Pharmacology of Bovine Respiratory Disease: Criteria for selecting antimicrobials, do aminoglycosides fit?

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Rational selection of antimicrobials involves working through an information overload. Spectrum, laboratory sensitivity data, clinical trial data, tissue tolerance, possibility of synergism or antagonism with another antimicrobial, route and frequency of administration, withdrawal time, cost, and label vs. extra-label use must be considered. This paper includes suggestions for evaluating some of these areas, with an emphasis on comparing and contrasting the aminoglycosides with other selected antimicrobials. **Evaluation of using characteristics of antimicrobials to guide drug selection is the main focus of this paper.** The evaluation of clinical trials for antimicrobial selection is not addressed, but should be included in the final selection decision.

Spectrum

All of the antimicrobials listed in table 1 could be described as having *Pasteurella haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus* "in their spectrum". Spending time considering additional potential pathogens such as *Actinomyces pyogenes*, *Staph.* spp., and *Strep.* spp., or placing emphasis on the ability to function in a completely anaerobic environment has little relevance to the majority of respiratory disease cases for which there is a reasonable chance of successful therapeutic intervention. (The floor is open to anyone who can explain the significance of *Mycoplasma* in bovine respiratory disease.)

Table 1 illustrates that *within the spectrum* is a somewhat loose term when looking at large populations of field isolates. It is tempting to draw snap conclusions from data such as this and pick the highest percent susceptibility as the most uniformly efficacious antimicrobial. It is also easy to use single isolate susceptibility results to justify regimen changes in the middle of a wreck. Have laboratory susceptibility tests evolved to the point of serving as a single source for selecting the most appropriate antimicrobial agent?

Table 1. Bovine Isolate Susceptibility Summary.

Pasteurella haemolytica	Ceftiofur	Tilmicosin	Tetracycline	Sulfadimethoxine	Gentamicin	Neomycin
ISU (112 isolates)						
Susceptible	99 %	84 %	71 %	19 %	98 %	83 %
Mod. Susceptible	1 %	10 %	4 %	2 %	1 %	0 %
Resistant	0 %	6 %	24 %	79 %	1 %	17 %
KSU (60 isolates)						
Susceptible	95 %	87 %	58 %	10 %	92 %	73 %
Mod. Susceptible	2 %	5 %	2 %	2 %	5 %	0 %
Resistant	3 %	8 %	35 %	88 %	2 %	27 %

Pasteurella multocida	Ceftiofur	Tilmicosin	Tetracycline	Sulfadimethoxine	Gentamicin	Neomycin
ISU (103 isolates)						
Susceptible	100 %	72 %	64 %	9 %	94 %	60 %
Mod. Susceptible	0 %	19 %	22 %	5 %	7 %	0 %
Resistant	0 %	9 %	14 %	86 %	0 %	40 %
KSU (54 isolates)						
Susceptible	83 %	57 %	67 %	20 %	81 %	56 %
Mod. Susceptible	2 %	28 %	13 %	0 %	15 %	0 %
Resistant	7 %	13 %	17 %	80 %	4 %	44 %

Iowa State University isolates collected from 1/1/95 to 12/31/95
Kansas State University isolates collected from 4/1/94 to 12/31/94, KSU percentages not adding up to 100% reflect the % of invalid breakpoints.
Pasteurella haemolytica and *multocida* breakpoints:

Ceftiofur	1, 10	Tilmicosin	6.25, 12.5
Tetracycline	4,8	Sulfadimethoxine	20, 40
Gentamicin	4, 8	Neomycin	8 (sensitive or resistant only)

Use of MICs for drug selection

Table 1 summarizes bacterial susceptibility data for bovine isolates of *Pasteurella haemolytica* and *Pasteurella multocida* from the Kansas State University and Iowa State University Diagnostic Laboratories. It is likely that many of these isolates are from previously treated cattle. However, this accurately reflects the isolates on which veterinarians base therapeutic decisions in production settings.

Breakpoint MIC determination gives a rough idea

of the concentration at which the submitted pathogen is inhibited by the antimicrobial in question. This determination is performed under absolutely ideal conditions for the antimicrobial, especially for the aminoglycosides. The susceptibility results in Table 1 were determined at near-neutral pH in an aerobic environment with no cellular debris. The activity of aminoglycosides is compromised by acidic and hyperosmolar conditions as well as low oxygen tension (bacterial uptake of aminoglycosides is an oxygen dependent process).[1] Aminoglycosides also tend to bind to cellular debris, especially free nucleic acids. These conditions fairly well describe the site of an advanced infectious process, raising the question of equivalence of the MIC determination environment and *in-vivo* conditions.

Reaching plasma concentrations above the pathogen MIC has been correlated with increased therapeutic success for some pathogens in several species of animals. Depending on the class of antimicrobial, we may want the concentration to stay above the MIC for an extended period with less emphasis on the peak concentration (beta-lactams, many protein synthesis inhibitors) or reach a high peak with less emphasis on duration (aminoglycosides, fluoroquinolones). These correlations have been demonstrated clinically with individual monitoring of serum concentrations and individually determined pathogen MICs. The dose of the antimicrobial is altered in these patients to adjust for the pathogen MIC and the individual pharmacokinetics of the patient to obtain the best therapeutic results. The clinical situation is obviously much different in a production medicine setting.

In production medicine we routinely rely on MICs derived from fatal cases, some of which have undergone extensive therapy. These results are then correlated with reported plasma pharmacokinetic data (used to determine the breakpoints to report an isolate as sensitive, moderately sensitive, or resistant) and applied to the population in question. In addition to the variation in pathogen susceptibility among the population, extensive variation in individual pharmacokinetics (and thus plasma and tissue concentrations of antimicrobials) should be expected. A reported maximal plasma concentration of 0.5 μg/ml for an antimicrobial might actually mean a range of 0.1 to 1.0 μg/ml with two-thirds of the population between 0.25 and 0.75 μg/ml. And this is the variation in healthy animals! Disease processes may throw in even more variation due to changes in body water, body temperature, metabolism, etc. We will not even attempt to crack open the subject of plasma/serum concentrations vs. tissue concentrations in this paper.

So, how do we account for all of these possible variations when interpreting MICs in a production setting? Repeated findings of "resistance" coupled with marginal clinical results (case fatality rate exceeding 5-10%, less than 60-70% first treatment success, excessive chronics) in the populations you work with may indicate a drug change as a consideration *in addition to* management adjustments. The most important information from MICs may be the observation that findings of resistance for a compound (using the same MIC breakpoints) are much more prevalent then previously encountered. A **sudden** change in the clinical response of an antimicrobial that has been **part** of a successful therapy program for an extended period should alert us to evaluate management factors first.

Is it necessary for an antimicrobial to completely inhibit growth *in-vitro* for adequate clinical response in immunocompetent cattle? Keep in mind that *Pasteurella haemolytica* produces large amounts of leukotoxin during rapid growth but this production is rapidly lost during late log phase and stationary growth periods *in-vitro*.[2] This suggests that inhibiting growth *in-vivo* may decrease leukotoxin production to an extent sufficient for the animals immune system to overwhelm the pathogen. Clinical response of oxytetracycline in northern calves and yearlings would suggest that absolute reliance on MIC results for drug selection may lead to missing some economic opportunities for our clients.

Are MICs appropriate as the **sole tool** in selecting the most efficacious antimicrobial? No they are not. An argument commonly voiced supporting extra-label use of aminoglycosides is superior susceptibility profiles on isolates submitted to diagnostic labs. It is clear from the data in table 1 that there is little difference between the aminoglycosides and the labeled compounds tilmicosin and ceftiofur (using the breakpoints described) when considering the population of submitted samples as a whole, the favorable bias towards aminoglycosides, and the inherent variability in applying MIC data to production settings.

Target animal toxicity

It is hard to defend the extra-label use of aminoglycosides in cattle when their toxicity potential is compared to labeled compounds. Neomycin is classified as the most nephrotoxic of the aminoglycosides.[3] It is not used systemically in human medicine for this reason.[1] The prolonged slaughter withdrawal times required by long-term retention of aminoglycosides in renal tissue are related to the mechanism of nephrotoxicity.[4]

The aminoglycosides are not the only antimicrobials capable of nephrotoxicity. It is also possible to adversely affect the kidneys with extremely elevated doses of oxytetracycline. Administration of 33 mg/kg (15 mg/lb) of oxytetracycline IV once daily for 3 days

induced a rise in BUN and the presence of renal casts in the urine of normal heifers.[5] In another report, 12 of 20 calves dying after treatment for respiratory disease with the above regimen for a period of 2 days showed renal tubular necrosis.[6]

These are examples of extra-label use, both compound selection and dose alteration of a labeled product, which create significant potential for target animal toxicity. The prescribing veterinarian would be solely responsible for adverse effects in both cases.

Bactericidal vs. bacteriostatic

In this author's opinion, entirely too much emphasis is placed on which of these categories an antimicrobial falls into. Categorization in this manner is nothing more than comparison of the minimal inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC). The MIC is the concentration which inhibits growth of the pathogen for 18-24 hours. Removal of the antimicrobial will allow growth in the culture to eventually resume. The MBC is the concentration at which growth does not resume even after removal of the antimicrobial. The culture is sterilized. Bactericidal compounds are those which have a MIC and MBC only a few dilutions apart. Bacteriostatic compounds have a wider difference between these two concentrations. Bacteriostatic compounds may act in a bactericidal manner *in-vivo* if adequate concentrations are reached . Toxicity, economics, or practical injection volumes may prevent us from achieving these bactericidal concentrations clinically.

So how do these *in-vitro* properties translate to something clinically useful for bovine respiratory disease? Considering that bactericidal compounds have both *outperformed* and *been outperformed by* bacteriostatic compounds in clinical trials, the short answer is that the translation requires a cosmic equation which only some of the more learned members of our profession possess. **If you feel a bactericidal antimicrobial is absolutely necessary, ceftiofur, ampicillin, and amoxicillin are available as labeled compounds.**

Hunting for synergism

Combination antimicrobial therapy appears to be commonplace for bovine respiratory disease. Synergism, suppression of resistance, or just the hope that "one of them will work" are often given as reasons. The combination of aminoglycosides and beta-lactams are the classic synergistic combination. The evidence for this combination is primarily derived from human work utilizing *E. coli*, *Pseudomonas*, or other routinely troublesome human pathogens.[7,8] Is it possible to extrapolate these results to therapy of *Pasteurella haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus* in cattle? At best, the extrapolation is shaky.

Some work has been published specifically addressing the activity of combined antimicrobials against *Pasteurella*. Tylosin and oxytetracycline demonstrated *in-vitro* and *in-vivo* (mouse model) synergism against *Pasteurella haemolytica* and *multocida* (1976).[9] Another study found a beneficial effect by combining erythromycin with spectinomycin or oxytetracycline as judged by *in-vitro* efficacy against *Pasteurella haemolytica* (1988).[10] However, when achievable *in-vivo* concentrations were considered, only the combination erythromycin and spectinomycin showed clinical potential. This study also demonstrated the wide variation in drug interactions among isolates of a bacterial species. Including concentrations which were clinically impractical, the combination of erythromycin and spectinomycin was considered synergistic in 15 of the 33 isolates, 12 of the 33 showed some additive properties, and 6 of the 33 isolates showed no change in MICs for the 2 antimicrobials.

It is important to stress that combination antimicrobial therapy of bovine respiratory disease has not been demonstrated as superior to single drug therapy through clinical trials. It is also likely that individual isolates of a pathogen species will react differently to drug combinations. There is laboratory evidence to support the concept of some drug combinations. Supporting a decision to use extra-label compounds because of a perceived need for synergism would be difficult if clinical evidence was required.

Cost

Balancing cost vs. efficacy is certainly valid when evaluating labeled compounds. Adopting extra-label compounds on the basis of cost is not described as a valid justification for extra-label use in compliance policy guide 7125.06, the guidelines in effect at the time of this writing.

Withdrawal time

Table 2 lists withdrawal times for selected antimicrobials. Withdrawal times listed for labeled compounds apply only when all aspects of the label are adhered to. The aminoglycoside extra-label use withdrawal times suggested by the Food Animal Residue Avoidance Data Bank (FARAD) are selected based on the information currently available. It is irresponsible to place a producer at risk for violative residues by using withdrawal times shorter than those on the label or, if extra-label use is selected, than those obtained from an authoritative source (i.e. FARAD). It is equally irresponsible

Table 2. Withdrawal times for selected antimicrobials

Antimicrobial	Withdrawal Time
Ceftiofur (Naxcel, Pharmacia & Upjohn)	0 days
Oxytetracycline (100 mg/ml products)	18-22 days[a]
Oxytetracycline (200 mg/ml long acting)	28 days[b]
Tilmicosin (Micotil, ElancoAnimal Health)	28 days
Sulfadimethoxine (Albon Injection-40%, Pfizer, Inc.)	5 days
Gentamicin	18 months[c]

[a] Withdrawal times vary according to product label
[b] Withdrawal time reported is for LA-200, Pfizer, Inc.
[c] Withdrawal time suggested by the Food Animal Residue Avoidance Databank

(and in violation of regulations) to sell cattle to another producer (backgrounder, feedlot, etc.) prior to the expiration of these withdrawal times without notifying the purchaser of the withdrawal, including individual identification of the appropriate animals. These difficulties are easily avoided by using labeled compounds with shorter withdrawal times.

Overall evaluation of antimicrobials for bovine respiratory disease

No one evaluation category stands by itself in selecting an antimicrobial. There is no scientific justification for the selection of aminoglycosides over first-line, labeled antimicrobials on the basis of spectrum, laboratory susceptibility summaries, or potential synergism with other antimicrobials for bovine respiratory disease. The extra-label use of aminoglycosides is certainly not supported by considering target animal toxicity potential or withdrawal times. There are no published clinical trials supporting the use of aminoglycosides in the therapy of bovine respiratory disease.

Concern over extra-label use of aminoglycosides in cattle has prompted several groups involved in beef production to act. The Academy of Veterinary Consultants (AVC) adopted a position statement against this practice. The National Cattlemen's Beef Association passed a resolution endorsing the AVC position statement. The American Association of Bovine Practitioners adopted a statement by vote of the membership which encourages members to refrain from the intramuscular, subcutaneous or intravenous extra-label use of the aminoglycoside class of antibiotics in bovine animals. It is clear that the use of aminoglycosides for therapy of bovine respiratory disease is no longer a uniformly accepted standard of practice.

Labeled, efficacious antimicrobials are available for bovine respiratory disease. These include compounds with single injection labels (tilmicosin, long-acting oxytetracyclines), very short withdrawal periods (ceftiofur, sulfadimethoxine), and varying levels of cost. Proper management of the antimicrobial (correct regimen), proper management of the cattle, and matching the right antimicrobial with the right population are necessary for efficacy. **Perceived superiority of the aminoglycosides for the therapy of bovine respiratory disease is not supported by pharmacodynamics, pharmacokinetics, or available clinical trial results.**

References

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