmacol Ther* 1999;22:68–71.
 38. Hyatt JM, McKinnon PS, Zimmer GS, Schentag JJ. The importance of pharmacokinetic/pharmacodynamic surrogate markers to outcome. *Clin Pharmacokinet* 1995;28:143–160.
 39. Nicolau DP, Quintiliani R, Nightingale CH. Antibiotic kinetics and dynamics for the clinician. *Med Clin North Am* 1995;79:477–495.
 40. Freeman CD, Nicolau DP, Belliveau PP, Nightingale CH. Once-daily dosing of aminoglycosides: Review and recommendations for clinical practice. *J Antimicrob Chemother* 1997;39:677.
 41. Tudor RA, Papich MG, Redding WR. Gentamicin disposition and dosage determination of once daily administration of gentamicin sulfate in horses after abdominal surgery. *J Am Vet Med Assoc* 1999;215:503–506.
 42. McFarlane D, Papich MG, Breuhaus B, et al. Pharmacokinetics of amikacin sulfate in sick and healthy foals, in *Proceedings*. 5th Conf Internatl Vet Emergency Crit Care Soc 1996.
 43. Dudley MN. Pharmacodynamics and pharmacokinetics of antibiotics with special reference to the fluoroquinolones. *Am J Med* 1991;91(suppl 6A):45S–50S.
 44. Wright DH, Brown GH, Peterson ML, Rotschafer JC. Application of fluoroquinolone pharmacodynamics. *J Antimicrob Chemother* 2000;46:669–683.
 45. Papich MG, Riviere JE. Fluoroquinolones. In: Adams HR, ed. *Veterinary pharmacology and therapeutics*, 8th ed. Ames: Iowa State University Press, 2001;898–917.
 46. Lode H, Borner K, Koeppel P. Pharmacodynamics of fluoroquinolones. *Clin Infect Dis* 1998;27:33–39.
 47. Walker RD. Fluoroquinolones. In: Prescott JF, Baggot JD, Walker RD, eds. *Antimicrobial therapy in veterinary medicine*, 3rd ed. Ames: Iowa State University Press, 2000;315–338.
 48. Giguère S, Sweeney RW, Bélanger M. Pharmacokinetics of enrofloxacin in adult horses and concentration of the drug in serum, body fluids, and endometrial tissues after repeated intragastrically administered doses. *Am J Vet Res* 1996;57:1025–1030.
 49. Langston VC, Sedrish S, Boothe DM. Disposition of single-dose oral enrofloxacin in the horse. *J Vet Pharmacol Ther* 1996;19:316–319.
 50. Pyörälä S, Panu S, Kaartinen L. Single dose pharmacokinetics of ciprofloxacin in horses, in *Proceedings*. Eur Assoc Vet Pharmacol Ther 1994;45–46.
 51. Turnidge JD. The pharmacodynamics of β -lactams. *Clin Infect Dis* 1998;27:10–22.
 52. Bertone AL, McIlwraith CW, Jones RL, et al. Comparison of various treatment for experimentally induced equine infectious arthritis. *Am J Vet Res* 1987;48:519–529.
- ^aUnasyn®, ampicillin-sulbactam, Pfizer Inc, New York, NY.
^bBaytril-Bayer Corporation, Shawnee Mission, KS.
^cGentocin, Schering Plough Corporation, Union, NJ.
^dNaxcel-Pharmacia, Kalamazoo, MI.
^eAB Biodisk, Piscataway, NJ; Zithromax, Pfizer, New York, NY.
^fUnpublished observations by the author.
^gOrbax, Schering Plough, Union, NJ.
^hMicotil, Elanco Animal Health, Indianapolis, IN.