Antimicrobial therapy in foals

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Antimicrobial therapy has long played a vital role in the treatment of equine bacterial diseases. However, the arsenal of equine-approved antimicrobial agents available to veterinarians is limited. Few antimicrobial drugs are licensed for use in horses, often requiring the clinician to resort to extra-label use. Unfortunately, many human drugs are not appropriate for use in horses because of poor oral bioavailability, cost, lack of species-specific pharmacokinetic data, or risk of serious adverse effects such as enterocolitis.

While development of new antimicrobials initially outpaced development of bacterial resistance, the trend has reversed over the last 10 years. This has resulted in emergence of resistant bacteria as a major problem worldwide. Although any use of antimicrobials has the potential to contribute to development of resistance, antimicrobial therapy is vital for controlling equine infectious disease. Thus, it is the veterinarian's responsibility to use antimicrobials judiciously. In general terms, judicious use is defined as the optimal selection of a drug, dose, dosing interval, and duration of therapy along with reduction of inappropriate or excessive use of antimicrobials. Judicious use of antimicrobials is essential to maximize treatment efficacy while minimizing development of bacterial resistance, occurrence of adverse reactions, and relapses. This technical bulletin provides an overview of current concepts that guide rational antimicrobial therapy in horses.

General principles of antimicrobial drug use in horses

A variety of veterinary organizations have developed generic recommendations for judicious antimicrobial drug use. The most comprehensive guidelines for equine practitioners is a consensus statement issued by the American College of Veterinary Internal Medicine.[1] Based on these guidelines, key prudent-use principles are:

- Antimicrobials should only be used when there is a reasonable likelihood that a bacterial infection is present.
- Whenever possible, antimicrobial therapy should be based on culture and in vitro susceptibility results.
- A drug with a spectrum of activity as narrow as possible should be selected.
- Extra-label use should be avoided when on-label options are available.
- Antimicrobial agents should be used for as short a period as necessary.
- Antimicrobials that are important for treating refractory or serious infections in humans should be reserved and only used after careful consideration, and only when culture and susceptibility results indicate that there are no alternatives.
- Methods to decrease the risk and incidence of infection should be emphasized in order to decrease the need for antimicrobials.

To underscore the last point, antimicrobial therapy should never be used as a substitute for good disease control and hygiene, appropriate medical and surgical practices, or as an alternative to sound animal husbandry.

In choosing the appropriate antimicrobial agent, the clinician must consider a variety of factors including: (1) the likely identity of the infecting microorganism(s), (2) their typical in vitro susceptibility patterns or the clinical response in equine patients infected with the same pathogens, (3) the nature and site of the infectious disease process, (4) the pharmacokinetic characteristics of the chosen antimicrobial agent in horses such as bioavailability, tissue distribution, and rate of elimination, (5) the pharmacodynamic properties of the antimicrobial agent selected, (6) its safety in horses, and (7) the cost of therapy. In all situations, therapy should be adjusted based on initial clinical response and, when available, results of culture and susceptibility testing.

Common bacterial pathogens of horses and their typical susceptibility patterns

Because the identity and in vitro susceptibility of an infecting microorganism are rarely known when therapy is begun, initial therapy is usually empirical and based on knowledge of the agents likely to be present and their historical susceptibility. In some cases, the most likely etiologic agent is highly predictable based on the clinical presentation and the horse's history. For example, abscessation of the submandibular and retropharyngeal lymph nodes is most likely caused by *Streptococcus equi* subspecies *equi* (*S. equi*). Lower respiratory tract infection in adult horses is most commonly associated with *S. equi* subspecies *zooepidemicus* (*S. zooepidemicus*), followed by non-enteric gram-negative bacteria such as *Pasteurella* spp.

On the other hand, pleuropneumonia in an adult horse may be caused by any one or combinations of a number of bacteria and thus requires bacteriologic culture of a tracheobronchial aspirate and pleural fluid to determine etiology. Similarly, peritonitis, urinary tract infections, musculoskeletal infections, cellulitis, and mastitis may be caused by a variety of bacteria, so that initial therapy with a broad-spectrum antimicrobial agent is recommended. The selection of the antimicrobial agent and route of administration will depend on severity of disease and site of infection.

Many infectious diseases involving the neonatal foal such as pneumonia, peritonitis, meningitis, osteomyelitis, septic arthritis, and omphalophlebitis are the sequelae of bacteremia. Gram-negative bacteria account for 70% to 95% of the microorganisms isolated from cultures of blood samples in equine neonates, with *Escherichia coli* being by far the most common isolate.[2,3] Gram-positive cocci account for approximately 25% of isolates.[4] Treatment protocols for equine neonates must include antimicrobials with a high level of activity against enteric gram-negative bacteria while providing adequate coverage against gram-positive microorganisms.

Bacteria that are typically considered to be contaminants or part of the normal microflora need not be tested for susceptibility. However, when pathogenic bacteria are identified, selection of an antimicrobial agent is often simplified because some common equine pathogens have predictable in vitro susceptibility profiles. For example, β-hemolytic streptococci and *Pasteurella* spp. are almost invariably susceptible to penicillin, ampicillin, and ceftiofur. In contrast, Enterobacteraceae, *Pseudomonas* spp., *Enterococcus* spp. and *Staphylococcus* spp. have unpredictable susceptibility profiles. In vitro susceptibility testing is particularly important for these bacterial species.

Causes of treatment failure

Therapeutic failure may occur when the disease process does not have a bacterial etiology, when there is a change in the bacterial population at the site of infection, or when the pathogens have become resistant to the chosen antimicrobial agent. Therapeutic failure may also result from pharmacokinetic factors that are often underappreciated by clinicians, for example when there is poor diffusion of the drug at the site of infection. The rate and extent of penetration of a drug into most sites outside the vascular space are determined by the drug's concentration in plasma, molecular charge and size, extent of plasma protein binding, and blood flow. Thus, effective antimicrobial drug concentrations may not be attained in tissues that are poorly vascularized (e.g., abscess, sequestered bone). In other tissues such as the central nervous system, the eye, and the prostate, a lipid membrane provides a barrier to drug diffusion. Lipophilic drugs such as macrolides, fluoroquinolones, tetracyclines, rifampin, trimethoprim, and chloramphenicol are more likely to diffuse across lipid membranes and reach therapeutic concentrations in these tissues. These drugs are also more likely to accumulate within cells and represent an advantage for the treatment of susceptible intracellular bacterial pathogens.

Therapeutic failure may occur when the microenvironment at the site of infection is not conductive to antimicrobial activity. For example, gentamicin requires an oxidative transport system to penetrate the bacterial membrane. Therefore, a given microorganism may be susceptible to gentamicin in vitro but the drug may be ineffective in an anaerobic microenvironment. Similarly, the acidic environment of infected tissues may reduce the efficacy of macrolides, fluoroquinolones, and aminoglycosides. Thus, the goal of antimicrobial therapy is to select an antibiotic that, in addition to exhibiting good antimicrobial activity against the infecting microorganism, will achieve therapeutic concentrations in the infected area.

Of course, noncompliance is a major cause of treatment failure. This is particularly true for antimicrobials used in an unapproved manner, in which case data may not be available to determine an appropriate dosage regimen. Nor can compliance be assumed when a horse owner treats an animal at a veterinarian's direction. There is general consensus that noncompliance occurs in a high percentage of treatment regimens in human and veterinary medicine. For example, compliance rates of 44% to 64% for canine antimicrobial treatment have been reported.[5,6] The reasons for noncompliance are manifold, and range from fractious animals to simple oversight on the part of the owner.

Minimum inhibitory concentration versus breakpoint – what is the difference?

In vitro bacterial susceptibility is determined by disk diffusion, concentration-gradient, or dilution methodologies. Disk diffusion provides qualitative susceptibility data whereas broth-dilution methods and the concentration-gradient test (E test) generate a minimum inhibitory concentration (MIC) expressed quantitatively in µg/mL. All of the tests assess inhibition of bacterial growth rather than killing of the pathogen as the endpoint. Susceptibility designations are determined by comparing the microorganism's MIC (or zone of inhibition if the disk diffusion method is used) to clinical breakpoints established by the Clinical Laboratory Standards Institute (CLSI).

Simply stated, an antimicrobial's clinical breakpoint is the concentration above and below which specific bacterial isolates are categorized as susceptible, intermediate, or resistant. Clinical breakpoints take an antimicrobial's MIC into consideration, but are based on additional interpretive criteria. Specifically, clinical breakpoints are determined by (1) the range of in vitro MICs of an antimicrobial for representative populations of specific bacterial pathogens, (2) pharmacokinetic parameters of the antimicrobial in target animal species (e.g., drug distribution at the site of infection), and when available, (3) results of clinical trials in the target species, the ultimate standard of efficacy. Clinical breakpoints are relevant for the specific bacteria, specific drug, and specific organ system infected only. As an example, the breakpoint for ceftiofur in horses is only relevant to *S. zooepidemicus* in equine lung, and infections in other organs caused by aberrant *S. zooepidemicus* infections would not necessarily have the same clinical breakpoint.

Results of in vitro susceptibility tests are presented to the clinician by designating the pathogen as susceptible, intermediate, or resistant. The CLSI defines the three susceptibility designations as follows:

- *Susceptible* – An infection caused by the specific isolate can be effectively treated with the recommended antimicrobial and dosage regimen; CLSI generally requires clinical response rates of at least 80% at a specific MIC before organisms are categorized as susceptible.
- *Intermediate* – An infection by the isolate can be treated at body sites where drugs are physiologically concentrated or when a high dosage can be used; also indicates a "buffer zone" that should prevent minor technical factors from causing major discrepancies in interpretations.
- *Resistant* – An infecting isolate is not inhibited by achievable concentrations of the drug with normal dosage schedules; clinical efficacy has not been reliable in treatment studies.

Interpreting MIC values

When species-specific breakpoints are used, pathogens with an MIC below an antimicrobial's susceptibility breakpoint have a higher probability for treatment success, and organisms with an MIC above the resistance breakpoint have a lower probability of treatment success. However, there is no evidence that efficacy increases the further the MIC is below the breakpoint. Conversely, it should be noted that a relatively high MIC in itself is not necessarily an indicator of resistance. Some resistance breakpoints have been set at >32 µg/mL or higher (e.g., the resistance breakpoint for *Pasteurella multocida* against tulathromycin for bovine respiratory disease is 64 µg/mL).

For the equine practitioner, an important limitation in interpreting the results of in vitro susceptibility data is that breakpoints for only a small number of drugs (ceftiofur, gentamicin, ampicillin) have been established for specific infections in horses. For all other antimicrobials, the breakpoints have been adapted from human or other domestic animal species data. For these antimicrobials, a result indicating susceptibility is unquestionably preferable to one indicating resistance. However, there are no data correlating the results to clinical efficacy and there is no guarantee that the breakpoint is valid for a given pathogen or site of infection in horses. For example, the CLSI breakpoint for susceptibility to doxycycline is ≤4 µg/mL based on human pharmacokinetic and clinical efficacy data. Administration of oral doxycyline to an adult horse at the recommended dosage of 10 mg/kg results in peak serum, synovial fluid and peritoneal fluid concentrations of approximately 0.5 µg/mL.[7] A pathogen isolated from the synovial fluid of a horse with a MIC of 4 µg/mL would be reported as susceptible even though such concentrations are far from achievable in horses. Based on pharmacokinetic data in horses, a breakpoint of ≤0.25 µg/mL would be more appropriate as a susceptibility standard for doxycycline.[7,8] Thus the lack of equine- and disease-specific interpretive criteria is one factor that may explain discrepancies between in vitro susceptibility and clinical response. By itself, in vitro susceptibility of a specific pathogen does not guarantee clinical outcome. Other factors, such as the host animal's age, immune status, and presence of mixed infections can contribute to individual clinical response.

Pharmacokinetic-pharmacodynamic data determine optimal dosage

Determination of the appropriate dose and dosing interval of an antimicrobial agent requires knowledge and integration of its pharmacokinetics and pharmacodynamic properties. The pharmacokinetic properties of a drug describe its disposition within the body and include drug absorption, distribution, metabolism, and excretion. Pharmacodynamic properties address the relationship between drug concentration and antimicrobial activity. Drug pharmacokinetic features, such as plasma concentrations over time and area under the serum concentration-time curve (AUC), when integrated with MIC values, can predict the probability of bacterial eradication and clinical success. These pharmacokinetic and pharmacodynamic relationships may also play an important role in preventing the genetic selection and spread of resistant strains.

The most significant factor determining the efficacy of β-lactams, trimethoprim-sulfonamide combinations, and most bacteriostatic agents such as macrolides, tetracyclines, and chloramphenicol is the length of time that serum concentrations exceed the MIC of the pathogen.[9] Increasing the concentration of the drug several-fold above the MIC does not significantly increase the rate of microbial killing. Rather, it is the length of time that bacteria are exposed to concentrations of these drugs above the MIC that dictates killing effect. Therefore, optimal dosing of such antimicrobial agents typically involves frequent administration.

Other antimicrobial agents such as the aminoglycosides, fluoroquinolones, and metronidazole exert concentration-dependent killing characteristics. Their rate of killing increases as the drug concentration increases above the MIC for the pathogen, so it is not necessary or even beneficial to maintain drug levels above the MIC between doses. Thus, optimal dosing of concentration-dependant drugs involves administration of high doses with long dosing intervals. With aminoglycosides and fluoroquinolones, the optimal C_{max}-to-MIC ratio is 8-10. Some drugs exert characteristics of both time and concentration dependent activity. The best predictor of efficacy for these drugs is the 24-hour AUC-to-MIC ratio. Glycopeptides, rifampin and, to some extent, fluoroquinolones fall into this category.[10]

Conclusion

Judicious use of antimicrobials consists of a discriminating approach to selection and administration of anti-infective agents that maximizes treatment efficacy while minimizing adverse effects and treatment failures. Perhaps the most important aspects of judicious use are to follow initial empirical treatment with culture and susceptibility testing by a diagnostic facility that uses CLSI standards, and then administer an antimicrobial agent with an indication and activity at the site of infection against the target pathogen that has been identified.

References

1. Morley PS, Apley MD, Besser TE, et al: Antimicrobial drug use in veterinary medicine. J Vet Intern Med 2005;19:617-629.
2. Marsh PS, Palmer JE: Bacterial isolates from blood and their susceptibility patterns in critically ill foals: 543 cases (1991-1998). J Am Vet Med Assoc 2001;218:1608-1610.
3. Wilson WD, Madigan JE: Comparison of bacteriologic culture of blood and necropsy specimens for determining the cause of foal septicemia: 47 cases (1978-1987). J Am Vet Med Assoc 1989;195:1759-1763.
4. Sanchez LC, Giguère S, Lester GD: Factors associated with survival of neonatal foals with bacteremia and racing performance of surviving Thoroughbreds: 423 cases (1982-2007). J Am Vet Med Assoc 2008; 233:1446-1452.
5. Grave K, Tanem H: Compliance with short-term oral antibacterial drug treatment in dogs. J Small Anim Pract 1999;40:158-162.
6. Adams VJ, Campbell JR, Waldner CL, et al: Evaluation of client compliance with short-term administration of antimicrobials in dogs. J Am Vet Med Assoc 2005;226:567-574.
7. Bryant JE, Brown MP, Gronwall RR, et al: Study of intragastric administration of doxycycline: pharmacokinetics including body fluid, endometrial and minimum inhibitory concentrations. Equine Vet J 2000;32:233-238.
8. Davis JL, Salmon JH, Papich MG: Pharmacokinetics and tissue distribution of doxycycline after oral administration of single and multiple doses in horses. Am J Vet Res 2006;67:310-316.
9. Andes D, Anon J, Jacobs MR, et al: Application of pharmacokinetics and pharmacodynamics to antimicrobial therapy of respiratory tract infections. Clin Lab Med 2004;24:477-502.
10. Craig WA: Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am 2003;17:479-501.

Additional reading

Papich MG, Davis JL: Antimicrobial therapy. In: Sellon DC, Long MT, eds. Equine infectious diseases. St Louis: Saunders-Elsevier; 2007. p. 578-591.

Weese S: Prudent use of antimicrobials. In: Giguère S, Prescott JF, Baggot JD, et al, eds. Antimicrobial therapy in veterinary medicine, 4th ed. Ames(IA): Blackwell Publishing; 2006. p. 437-446.

Wilson WD: Rational selection of antimicrobials for use in horses. Proc Annu Conv Am Assoc Equine Pract; 2001. p. 75-93.