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Antimicrobials and BRD

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Abstract

Pharmacodynamics is limited with respect to its ability to provide precise predictions to guide therapy because of complications related to the bound versus unbound state of the agent, tissue versus plasma concentrations, drug degradation over time, variations among microorganisms, and factors associated with the specific environment at the infection site. Antimicrobial susceptibility testing is likewise imprecise when applied to an individual animal; however, it is valuable on an animal population basis.

Keywords: pharmacodynamics, antimicrobial suspectibility

Introduction

Excellent datasets are available for antimicrobial therapy of bovine respiratory disease (BRD). Pivotal studies give a good picture of expected therapeutic outcomes (with some caveats) for the effects of respiratory therapy and respiratory control treatments related to treatment outcome, case fatality, and suppression of subsequent morbidity.

This article addresses some BRD complex (BRDC) therapeutic caveats related to applying pharmacological principles; and, it also includes many questions from the point of view of a feedlot veterinarian struggling to understand the best approaches to designing BRDC therapeutic and preventive programs.

Pharmacodynamics (PD)

PD can help us rule out unreasonable treatment options but we need to watch the illusion that this field provides us with a laser-guided smart bomb for therapeutic prediction. PD has been over-simplified and possibly over-interpreted. We use PD parameters (time above minimal inhibitory concentration [MIC], peak concentration : MIC ratios and AUC : MIC ratios) to compare pharmacokinetics to pathogen MICs in an attempt to predict therapeutic outcome. The pharmacokinetic values used are complicated by making decisions on bound versus unbound drug (the literature and regulatory agencies are moving to unbound concentrations) and on tissue versus plasma concentrations. Tissue concentrations should be viewed with suspicion without clinical confirmation of the relationship between these concentrations, pathogen MICs and clinical outcome.

Researchers weigh up a drug standard and put them in the broth to see what happens, yet very rarely confirm the stability of the compound in the broth. In our laboratory, Dr Brian Lubbers confirmed that oxytetracycline has an 18-h degradation half-time in brain-heart infusion broth (BH-1) as confirmed by mass spectrometry. So when *in vitro* work is published assuming steady concentrations in the culture, we may be actually looking at a declining concentration depending on the matrix/drug combination.

Likewise, there are many issues clouding the application of PD parameters. How does a PD parameter for an *Escherichia coli* determined in a mouse thigh infection model apply to a *Mannheimia haemolytica* isolate in a bovine lung when treated with another member of that antimicrobial group? How do PD parameters determined for 24-h dosing intervals apply to extended-release antimicrobials?

Pharmacodynamic/pharmacokinetic modeling is useful as a tool for targeting initial drug investigations, for guiding design of dose exploration studies and for guiding therapy of extra-label diseases or pathogens with higher MICs than were considered for the label

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population. We can probably rule out some really unreasonable antimicrobial regimens in relation to pathogen MICs, but do not hold the illusion of precision adequate to give exact dosing alterations for pathogens with MICs two dilutions apart.

Is antimicrobial susceptibility testing of value in selecting antimicrobial therapy for BRDC?

Of all the animal health related meetings to be discussing antimicrobial susceptibility testing, a meeting on BRDC has the most Clinical and Laboratory Standards Institute (CLSI) approved breakpoints to cite. In the M31-A3 document (1), you will find interpretive criteria for the following antimicrobials related to BRDC: ceftiofur, tilmicosin, tulathromycin, danofloxacin, enrofloxacin, florfenicol and spectinomycin sulfate (currently unavailable).

Antimicrobial susceptibility testing standards are available in the CLSI M31-A3 publication. A detailed explanation is contained in CLSI publication M37-A3. The breakpoint approval process uses varying combinations of PK/PD modeling, examination of 'wild-type' pathogen population MIC distributions (an epidemiological breakpoint), and evaluation of pathogen MICs linked with clinical outcome. The results of these three approaches are not published in the CLSI documents, but are utilized in developing the final interpretive criteria.

Indeed, the use of these tests can be valuable in evaluating trends in antimicrobial susceptibility in populations of BRD patients. Does a resistant result guarantee a lack of clinical response? No. Does a susceptible result guarantee a positive clinical response? No. It is about populations, and when appropriately conducted and applied to populations of BRDC patients susceptibility testing can help place populations of animals in the context of higher or lower clinical response rates. All of the BRDC discussions related to the application of susceptibility data to treatment outcome are subject to the controversy on the relation of isolates from different aspects of the respiratory tract to what is actually going on in the lung.

Misleading directions in clinical data

We mislead ourselves when we focus on mortality and case fatality only, rather than also paying close attention to railers (those sold early due to lack of response to therapy) as a means of evaluating respiratory disease therapy. From personal experience, case fatality rates determined by BRDC morbidity and deaths for a feedlot over a given time period are different from those calculated for individual groups of cattle for the entire feeding period. Railers and chronics often equal 50–100% of the mortalities.

Looking at days-on-feed (DOF) over which respiratory disease mortalities occur rather than DOF at fatal disease onset (FDO) and days to death is another misleading activity. The majority of current record systems are not designed to deliver these data without going back through and manually evaluating individual animal records.

We are also misled when we take data from pivotal and post-approval marketing studies that were done in very high-risk calves and apply these differences in treatment response and subsequent performance to lower risk categories of cattle. Another misleading activity is considering fever reduction in response to antipyretic therapy to be a driver of therapeutic response because fever reduction in response to antimicrobial therapy is an indicator of therapeutic efficacy.

Things we do not know

What effect does revaccination in the face of a BRD outbreak have on subsequent morbidity, case fatality and railer rates? What effect does routine revaccination in the feedlot have on these parameters? What is the optimal duration of therapy for BRD?

Do not confuse dose finding studies, or studies where we wait different time periods after a single-injection therapy to determine how long we can wait until classifying an animal as a success or failure, with studies actually designed to determine the optimal period of antimicrobial exposure.

If you want to have a very short bibliography on an article, write one on determination of optimal therapeutic duration. We recently queried the listserv for the American College of Veterinary Clinical Pharmacology and came up with about seven articles in human and veterinary medicine that addressed duration as the outcome parameter of the research. This applies to both the duration of antimicrobial exposure (confounded by the shape of the exposure curve) during an individual regimen and to the number of regimens to which a non-responding BRDC patient should be subjected.

And speaking of number of regimens, should subsequent regimens for non-responding BRDC cattle utilize a different antimicrobial? I have not seen reports on this subject in the peer-reviewed literature. The only cases where I have observed second regimens being the same as the first are pivotal trials where the sponsor wanted to take out potential confounders in overall response rates due to another drug being the second treatment. In these studies, second treatment responses were very similar to studies where the first and second treatments were different.

The question becomes whether the first BRDC treatment failure animal needs a different antimicrobial or more time of antimicrobial exposure to continue recovery.

Is antimicrobial resistance in BRDC pathogens having an impact on therapeutic response in the field? This is related to the question above, that of resistant pathogens

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being involved in treatment failures. There are so many factors involved in BRDC therapeutic response that it would be hard to tease out, even if several years worth of datasets with pathogens attributable to the lung correlated to treatment response were available. At present we are relegated to dueling anecdotes.

Is diagnostic laboratory data trustworthy to guide us in evaluating antimicrobial resistance trends in BRDC pathogens (or, in any pathogens)? Is D-lab data inherently flawed by selection bias when considered for evaluation of resistance trends? There would be a simple way to find out that of doing a case control study on submissions with resistant and susceptible isolates to evaluate predisposing factors.

For those who point out that the resistance seen in some cases may be due to previous antimicrobial exposure, I would ask them to explain some of the trends seen in diagnostic laboratory data. Are we seeing more animals exposed to antimicrobials as compared to previous years? Or, are we seeing more animals carrying low numbers of resistant clones that then multiply in the favorable environment of antimicrobial exposure?

What are the best criteria to classify cattle as needing treatment for control of respiratory disease?

What is going on with groups of cattle that keep giving us morbidity throughout the feeding period with some pretty depressing case fatality rates for those pulled later in the feeding period?

Mike's hypothesis

I have been involved with ongoing morbidity challenges in these issues regarding single source groups of cattle and have participated in decisions to just stop feeding cattle from these producers. They are often shiny groups of cattle, and are negative for things like persistently infected BVD carriers (BVD PI has given us a whipping boy for a lot of problems for the last few years) and we search frantically for an infectious cause, which if we run enough tests we will eventually find. We chase the trace element path, and there have been some painful lessons on my part about how feeding practices can have an effect on this type of morbidity on a feedlot-wide basis. But what about a yard with great health numbers that has occasional lots of cattle that just pick at us with respiratory disease morbidity for the entire feeding period?

The holy grail of disease outcome prognostication and therapeutic guidance still eludes us. Blessings on those who continue to search. I am very interested in those working on the return to the stethoscope in production environments and who are implementing structured evaluation criteria to aid interpretation.

References

CLSI Publication M31-A3 – Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard – Third Edition. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087–1898, USA. Available online at webstore.ansi.org

CLSI Publication M37-A3 – Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters for Veterinary Antimicrobial Agents; Approved Guideline – Third Edition. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087–1898, USA. Available online at webstore.ansi.org

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