

UPDATE ON THE VETERINARY ANTIMICROBIAL DECISION SYSTEM

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INTRODUCTION

The long-term goal of the Veterinary Antimicrobial Decision Support System (VADS) is to support the veterinary profession in preserving the efficacy of antimicrobials for therapeutic use in animals and humans. VADS is being developed as a web-based, peer-reviewed antimicrobial decision support system centered on therapeutic applications that will allow food animal veterinary practitioners to utilize all available information in the construction of antimicrobial regimens. The system will provide information necessary for incorporation of inputs such as susceptibility test results and consideration of potential public health impacts in the process of designing food animal therapeutic antimicrobial regimens. The rationale for this approach is that enabling the practicing veterinarian to efficiently utilize all currently available information when making antimicrobial use decisions is the first step towards judicious use. This system is unique in that pharmacokinetic, pharmacodynamic, clinical trial, and pathogen susceptibility information will be interpreted by clinical pharmacologists and reviewed by other experts in the appropriate fields prior to including it in the system. Users may either use the information as provided or examine the transparent review process used in constructing the system. In addition, by compiling available information to support prudent antimicrobial use, the VADS System will also emphasize what information is not available, thereby aiding researchers in targeting research goals. Startup funding has been provided by the Academy of Veterinary Consultants (AVC), the American Association of Bovine Practitioners (AABP), the American Association of Swine Veterinarians (AASV), the American Veterinary Medical Association (AVMA), the National Cattlemen's Beef Association (NCBA), and the National Pork Producers Council (NPPC).

STRUCTURE OF THE VADS SYSTEM

The user of the VADS System will enter through a page defining the goals of the system, who is eligible to subscribe, and how to do so. The VADS System is intended for use only by veterinarians and veterinary students. Part of the development process will be to select a suitable method for confirming the identity of subscribers.

Once a user has satisfied entry requirements, they may access tutorial programs and disease-specific antimicrobial information. The tutorial programs are designed to educate veterinarians on subjects essential to judicious antimicrobial use. These subjects will include:

- a. a link to the text of the Animal Medicinal Drug Use Clarification Act and regulations
- b. links to the text of relevant compliance policy guidelines,
- c. the extralabel drug use algorithm developed by the AVMA,
- d. species specific antimicrobial use guidelines developed by practitioner groups,
- e. a summary of the mechanisms of action, resistance development, general spectrum, pharmacokinetics and pharmacodynamics for antimicrobials covered in the system,
- f. an explanation of applications and limitations of susceptibility breakpoints,
- g. direct links to the approved animal drug database
- h. a description of the practical pharmacokinetic concepts necessary to adjust regimens utilizing information in the database (this section is not necessary for a veterinarian to use the database), and
- i. a summary of general concepts of bacterial resistance with emphasis on potential food-borne pathogens and current concepts in preventing resistance.

The veterinarian or student may then select from a list of disease categories. After a specific disease application is selected, the user may access additional related information, including:

- a. zoonotic potential of pathogens associated with the disease indication, including human health implications of resistance developing in these pathogens,
- b. biological characteristics of the associated pathogens (e.g., general microbiology, persistence in the environment),
- c. epidemiology of the disease,
- d. preventive measures to minimize or eliminate the need for antimicrobial therapy in the future (e.g., vaccines, hygiene, biosecurity).

PHARMACOKINETIC DATA EVALUATION AND MODELING

Standard operating procedures (SOPs) for evaluating pharmacokinetic literature, performing additional modeling of available data, and graphically representing pharmacokinetic profiles in relationship to MIC breakpoints are being developed. Additional pharmacokinetic modeling utilizes WinNonlin (Pharsight Corporation, Mountain View, CA), a commercially available pharmacokinetic program. Objectives of the additional modeling include projecting dose accumulation utilizing single dose data and confirming linearity of dose response.

A major challenge is extrapolating data from 6-10 animals to an entire population. Current efforts center around using @Risk, a risk analysis software program (Palisade corporation, Newfield, NY), to apply Monte Carlo simulation techniques to the problem. For example, ampicillin trihydrate pharmacokinetic data from calves is used to construct population distributions for maximal concentration (C_{max}), time of maximal concentration (T_{max}), and elimination half time (T_{1/2} beta). One thousand "virtual animals" are then created with serum concentration curves based on C_{max}, T_{max}, and T_{1/2} beta values randomly sampled from the respective distributions. Each of these curves are then used to calculate time above MIC for different pathogen MICs. Different doses are modeled in the same manner. The results of these models are combined with the desired pharmacodynamics (e.g., 80% of the dosing interval above the MIC for Gram negative pathogens) to derive estimates of the percent of a population of animals that will be adequately treated with different dose regimen/pathogen MIC combinations. This approach may be altered to account for antimicrobials with concentration-dependent killing or AUIC dictated efficacy. The data and procedures used in the construction of all extralabel regimens will be readily available for review and comment on the website.

PATHOGEN SUSCEPTIBILITY DATA

Pathogen data will include retrospective susceptibility profile information as well as interpretation of susceptibility testing results. One of the main goals of the system is to provide a science-based method for practitioners to address changes in pathogen susceptibility profiles. To achieve this goal, applicability of the NCCLS breakpoints to each drug/pathogen combination will be discussed. Modifications of labeled and suggested ext ralabel regimens in relation to susceptibility information, including the recently adapted extended dilution plates being used in diagnostic laboratories, will be included where appropriate. A discussion of susceptibility testing, validated vs. non-validated breakpoints, and basic pharmacodynamics of antimicrobials are contained elsewhere in these proceedings (Apley MD. Rational Use of Culture/Sensitivity Data).

REVIEW PROCESS

Review will initially be established for bovine and swine applications. The database may eventually be expanded to other species, but limiting applications is necessary for a reasonable startup time. Each review panel will consist of a clinical pharmacologist, a microbiologist, a regulatory official with pharmacokinetic or toxicology training, a Food Animal Residue Avoidance Databank representative, and 6 other veterinarians with clinical expertise. For the bovine panel, 4 clinical veterinarians will be nominated by the American Association of Bovine Practitioners, and 2 by the Academy of Veterinary Consultants. For the swine panel, 6 members will be nominated by the American Association of Swine Practitioners.

INITIAL COVERAGE

Tables 1 and 2 contain the initial therapeutic targets for the VADS System.

Table 1: Proposed therapeutic categories and pathogens for initial coverage, swine applications

Respiratory disease	Streptococcus suis Actinobacillus suis Actinobacillus pleuropneumoniae Haemophilus parasuis Pasteurella multocida Bordetella bronchiseptica Salmonella cholerasuis Mycoplasma hyopneumoniae
Enteric disease	Escherichia coli Salmonella spp. Serpulina hyodysenteriae Serpulina spp. Lawsonia intracellularis Clostridium perfringens
Other	Leptospirosis Staphylococcus hyicus Mycoplasma hyosynoviae Erysipelothrix rhusiopathiae Eubacterium suis Streptococcus spp.

Table 2: Proposed therapeutic categories and pathogens for initial coverage, bovine applications

Respiratory Disease Complex	Mannheimia (Pasteurella) haemolytica Pasteurella multocida Haemophilus somnus Mycoplasma bovis
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	Arcanobacterium (Actinomyces) pyogenes (secondary) Staphylococcus spp. (secondary) Streptococcus spp. (secondary)
Enteric disease and associated septicemia	Escherichia coli Salmonella spp. Clostridium perfringens Cryptosporidium parvum
Mastitis	Staphylococcus aureus Streptococcus agalactiae Mycoplasma bovis Streptococcus spp. (environmental) Klebsiella E. coli Pseudomonas Arcanobacterium (Actinomyces) pyogenes
Footrot	Fusobacterium necrophorum Bacteroides nodosus
Metritis	Actinomyces pyogenes multiple anaerobes and aerobes
Infectious keratoconjunctivitis	Moraxella bovis
"Lumpy jaw"	Actinomyces bovis
"Woody tongue"	Actinobacillus lignieresii
Anaplasmosis	Anaplasma marginale
Leptospirosis	Leptospira spp.
Central nervous system disease	Listeria monocytogenes Haemophilus somnus
Clostridial infections	Clostridial spp.