Respiratory antimicrobial therapy

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When considering any kind of therapy one must consider the basic concepts of pharmacology, and this is particularly true in the treatment of respiratory infections. The first concept to address relates to the simple question of whether the antimicrobial selected is appropriate for the likely target of the therapy. To understand this one must have a concept of the drug's mechanism of action and how that relates to the different classes of bacteria. Secondly, how is the drug to be delivered, and is that route of delivery likely to achieve therapeutic concentrations of the drug at the affected site? There are key factors in the physiology of the lung that profoundly affect our ability to effectively deliver antimicrobials to the lower respiratory tract, and the failure to take these into account will preclude effective treatment. The physical and pharmacologic characteristics of the different antimicrobials and their interactions with the respiratory tract will also have a significant influence on the efficiency and efficacy of our treatment of lower respiratory infections.

The most common invaders of the lower respiratory tract are those organisms comprising the normal population of the upper respiratory tract. *Streptococcus equi zoopidemicus* is the most common pathogen encountered, but polymicrobial infections are common. These often involve organisms such as *Actinobacillus equuli, Bordetella bronchiiseptica, E coli* and *Pasteurella* spp. Anaerobic involvement is common in horses with pleuropneumonia or pulmonary abscessation, with *Bacteroides* spp, *Fusobacterium* spp, *Peptostreptococcus* spp, and *Clostridim* spp being commonly isolated. Due to the polymicrobial nature of many pulmonary infections broad-spectrum therapy is generally indicated. *Rhodococcus equi* is a primary pulmonary pathogen of foals and requires treatment with drugs capable of achieving high intracellular concentrations.

Beta-lactam antibiotics bind to penicillin binding proteins, interfering with bacterial cell wall synthesis, leading to formation of defective cell walls that are osmotically unstable. Cell death usually results from cell lysis. These drugs include the penicillins, synthetic penicillins, cephalosporins and carbapenems. Modifications of the basic penicillin or cephalosporin molecule confer differences in antimicrobial activity, as seen with the synthetic penicillins and third generation cephalosporins, which exhibit increased gram-negative spectrum. Increased stability against beta-lactamases may also be achieved (carbapenems). These drugs must be present in the tissues at concentrations greater than the minimum inhibitory concentration (MIC) throughout most, preferably all, of the dosage interval in order to be effective. This makes them 'time-dependent' antimicrobials. Penicillin G is the most commonly utilized beta-lactam antimicrobial in horses, and is administered at 20,000 IU/kg, with the procaine suspension being administered intramuscularly (IM) every 12 hours and the aqueous solutions of sodium or potassium penicillin being administered intravenously (IV) every 6 hours. Toxicity is low for the penicillins, and is often due to reactions to intravenous/intra-arterial injection of the procaine form, although anaphylactic reactions have been reported. Penicillins may be combined with beta-lactamase inhibitors, such as clavulanic acid, which are believed to protect the penicillin from breakdown by the beta-lactamases.

The primary cephalosporin administered to horses is ceftiofur, a third generation drug. It is considered to have a broad spectrum, with an emphasis toward gram-negative coverage. It is usually administered at 2.2 to 4.4 mg/kg IM or IV every 12 hours (Naxcel). Alternatively the ceftiofur crystalline free acid (Excede) form can be administered as two intramuscular injections, 4 days apart, at a dose of 3.0 mg/lb (6.6 mg/kg). There are anecdotal reports of severe colitis associated with ceftiofur administration; especially in weanling aged horses and horses in heavy training. The possibility for kidney damage also exists with this drug, although this is rarely reported. Ceftiofur has also been empirically administered to horses by aerosol, at 1 mg/kg in sterile water every twelve hours.

The aminoglycosides continue to constitute a major component of the equine clinician's armamentarium, despite the potential for nephrotoxicity. These drugs exhibit primarily a gram-negative spectrum. Their mechanism of action involves binding to the bacterial 30s ribosomal subunit, and interference with the translation of mRNA thereby inhibiting bacterial protein synthesis. They may also interfere with the initiation of DNA replication. The bacterial penetration of aminoglycosides is in part an oxygen-dependent transport process and partially accomplished by passive diffusion. The dependence on oxygen-driven transport renders anaerobes resistant to the aminoglycosides. The role of passive diffusion leads to a dependence on high tissue concentrations of the drug to achieve high intracellular concentrations, making these compounds what are known as "concentration-dependent." Routes of administration and/or dosage schedules that are associated with high peak concentrations at the site of infection, such as once-daily dosing may be associated with improved clinical responses. Gentamicin is dosed to adult horses at 6.6 mg/kg IV or IM every 24 hours, while amikacin is typically dosed at 15 to 20 mg/kg IV every 24 hours in adult horses.

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Tetracyclines interfere with protein synthesis. They are bacteriostatic and broad spectrum, possessing activity against a wide variety of bacteria, protozoa, as well as *Mycoplasma and Rickettsia*. These compounds are time-dependent in nature. The most commonly used compounds in the equine are oxytetracycline and doxycycline. Toxicity has been reported due to disturbance of gastrointestinal flora leading to the development of colitis. As the tetracyclines are primarily eliminated via the urinary tract there is the risk for toxicity in animals with renal insufficiency. Rapid intravenous injection of oxytetracycline is associated with collapse in horses, perhaps due to chelation of calcium in the blood. Oxytetracycline is administered to horses at 2.5 to 8 mg/kg slowly IV once or twice daily, usually diluted in 0.5 to 1 liter of normal saline and administered over 30 minutes. Doxycycline is administered at 10 mg/kg orally twice daily, and has not been reported to be associated with colitis at this dose. Due to increased cost as well as variable pharmacokinetics associated with doxycycline, minocycline has been increasingly used in horses, at a dosage of 4 mg/kg orally twice daily.

Chloramphenicol also inhibits protein synthesis, and is considered to be bacteriostatic. The half-life of chloramphenicol is short, requiring frequent dosing (6-hour intervals). The drug is widely distributed to the tissues, and has a wide spectrum of action including both gram-positive and gram-negative bacteria, as well as *Rickettsia, Mycoplasma* and anaerobes. It is a time-dependent drug, and due to its short half-life it must be administered frequently to maintain adequate tissue concentrations. Animal toxicity is rare and is associated with reversible or irreversible bone marrow suppression. Human health concerns due to aplastic anemia have made it illegal to use this drug in food animals, and necessitate thorough client education when dispensing this drug (avoid contact with aerosolized drug or contact with mucous membranes). Chloramphenicol is administered to horses and foals at 50 mg/kg orally every 6 hours.

The macrolides (erythromycin, azithromycin, clarithromycin) also inhibit protein synthesis. They are considered to be bacteriostatic, and have a broad spectrum. Their primary application is in the treatment of rhodococcal pneumonia in foals. The use of erythromycin in adults has been associated with the development of colitis, which can be fatal, and should therefore be avoided. Macrolides are eliminated by hepatic metabolism and can affect the pharmacokinetics of other drugs metabolized by the P450 system. Erythromycin administration in foals with rhodococcal pneumonia has been associated with frequent hyperthermia and diarrhea, and this drug is no longer commonly used for this purpose in most areas of the US. Azithromycin is used at 10 mg/kg orally once daily for 5 to 7 days, then every other day. Clarithromycin is used at 7.5 mg/kg orally twice daily. Rifampin therapy is typically administered in conjunction with the macrolides in the treatment of rhodococcal pneumonia due to synergistic effects. The combination of clarithromycin-rifampin has been shown to be more effective than erythromycin-rifampin or azithromycin-rifampin in the treatment of rhodococcal pneumonia.¹

Rifampin is a macrocyclic antibiotic and is used primarily in horses as an adjunct therapy to the macrolides for treatment of rhodococcal pneumonia. It can be combined with other antibiotics for treatment of abscesses, but should never be used alone due to rapidly developing resistance. The dose in foals is 5 mg/kg orally twice daily, while it is administered at 10 mg/kg orally twice daily in adults. Rifampin is reported to be particularly effective against staphylococcal infections. Rifampin is always used in combination with another antimicrobial as resistance develops rapidly when it is used as a sole therapy. Rifampin will cause reddish discoloration of the urine.

Fluoroquinolones inhibit bacterial DNA supercoiling, thereby interfering with bacterial reproduction. These drugs have a relatively broad spectrum, with excellent activity against gram-negative organisms, but minimal activity against *Streptococci*. They are bactericidal, and they achieve higher concentrations in the respiratory tract than in the serum. The fluoroquinolones exhibit peak concentration-dependent bactericidal effects and prolonged post-antibiotic effects, similar to the aminoglycosides. As a result they can be given at relatively high doses at a decreased frequency. Toxicity is primarily due to the effects on cartilage maturation, resulting in a contraindication to their use in growing animals. Significant elimination occurs via the urinary tract. *Enrofloxacin* is the most commonly used compound, and is administered at 7.5 mg/kg orally once daily or at 5 mg/kg IV once daily.

Potentiated sulfon compounds are very commonly used, and these drugs interfere with the synthesis of folic acid, and their effect is bactericidal. These compounds distribute well to the tissues, including the respiratory tract. Toxicity is most commonly associated with disturbance of gastrointestinal flora associated with the development of colitis. Resistance is very common, due to their ubiquitous use, rendering these compounds of decreasing clinical utility. When organisms are susceptible, however, they can be employed quite effectively. Dosage of *triamethoprim/sulfamethoxazole* is 30 mg/kg orally every 12 hours.

*Metronidazole* is a nitroimidazole antimicrobial that is highly effective against anaerobic organisms. This drug is administered in an inactive form, but once it diffuses into the bacterial cell it is reduced to a number of reactive intermediates that are responsible for damage to the components of the bacterial cell, leading to cytotoxicity. This unique mechanism results in selective toxicity against anaerobes and microaerophilic organisms. Metronidazole
therapy should be administered to any adult equine patient suspected of having pulmonary abscession or pleural involvement. The typical dosage is 15 mg/kg orally every 8 hours.

While we are all familiar with the common synergistic drug combinations, such as trimethoprim/sulfa and penicillin/gentamicin there are other antimicrobial combinations with the potential for synergism. High rates of synergy have been observed in vitro with combinations of penicillins and fluoroquinolones, rifampin and cephalosporins, chloramphenicol and cephalosporins, and fluoroquinolones and cephalosporins. Additive effects are often seen as well, such as those observed with macrolides and rifampin.

One of the major limitations of systemic antimicrobial therapy for the treatment of lower respiratory infectious disease is the low pulmonary penetration of many antimicrobials, and it has been shown in human patients that the therapeutic outcome of respiratory infections is more closely associated with airway rather than serum antimicrobial concentrations. The rate of absorption, serum half-life and time-concentration relationships within the lung determine the frequency and route of administration required to achieve and maintain therapeutic concentrations at the site of infection. Drugs that are highly lipid soluble are generally absorbed better following oral administration and distribute more fully to all of the tissues, including the lung, while water soluble drugs tend to be more poorly absorbed and tend to distribute primarily within the extracellular water. The water-soluble drugs also tend to penetrate epithelia poorly, limiting their ability to achieve therapeutic concentrations within the lumen of the respiratory tract. The presence of inflammation will, however, allow for increased tissue permeability of the respiratory mucosa. The resolution of inflammation allows for epithelial restitution, which limits the ability of water-soluble drugs to maintain therapeutic respiratory concentrations as healing progresses. Recurrent infections may therefore result.

The pharmacodynamic characteristics of the different antimicrobials also impact on decisions regarding the route and frequency of administration. The two fundamental classes of drugs are the time-dependent and the concentration-dependent antimicrobials. Time-dependent antimicrobials, such as the beta-lactams, require that the concentration at the site of infection be maintained above the minimum inhibitory concentration (MIC) for as much of the treatment interval as possible. These drugs benefit from intramuscular and oral administration, as slower absorption provides for lower serum concentrations that are maintained for longer periods of time. Peak-concentration dependent drugs require high peak serum concentrations for maximal efficacy (10 times greater than MIC for the aminoglycosides), but do not require high concentrations throughout the treatment interval. These compounds benefit from intravenous or topical administration, with prolonged treatment intervals.

Aerosol administration of antimicrobials has been demonstrated to achieve high concentrations of these agents at the respiratory mucosal surface, while minimizing the development of systemic side effects. Other potential advantages to delivering medications to the lower respiratory tract by aerosolization include a decrease in the total dose administered, avoidance of systemic side effects and a rapid onset of action. The administration of antimicrobials by aerosolization does have limitations, however, including potential problems with drug delivery and pulmonary irritation, as well as the expense of the required equipment and the time required for administration. We have primarily used gentamicin (2.2 mg/kg diluted to 20 mL with sterile saline), ceftriaxone (2.2 mg/kg diluted to 20 mL with sterile water) for aerosol administration in our clinic. Aerosolized gentamicin has been demonstrated to achieve higher local concentrations with minimal systemic absorption and minimal lower respiratory inflammation.1,4

Therapy of equine viral respiratory disease is primarily by means of rest, anti-inflammatories and treatment of secondary bacterial infections as necessary. Specific antiviral therapy against herpesviruses with acyclovir is an area of debate due to recent evidence that therapeutic levels are difficult to achieve following oral administration. Valacyclovir has superior oral absorption, but is primarily reserved for the treatment of EHV-1 neurological disease. Ribavirin holds some promise as an inhaled therapy for influenza, but is not yet clinically applicable in the horse.

Antifungal treatment is rarely required in equine pneumonia, and fungal pneumonia is typically associated with severe debilitation and neutropenia, leading to a state of immunosuppression and is usually fatal. The most commonly used antifungal in horses is probably amphotericin B, but this drug has a high potential for toxicity and should only be used when fungal involvement is definitively proven. Aerosolized delivery of amphotericin B has been utilized in humans with fungal pneumonia, but although it shows some potential clinically appropriate dosing regimens have not been determined in the horse. Azole antifungals may represent a superior approach, due to their superior safety profiles. Inhaled itraconazole has been reported to be effective in equine fungal pneumonia, and oral voriconazole is well absorbed in the horse and should be efficacious against Aspergillus organisms based upon human studies.

Careful consideration of the site and extent of the infection, as well as the likely pathogens involved, will guide the clinician to the selection of an optimal antimicrobial regimen for the treatment of respiratory infections. An
understanding of the pharmacologic characteristics of the drugs available will also aid in ensuring that therapeutic concentrations can be achieved at the site of infection, allowing for effective treatment.

REFERENCES