Using Individual Animal Susceptibility Test Results in Bovine Practice

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KEYWORDS

• Antimicrobial susceptibility testing • AST • Veterinary diagnostic
• In vitro diagnostics • Responsible antimicrobial use

KEY POINTS

- Interpretive criteria developed by the Clinical and Laboratory Standards Institute for veterinary applications are specific to animal host species, bacterial pathogen, disease process, antimicrobial, and antimicrobial dosing regimen.
- Veterinary-specific interpretive criteria should be used (when available), because they provide the most predictive in vitro–in vivo relationship.
- When specific interpretive criteria do not exist for a veterinary application, laboratories may report interpretive criteria approved for other veterinary applications or developed from human data.
- When specific interpretive criteria do not exist for a veterinary application, practitioners can utilize specific microbiological, pharmacologic, and clinical evidence as an alternative to other veterinary or human breakpoints to evaluate antimicrobial therapies.

INTRODUCTION

Antimicrobial susceptibility testing (AST), as a laboratory procedure, was an integral part of the discovery of penicillin. In 1929, Alexander Fleming revolutionized modern medicine by describing a substance produced by *Penicillium,* which he termed "penicillin."[1] In that same article, Dr Fleming also described "Methods of examining cultures for antibacterial substance," an agar plate and broth dilution method, which are the precursors to modern AST. Shortly thereafter began the discussion on the utility of AST to predict clinical outcome,[2] a discussion that continues today.[3]

As testing methods have become standardized, AST reproducibility has been improved. To avoid many of the pitfalls AST can present, clinicians should verify

The author has nothing to disclose.
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Vet Clin Food Anim 31 (2015) 163–174
http://dx.doi.org/10.1016/j.cvfa.2014.11.008 **vetfood.theclinics.com**
0749-0720/15/$ – see front matter

that their laboratory uses current testing methods and interpretive criteria approved by the Clinical and Laboratory Standards Institute (CLSI).[4]

Perhaps the most challenging aspect of AST lies in the interpretation and application of test results to the clinical patient. The value of cumulative AST data in empiric therapy for prescribing and monitoring of antimicrobial resistance has been discussed elsewhere.[5,6] The focus herein is on the application of AST results to the individual animal.

TERMINOLOGY

Although many of the technical aspects of how to perform AST in the laboratory have been standardized,[7,8] there remains a generalized lack of standardization of the terminology associated with this diagnostic test.[9] To fully comprehend AST results and their application to clinical case management, practitioners should understand the basic terminology associated with testing. For AST in North America, the primary entity that develops testing standards is CLSI. **Box 1** includes terms and definitions adapted from the most recent CLSI document.[10]

BREAKPOINT DEVELOPMENT PROCESS

A complete description of the process by which veterinary breakpoints are developed can be found in the most current CLSI document[11] and has been reviewed previously.[12,13] To develop a breakpoint, 3 types of data are used to determine the most appropriate cutoff values for "S," "I," and "R."

- Wild-type cutoff (CO_{wt}): The wild-type cutoff or minimum inhibitory concentration (MIC) distribution is a histogram of a population of bacterial isolates categorized by MIC value for an antibiotic (**Fig. 1**). The ultimate goal of the wild-type cutoff is to divide the bacterial population into 2 categories: wild type and non–wild type. Wild-type bacteria are ones that do not possess an acquired or mutational resistance element (ie, the susceptible population), whereas non–wild-type bacteria do possess these resistance characteristics. Because different bacterial species may have different MIC distributions to the same antimicrobial, breakpoint values are specific to an antimicrobial–bacterial pathogen combination.
- Pharmacokinetic/pharmacodynamics (PK/PD) cutoff ($CO_{pk/pd}$): The effectiveness of an antimicrobial agent is generally associated with 1 of 3 PK/PD indices: the time that free drug (non–protein bound) concentrations are greater than the MIC (f T>MIC), the free drug peak concentration to MIC ratio (f C_{max}:MIC), and the free drug area under the plasma concentration curve to MIC ratio (f AUC:MIC).[14] During the breakpoint development process, the pharmacokinetic properties of the specific antimicrobial in the host animal species are evaluated against the bacterial MICs to determine whether the target PK/PD index can be achieved. Because altering the dose regimen (increasing or decreasing the total dose or frequency of dosing, or using alternative routes of administration) will have an impact on the pharmacokinetic properties of the antimicrobial, breakpoint values are specific to the dose, route, and duration of therapy evaluated in the breakpoint development process. Many clinicians interpret this as meaning that a resistant isolate can be effectively treated by increasing the dose. This is not universally correct and this strategy should only be utilized in a few, specific clinical situations.
- Clinical cutoff (CO_{cl}): The final piece of data used to establish a veterinary breakpoint is to correlate in vivo treatment outcomes with the MIC of the specific