

ANTIMICROBIAL THERAPY IN PRACTICE

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Antibiotics are one of the most commonly prescribed drugs used in equine medicine. They are an essential tool in the treatment of bacterial infections, and can also play an important role in preventing infections, such as post-operative infections. Rational use of antibiotics is essential to maximize efficacy, to minimize toxicity, and to prevent the development of antimicrobial resistance. The decision whether to use an antimicrobial, what antimicrobial to use and for how long to use it for should be based on knowledge of the bacterial species involved and the efficacy of antibiotics against those pathogens, taking into account the site of infection. From a practical view point, the choice of antibiotic is often made based on availability, available route of administration, and cost. Despite the restrictions our clients place on us, however, logical antibiotic choices can be made within the framework of these restrictions.

Why do we need to worry about the choice of antibiotic?

Since the discovery of antibiotics in the 1930s, morbidity and mortality due to bacterial infections in both humans and animals has been dramatically reduced. As such, they are now considered essential for human and animal health. Unfortunately, use of antibiotics promotes the development of antibiotic resistance by bacteria. Resistant bacteria are capable of causing serious infections, not only in hospitalized patients, but also in animals treated at their home farm. A huge amount of research has been directed at identifying risk factors for the development of antibiotic resistance, and how to minimize its impact. Responsible use of antibiotics is considered an essential part of this effort; that is, using an antibiotic only when a bacterial infection is present (or in select cases, prophylactically), as well as using an appropriate antibiotic for a minimum period of time.

The veterinary profession is often blamed by human doctors for the majority of antibiotic resistance, despite no real evidence to support this claim. However, there is considerable pressure to limit the antibiotics available to veterinarians, which could severely impact our ability to treat our patients. As such, we should make every effort to use antibiotics 'responsibly' – not only will this result in the best outcome for our patients, but it may also help prevent the imposition of prescribing restrictions.

Does the horse need antibiotics?

There are two main situations where antibiotics are used: treatment or prophylaxis

Using antibiotics therapeutically

Antibiotics are used in the treatment of an established bacterial infection which the horse's immune system cannot clear. In many situations, a presumptive diagnosis of bacterial infection will be made, based on presence of a fever, purulent discharge etc. In other situations, it may be necessary to obtain a culture to establish bacterial infection eg a foal with sepsis. The importance of the immune system cannot be underestimated – both the innate and adaptive immune system play a major role in protecting the body from pathogen invasion, and from eliminating pathogens if they do invade.

Prophylaxis

The second reason you may prescribe antibiotics is to prevent a bacterial infection from becoming established. Most commonly, this will be associated with peri-operative antibiotic administration, although treating horses with lacerations and wounds could also be considered a form of prophylaxis. The expected infection rate without antibiotics, the potential sequelae of a post-operative infection and the risks associated with antibiotic use (eg diarrhoea, development of resistance) should all be taken into account when deciding if peri-operative antibiotics are appropriate.

How do you choose which antibiotic?

Once you have decided that antibiotics are indicated, the next question to answer is which drug to use. There are many different factors which practitioners take into account when choosing an antibiotic. Answering a series of questions relating to the drug itself, and the infection you are aiming to treat/prevent will help in the choice of an appropriate drug.

Can you predict which bacteria are causing the infection?

In some situations, you will be able to predict the causative bacteria. Typically, this is based on the horse's clinical signs and your own experience with similar cases. For example, you can predict that a horse with purulent nasal discharge and lymphadenopathy will be infected with *Streptococcus equi var equi*, especially if other horses are similarly affected. If you cannot predict the organism(s) involved, it may be appropriate to perform a bacterial culture of the presumed site of infection. In some situations however, while you may strongly suspect a bacterial infection, the site remains unclear, or inaccessible for sampling. In these situations, you may need to start empirical antibiotic treatment.

Does the bacterial species involved have a predictable sensitivity pattern?

For some bacterial species, sensitivity to particular antimicrobials can be predicted because of a lack of identified resistance. The classic example of this would be the predictable sensitivity of *Streptococcus* spp to penicillin. In other cases, in particular gram negative bacteria such as *E coli* and *Pseudomonas* spp, sensitivity patterns are unpredictable, as these isolates can rapidly develop resistance. In these cases, sensitivity patterns are recommended.

When do I use a 'big gun' antibiotic?

Although the range of antibiotics available to us as equine vets is relatively limited, we can categorize the drugs into Primary, Secondary or Tertiary drugs, based on their spectrum of activity and importance to human and veterinary medicine. Recommendations made by organizations such as the American College of Veterinary Medicine are to use a Primary drug (which tend to be older, more narrow spectrum drugs such as penicillins or tetracyclines) for the majority of infections, if culture and sensitivity is not available. Secondary drugs, which include newer drugs with an extended spectrum of activity, should be reserved for more serious infections or when sensitivity testing indicates that a Primary drug will be ineffective. Tertiary drugs should only be used when treating animals with clinically important infections when sensitivity testing indicates resistance to all Primary and Secondary drugs. The classification of drugs into these various classes will depend somewhat on what drugs are available, as well as the regulatory issues of each country. (see below)

Once a sensitivity pattern has been predicted or established, the next question to answer is how that *in vitro* sensitivity pattern relates to the clinical condition you are treating.

Will the antibiotic you choose:

a) Get to the site of the infection?

For most tissues, the antibiotic concentrations in the plasma will be similar to the drug concentration in the extracellular space (ie where you want it to get), because there is no barrier to diffusion between the vascular space and extracellular space. However, in some situations, a lipid membrane is present which presents a barrier to drug diffusion – in these cases, such as the central nervous system and the eye, a drug will need to be fairly lipid soluble, or be actively transported across the barrier to reach effective concentrations.

Similarly, if infection with a known intracellular pathogen is suspected an antimicrobial with intracellular penetration is required. The best example here would be infection with *R equi* – whilst *in vitro* sensitivity suggests efficacy of antimicrobials such as aminoglycosides, *in vivo* treatment with these drugs results in treatment failure. Drugs such as rifampin and erythromycin, which acquire adequate intracellular concentrations must be used.

b) Be effective at the site of the infection?

Bacterial infections are often associated with the accumulation of purulent debris, and the formation of abscesses. Antimicrobial efficacy in these situations can be limited, even if *in vitro* sensitivity suggests efficacy. For example, aminoglycosides such as gentamicin are typically ineffective in treatment of abscesses because (1) pus and necrotic debris may bind and inactivate the drug (2) the acidic environment of the abscess decreases drug efficacy; and (3) the anaerobic environment decreases drug efficacy because aminoglycoside uptake into bacterial cells depends on oxygen.

How do I decide which dose to use?

Once you have decided on the drug to use, the dose must be decided. Although drugs which are licensed for use in horses will have dosage recommendations on the label, many drugs in equine medicine are used in an extra-label fashion, so dosage regimes appropriate for horses are not provided. Even if the drug is labeled for use in horses, in many situations, the label dosage regime (either the frequency or the amount) is no longer the recommended dose. For example, of the 9 antimicrobials licensed for systemic use in horses, I would consider the label recommendations appropriate in only two of the drugs. Remember that label indications are very specific, and are based on treatment of specific bacterial species. For example, ceftiofur is licensed for the treatment of horses with bacterial respiratory disease in which *Streptococcus* spp. (including *Streptococcus zooepidemicus* and *Streptococcus equi*), *Staphylococcus* spp. and/or *Pasteurella* spp are involved. The label dose rate is 2mg/kg IM SID. However, if ceftiofur is used in an extra-label fashion to treat bacteria other than those listed, which have a higher MIC, then therapeutic concentrations will be maintained for less than 8 hours. Cephalosporins such as ceftiofur are time dependent antibiotics, where efficacy is directly related to the duration drug concentration is maintained

above the MIC of the target organism. Thus a period of 18 hours or more when drug concentration is below the MIC is unlikely to be effective.

The table below lists suggested doses of commonly used antibiotics, based on current recommendations.

Drug	Dose (mg/kg)	Frequency	Route of administration	Notes
Penicillin (procaine)	22,000IU/kg	BID	IM	
Penicillin (Na/K)	22,000IU/kg	TID-QID	IV	
Gentamicin	6.6-8.8	SID	IV	Higher dose may be necessary in foals
Amikacin	20-30	SID	IV	Higher dose for foals
Trimethoprim/sulfadiazine	15-24	BID	IV	
Trimethoprim/sulfadiazine	30	BID	PO	
Ceftiofur	2	SID-BID	IM	SID for label isolates. Higher dose for extended spectrum
Cefquinome	1	SID-BID	IM/IV	SID for adults with Strep infection. BID for foals
Oxytetracycline	5-10	SID-BID	IV	
Doxycycline	10	BID	PO	
Rifampin	5-10	SID/BID	PO	
Erythromycin	25	TID	PO	
Metronidazole	15-20	BID-QID	PO/IV	

Are there alternate or supplementary routes of antibiotic delivery?

Whilst systemic administration of antibiotics is widely practiced, high concentrations of drugs can also be delivered via a local or topical route. For example, bacterial keratitis is best treated by topical administration of drugs. Local perfusion of antibiotics, especially aminoglycosides and cephalosporins, can be especially useful as an adjunctive therapy in the treatment of synovial sepsis, as can direct instillation of the drugs into the synovial structure.

Are there regulatory issues regarding the chosen antibiotic?

Depending on the country in which you practice, there may be regulatory guidelines to follow regarding use of particular antimicrobials. Guidelines must be followed if horses are intended for human consumption – in other situations, extra-label usage may be appropriate.

How long do I need to treat the horse for?

In comparison to human medicine, where relatively clear guidelines exist for duration of treatment for many diseases, these guidelines tend to be lacking in equine medicine. In most situations, the initial antimicrobial drug(s) are administered for 3-4 days. If during this time, there has been no clinical response, then a change in antimicrobial may be considered. It is also worth re-assessing whether the infection is truly due to a bacterial infection. If samples for culture were not obtained prior to starting treatment, it may then be appropriate to take samples so that they can be used to guide treatment.

If the horse appears to be responding, then the duration of treatment will vary – in most cases, treatment should be continued for several days beyond the resolution of clinical signs. However, in some cases, clinical signs will resolve without resolution of the bacterial infection, and monitoring acute phase proteins, as well as ultrasound and radiographic re-evaluation may be appropriate.

Do I need to monitor for toxicity?

Some drugs are associated with toxicity, especially in compromised/toxic/hypovolaemic animals. For example, aminoglycosides should be used with caution in animals with renal disease, as they can be nephrotoxic. Routine monitoring of renal function may be appropriate if potentially nephrotoxic drugs are used in hypovolaemic animals or those with renal dysfunction.

Antimicrobial associated diarrhoea can develop in any horse treated with antibiotics, at any time during (or after) treatment. Although in some cases the disease is mild, it can be severe, with mortality as high as 30%. There does however appear to be some geographic variation regarding the occurrence of this condition, as well as the drugs most frequently associated with its development. If possible, antibiotic treatment should be discontinued, although treatment with metronidazole may be appropriate if *Clostridium* spp are considered part of the aetiology. If antibiotics are deemed to be necessary, changing the drug class, or giving a drug parenterally rather than enterally may help. Local treatment can also be considered. I will typically discontinue antibiotics if at all possible, and treat locally if necessary. If systemic treatment is still necessary, I will use a penicillin/gentamicin combination, as in my experience it is rarely associated with development of diarrhoea.

Summary

Antibiotics are essential in the treatment of many bacterial diseases in horses. Choosing when to use an antibiotic, what antibiotic to use and for how long to use it should be based on a combination of factors, including regulatory guidelines, suspected/known disease, the bacteria involved and the practicalities of administration.