Update on Antibiotic Therapy in the Horse

Benjamin R Buchanan, Brazos Valley Equine Hospital, Navasota, TX

Introduction
Use of antimicrobials is a common practice of veterinarians. This proceedings will review the common antimicrobials used and identify those that are frequently misused. Extra-label use is a common necessity in equine practice and understanding the spectrum and mechanism of antimicrobials is important to appropriate use.

Common points to consider for antimicrobial use include: expected bacteria for anatomical location being targeted, prophylactic antibiotics given before surgery or induction of anesthesia, bacteriocidal vs bacteriostatic, and concentration and time dependent antibiotics have different dosing strategies.

BETA LACTAMS
Penicillins
1. The mechanism of action is to inhibit mucopeptide synthesis in the cell wall. At appropriate doses and frequency they are bactericidal.
2. This class of bacteria has excellent gram positive activity with some resistance by Staphylococcus spp. As a class there is a very limited gram negative spectrum and they should be combined with a gram negative antibiotic, like aminoglycosides, to cover a broad spectrum. Penicillins have a good anaerobic spectrum except for Bacteroides which produces beta-lactamase enzymes.
3. As an organic acid, penicillins are highly ionized in plasma and have great tissue distribution. Due to their lack of lipid solubility they do not penetrate biologic membranes very well. They have reduced activity in the acid environment of abscesses and necrotic tissue.
4. Penicillins are time dependent and need frequent dosing to maintain levels above the MIC.
5. Penicillins are useful for treating gram positive infections and some clotridial infections. It is especially effective against Streptococcus spp. It is synergistic when combined with an aminoglycoside

Cephalosporins
1. The mechanism of action is to inhibit mucopeptide synthesis in the cell wall. At appropriate doses and frequency they are bactericidal.
2. The spectrum of the specific cephalosporin depends on the drug. While classically classified into generations, newer terminology classifies them into 7 groups based on spectrum and route of administration.
   a. Ceftiofur – bacteriocidal with a broad antimicrobial spectrum including G+, G- and anaerobes.
   b. Cefazolin – primarily G+
   c. Cefotaxime - primarily G-
3. Like penicillins, cephalosporins are widely distributed in tissues.
4. Cephalosporins are time dependent and need frequent dosing to maintain levels above MIC. Depot formulations (like Exceed) are designed to maintain levels on less frequent administration.
5. Ceftiofur is the main product used in veterinary medicine for a variety of mixed infections. It is often combined with an aminoglycoside when a greater gram negative coverage is needed.

AMINOGLYCOSIDE
1. The mechanism of action is to bind to 30s ribosomal subunits and disrupt protein synthesis. They are bacteriocidal.
2. The spectrum is aerobic gram negative and some Mycoplasma spp, Mycobacteria spp, and Staphylococcus spp.
3. As a highly polar base the drug is distributed to extracellular fluid. This has poor penetration into cells and tissue. Because oxygen is required for the uptake of aminoglycosides, there is a limited effect in low oxygen and acidic environments. This limits their ability to treat infections in abscesses and necrotic tissue. There is a significant post antibiotic effect.
4. Aminoglycosides are concentration dependent. When possible dosing is adjusted based on therapeutic drug monitoring.
5. Gentomycin are frequently combined with beta-lactams to provide a broad spectrum coverage. They are also used exclusively when appropriate for treatment of joints and in regional limb perfusions.

POTENTIATED SULFONAMIDES
1. The mechanism is two pronged with the trimethoprim and sulfa component each inhibiting a different part of the pathway for folic acid synthesis. In combination with trimethoprim, they are bacteriocidal.
2. The spectrum is broad against G+ and G- aerobes and some limited effect on anaerobes.
3. As highly lipid soluble drug, potentiaed sulfas distribute well throughout the body and into many tissues. They achieve high concentrations in the CNS. Because of the availability of folic acid to bacteria in area of necrosis, there is limited effect in necrotic tissue.
4. Potentiated sulfas are time dependent antimicrobials. Because of the rapid elimination of trimethoprim in the horse, potentiated sulfas in a 1:5 ratio must be given twice daily to maintain concentrations above the MIC. Sulphadiazine is reported to be superior to sulphamethoxazole in the horse.
5. Potentiated sulfas are a very common antibiotic due to their relative low cost, ease of administration, availability, and broad spectrum. They are primarily used to treat simple infections, although the tissue penetration makes them attractive for treating septic foci when sensitive.

MACROLIDES
1. Macrolides inhibit the 50s ribosomal subunit and protein synthesis. Generally considered bacteriostatic, they may be bacteriocidal at higher doses.
2. The spectrum is predominately G+ aerobes and some limited effect on G- aerobes and anaerobes. They are the primary class of drugs used to treat Rhodococcus equi.
3. As highly lipid soluble drugs, macrolides are widely distributed in the body and have excellent penetration into cells and tissues. The newer macrolides have very high concentration in lung fluid.
4. Macrolides are time dependent. Newer drugs have slower elimination and better absorption leading to extended dosing intervals.
5. Macrolides are used primarily to treat Rhodococcus equi infections in foals. As a class they have a very high risk of a severe and fatal bacterial induced colitis in adult horses.

RIFAMPIN
1. The mechanism of rifampin is to inhibit RNA polymerase interrupting the transcription of RNA to DNA and subsequent protein synthesis.
2. Rifampin has a narrow spectrum of activity against primarily G+ aerobes, anaerobes, and non-enteric G- aerobes. It has good activity against Rhodococcus equi, Mycobacterium spp, Corynebacterium spp, and Streptococcus spp. Resistance is reported to develop rapidly when used as a sole antimicrobial and Rifampin should always be used in combination with other agents. There is in vitro evidence of antagonism with florquinolones.
3. As a highly lipid soluble drug, it is distributed to most tissues and has excellent penetration into cells including phagocytes. It remains active intra-cellularly and in acidic environments.
4. Rifampin is a time dependent antibiotic
5. Rifampin is primarily combined with macrolides, penicillins, chloramphenicol, and potentiated sulfas to treat abscesses. Recent evidence shows absorption of rifampin enzymatically inhibits the absorption of macrolides. Drug Metab Dispos 2011 Sep;39(9):1643-9.

FLUOROQUINOLONE
1. The mechanism of action is to inhibit the DNA gyrase responsible for coiling DNA. They are bacteriocidal.
2. The spectrum is limited to G- aerobes and has limited G+ activity with the exception of some Staphylococcus spp.
3. As a highly lipid soluble drug, it is distributed well into most tissues including low levels into the CNS and eye.
4. Fluoroquinolones are concentration dependent antimicrobials
5. Baytril is the primary member of this class used in horses. It should be used for G- infections after culture. As a routine first choice antibiotic it is not appropriate as a single agent due to its lack of gram positive coverage.

TETRACYCLINE
1. The mechanism of action is to inhibit the 30s ribosomal subunit interrupting protein synthesis. While generally thought to be bacteriostatic, they can be bacteriocidal at high concentrations.
2. Tetracyclines have a broad spectrum of activity with some anaerobic coverage. There effect on rickettsial, anaplasmal and ehrlichial organisms is good.
3. Tetracyclines are widely distributed in the body except into CNS.
4. Tetracyclines are time dependent at lower doses and dose dependent at higher doese
5. Well recognized for their importance in treating anaplasmosis, lymes disease, and rickettsial organisms, tetracyclines are also a useful broad spectrum antibiotic for respiratory infections. Additionally there is interest in the attenuation of the matrix metalloprotease activity, anti-fibrotic activity, anti-inflammatory activity, and anti-collagenase activity. As such Doxycycline is frequently used as an adjunct therapy in laminitis.

CHLORAMPHENICOL
1. The mechanism of chloramphenicol bind to the 50s ribosomal subunit interrupting protein synthesis. They are bacteriostatic
2. Chloramphenicol has a very wide spectrum of activity that includes G+, G-, and anaerobes.
3. As a highly lipid soluble drug it is widely distributed throughout the body achieving therapeutic levels in the liver, kidney, synovial fluid, peritoneal fluid, and CSF.
4. Chloramphenicol is a time dependent drug
5. Chloramphenicol is a useful drug for abscess and chronic bacterial infections.

**METRONIDAZOLE**

1. The mechanism of metronidazole acts by damaging DNA and inhibiting DNA repair
2. Metronidazole has a very narrow spectrum of activity that includes most anaerobic and protozoal infections
3. Widely distributed in the body, metronidazole can be found in most tissues and the CNS after dosing.
4. Metronidazole is generally a dose dependent antibiotic, but can be time dependent for certain bacteria.
5. Metronidazole is indicated for the treatment of anaerobic infections.