

PRUDENT USE OF ANTIMICROBIALS



BASICS

OVERVIEW

- Antimicrobial drugs include any natural, semi-synthetic, or synthetic substance, including antifungal, antiviral, and antibacterial agents that kill or inhibit the growth of a microorganism with little or no damage to the host.
- While technically not the same thing, antimicrobial agents and antibiotics are often used synonymously.
- Historically, used in food-producing animals to treat known disease(s), prevent common disease(s) and promote animal growth.
- Lack of efficacy from bacterial antimicrobial resistance has become an important public health issue in both human and veterinary medicine. Infections caused by resistant bacteria are associated with a much higher morbidity and mortality
- Limited data show that food animal production accounts for a large proportion of antibiotic use
 - Institute of Medicine (1989) estimated that in the US 16 million pounds of antimicrobials were for nontherapeutic animal use
 - Union of Concerned Scientists estimated 25 million pounds of antimicrobials were used nontherapeutically in cattle, chickens and swine
 - Animal Health Institute (industry sponsored) estimated only 3 million pounds were used nontherapeutically.
- To limit the development of resistance, the United States Food and Drug Administration (FDA) currently recommends:
 - Medically important antimicrobial drugs in food-producing animals should be limited to those uses necessary for assuring animal health. Administration of these drugs to promote growth or improve feed efficiency is not judicious use; uses for treatment, control or prevention of specific diseases are deemed necessary for assuring health.
 - Medically important antimicrobial drug use in food-producing animals should be limited to those with veterinary oversight or consultation.

GENERAL PRINCIPALS OF ANTIMICROBIAL USE

- It is not appropriate to use antimicrobials in food-producing animals to promote growth or improve feed efficiency
- Overall goal is for adequate concentration(s) at infection site for sufficient time periods to destroy all disease-causing microorganisms or to weaken them enough to allow the animal's immune system to clear the infection, while not causing toxicity or other adverse reactions in the host.
- Choice of antimicrobial drug, formulation, route of administration, dosage regimen, duration of administration, and appropriate withdrawal time in food-producing species must be considered.

CONSIDERATIONS IN CHOOSING ANTIMICROBIAL AGENTS

- Suspected or known microorganism
- Risk
 - Development of drug resistance
 - Harm to fetus or neonate
 - Toxicity or adverse reactions
 - Tissue residues
- Pharmacokinetic (PK) properties
 - Route of administration
 - Physiochemical drug properties – lipophilic drugs penetrate barriers more readily
 - Distribution to site of infection
 - Metabolism
 - Elimination (e.g. renal or gastrointestinal)
- Pharmacodynamic (PD) indices
 - Time or concentration dependent activity (see below)
 - Minimum Inhibitory Concentration (MIC)
- Principals of treatment
 - PK considerations
 - Site of infection
 - Immunocompetency
 - Dosage modification for organ failure, neonates, geriatrics
- Cost

DETERMINATION OF THE CORRECT DOSAGE REGIMEN

- An antimicrobial drug approved for the particular species and specific condition should be used according to the label instructions. If this is not the case, veterinarians may need to design dosage regimens for appropriate antimicrobial drugs based on PK indices (i.e. bioavailability, tissue distribution, half-life) and formulation properties of the drug.
- Other considerations include whether the activity of the drug is concentration-dependent or time-dependent and if it exhibits a significant post-antibiotic effect.
 - Concentration-dependent – kill at a greater rate or to a greater extent with increasing concentrations at the site of infection.
 - Time-dependent - kill at the same rate regardless of the concentration once the required threshold concentration has been reached.
- As a general rule, the concentration of time-dependent drugs is maintained above the minimum effective concentration for as long as possible between administrations, whereas this is less important with concentration-dependent drugs.
- Fluoroquinolones and aminoglycosides are considered to be concentration-dependent, and the β -lactams and macrolides time-dependent. However, these properties also depend on the specific microorganism (e.g., it has been suggested that the activity of aminoglycosides as adjunctive therapy for *S. aureus* or enterococci may be concentration independent).
- Strategies to improve efficacy differ between these two categories:
 - Time-dependent drugs – consider using continuous infusions, agents with long serum half-lives or repository formulations, or concomitantly administering elimination inhibitors
 - Concentration-dependent drugs – consider administration of higher doses, perhaps less frequently
- Post-antibiotic effect (i.e., continued killing or inhibition of microorganism growth at the infection site despite concentrations falling to levels lower than the effective concentration) makes it possible to lengthen periods between dosing. This effect is generally associated with

drugs that inhibit protein or nucleic acid synthesis (e.g., aminoglycosides and fluoroquinolones).

GUIDELINES - PRUDENT USE OF ANTIMICROBIAL AGENTS

Ensure efficacy

- Use appropriate antimicrobials for disease with accurate bacteriological diagnosis and sensitivity testing
- Handle and store antimicrobial agents correctly to ensure potency, eliminate the use of expired products and prevent treatment errors.
- Start treatment in high mortality cases or rapid disease spread based on clinical diagnosis alone, but adjust therapy if not successful or following the results of bacterial identification and sensitivity.
- Restrict extralabel use to those conditions for which there is no suitable licensed product and under the guidance of a veterinarian within a valid client-patient-veterinarian relationship.
- Train all personnel involved in antimicrobial use about correct dosage regimens, injection site precautions, and record keeping.
- Keep accurate, detailed, and current records to monitor trends in antimicrobial susceptibility and identify any potential reasons for treatment failure.

Prevention of residues in food of animal origin depends on

- Accurate and complete records of treatments
- Identification of treated animal(s) or animal group.
- Utilization of appropriately extended withdrawal periods if a drug is used in an extralabel manner.
- Clearly identify treated animals to prevent them from entering the human food chain prior to the required withdrawal period having elapsed.

Prevention of development of resistance and spread of resistant bacterial organisms

- Limit the use of antibiotics in veterinary species by:
 - Preventing disease through good husbandry practices (maintaining sanitation and hygiene, providing high quality feed and protection from the elements),
 - Using efficacious alternatives to antibiotics such as vaccines, probiotics and by applying biosecurity measures
 - Treating only sick or legitimately at-risk animals.
 - Avoid use as growth promotants or to increase feed efficiency
- Choose antibiotics with a narrow spectrum of activity first, with broad-spectrum antibiotics reserved for cases caused by multiple infectious agents or with known resistance to narrow spectrum drugs.
- Continue treatment for as long as needed to prevent recrudescence of infection, but for as short as possible to minimize the exposure of the bacterial population to the antimicrobial
- Avoid using newer generation antibiotics that have important applications in human medicine.
- Avoid prolonged oral use since most of the concern regarding resistance is associated with the transfer of resistant bacteria that inhabit the animal's gut to humans (either through the feces, contaminated water or contamination of food of animal origin during processing).
- Minimize environmental contamination by disposing of outdated products according to label instructions and minimizing soil or water contamination.



MISCELLANEOUS

ABBREVIATIONS

- FDA = Food and Drug Administration
- PD = pharmacodynamics
- PK = pharmacokinetics
- MIC = Minimum Inhibitory Concentration

Suggested Reading

- USDA FDA CVM. The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals. April 13, 2012. Available at: <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf>. Downloaded May 23, 2016.
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