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RATIONAL ANTIMICROBIAL THERAPY: WHAT WORKS, WHERE, AND WHY?
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INTRODUCTION
Antibiotic therapy has made many advances that has given veterinary medicine a large number of effective drugs and provided pharmacokinetic and pharmacodynamic information to guide dosing. New approaches to bacterial identification and susceptibility testing have helped to provide information for the most appropriate drug selection. This presentation will review the current concepts that guide antibiotic therapy in veterinary medicine and provide important strategies for effective dosing.

BACTERIAL SUSCEPTIBILITY

Usually Susceptible Bacteria
Staphylococcus isolated from small animals is usually S. intermedius, although S. aureus are identified often as well. S. intermedius will usually have a predictable susceptibility to β-lactamase resistant β-lactam antibiotics such as amoxicillin combined with a β-lactamase inhibitor (Clavamox), or first-generation cephalosporin such as cephalexin or cefadroxil, or the third-generation cephalosporin, cefpodoxime (Simplicef). Staphylococcus also is susceptible to oxacillin and dicloxacillin but these are not used as commonly in small animal medicine. Despite frequent use of first-generation cephalosporins for S. intermedius most are still susceptible. Most staphylococci are also sensitive to fluoroquinolones. The majority of staphylococci are sensitive to lincosamides (clindamycin, lincomycin), trimethoprim-sulfonamides, or erythromycin, but resistance can occur in as high as 25% of the cases.

If the bacteria is an anaerobe (for example, Clostridium, Fusobacterium, Prevotella, Actinomyces, or Porphyromonas) predictable results can be attained by administering a penicillin, chloramphenicol, metronidazole, clindamycin, amoxicillin-clavulanic acid, or one of the second-generation cephalosporins such as cefotetan or cefoxitin. Metronidazole is consistently highly active against anaerobes including B. fragilis. The activity of first-generation cephalosporins, trimethoprim-sulfonamides/ormetoprim-sulfonamides, or fluoroquinolones for an anaerobic infection is unpredictable. If the anaerobe is from the Bacteroides fragilis group, resistance may be more of a problem because they produce a beta-lactamase that may inactivate 1\textsuperscript{st} generation cephalosporins and ampicillin/amoxicillin. Some of these Bacteroides may also be resistant to clindamycin. More resistant strains of Bacteroides have been observed in recent years (Jang et al 1997).

Problem, or Resistant Bacteria
If the organism is Pseudomonas aeruginosa, Enterobacter, Klebsiella, Escherichia coli, or Proteus, resistance is anticipated to the more commonly-used antibiotics and a susceptibility test is advised. Testing for susceptibility should follow accepted standards, such as those published by the Clinical Laboratory Standards Institute (CLSI, formerly NCCLS) (NCCLS 2004). In one report, among nonenteric E. coli, only 23% were sensitive to a 1\textsuperscript{st} generation
cephalosporin and less than half were sensitive to ampicillin. In the same study, 13%, and 23% were intermediate or resistant to enrofloxacin, and orbifloxacin, respectively (Oluoch, et al 2001). In urinary tract infections (Torres et al, 2005) half of the E. coli were resistant to cephalexin, and only 22% were sensitive to enrofloxacin. These data as well as other studies has guided our selection of empirical antibiotics for infections caused by these organisms. For initial therapy we usually expect the gram-negative enteric bacteria to be susceptible to fluoroquinolones and aminoglycosides. An extended-spectrum cephalosporin (second- or third-generation cephalosporin) usually is active against enteric-gram negative bacteria, but will not be active against Pseudomonas aeruginosa. If the organism is a Pseudomonas aeruginosa, inherent resistance against many drugs is common, but it may be susceptible to fluoroquinolones, aminoglycosides, or extended-spectrum penicillin such as ticarcillin or piperacillin. Isolates of Pseudomonas aeruginosa from otitis are usually sensitive to ceftazidime and ticarcillin, but less sensitive to enrofloxacin and gentamicin. When administering a fluoroquinolone to treat Pseudomonas aeruginosa the high-end of the dose range is suggested. Of the currently available fluoroquinolones, (human or veterinary drugs) ciprofloxacin is the most active against Pseudomonas aeruginosa.

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 (Nix et al, 1991). There is really no such thing as “good penetration” and “poor penetration” when referring to most drugs in most tissues. Pores (fenestrations) or microchannels in the endothelium of capillaries are large enough to allow drug molecules to pass through unless the drug is restricted by protein binding in the blood. In these cases in which drug diffusion is perfusion-rate limited (determine primarily by blood perfusion), the unbound drug concentration in plasma should parallel the drug concentration in tissue fluid. Tissues lacking pores or channels may inhibit penetration of some drugs (discussed below).

In some tissues a lipid membrane (such as tight junctions on 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. A functional membrane pump (p-glycoprotein) also contributes to the barrier. There also is a barrier between plasma and bronchial epithelium (blood:bronchus barrier). This limits drug concentrations of some drugs in the bronchial secretions and epithelial fluid of the airways. Lipophilic drugs may be more likely to diffuse through the blood-bronchus barrier and reach effective drug concentrations in bronchial secretions.

Intracellular Infections
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. Intracellular infections present another problem. Intracellular organisms such as Brucella, Chlamydia, Rickettsia, Bartonella and Mycobacteria are examples of intracellular pathogens. For drugs to reach intracellular sites, they must
be carried into the cell or diffuse passively. Generally, lipid-soluble drugs are best able to diffuse through the cell membrane for intracellular infections. Examples of drugs that accumulate in leukocytes, fibroblasts, macrophages, and other cells are fluoroquinolones, lincosamides (clindamycin, lincomycin), macrolides (erythromycin, clarithromycin), and the azalides (azithromycin) (Pasqual, 1995). β-lactam antibiotics and aminoglycosides do not reach effective concentrations within cells. Fluoroquinolones and tetracyclines such as doxycycline are frequently administered to treat *Rickettsia* and *Ehrlichia* infections. There is good evidence for efficacy of doxycycline or fluoroquinolones (enrofloxacin is the only one tested) for treating *Rickettsia*, but only doxycycline should be considered for its efficacy for treating canine ehrlichiosis.

**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 (glycocalyx) at the site of infection (Smith 2005). Cellular debris and infected tissue can inhibit the action of trimethoprim-sulfonamide combinations through the secretion of thymidine and PABA, both known to be inhibitors of the action of these drugs. This may explain why trimethoprim-sulfonamide combinations have not been effective in some infected tissues. Cations can adversely affect the activity of antimicrobials at the site of infection. Two important drug groups diminished in activity by cations such as Mg²⁺, Al³⁺, Fe³⁺, and Ca²⁺ are fluoroquinolones and aminoglycosides. (Cations such as magnesium, iron, and aluminum also can inhibit oral absorption of fluoroquinolones.)

An 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 (eg, extremities during shock, sequestered bone fragments, and endocardial valves).

**PHARMACOKINETIC-PHARMACODYNAMIC (PK-PD) PRINCIPLES**

To achieve a cure, the drug concentration in plasma, serum, or tissue fluid should be maintained above the minimum inhibitory concentration (MIC), or a 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 peak concentration and the time above the MIC that is needed for a cure. Pharmacokinetic-pharmacodynamic (PK-PD) relationships of antibiotics attempt to explain how these factors can correlate with clinical outcome (Hyatt et al. 1995). The $C_{\text{MAX}}$ is simply the maximum plasma concentration attained during a dosing interval. The $C_{\text{MAX}}$ is related to the MIC by the
**REFERENCES CITED**

4. NCCLS (2004): Performance standards for antimicrobial susceptibility testing; fourteenth informational supplement. M100-S14, 2004; 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087.