Making the Antibiotic Choice for Treating Bovine Respiratory Disease

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Introduction

Bovine respiratory disease (BRD) is a major cause of economic loss in feedlot calves. A review of published reports of morbidity and mortality rates in North American feedlot cattle found the incidence of morbidity ranged from 0-69% and mortality rate ranged from 0-15%.[1] The National Cattleman's Association and the National Livestock Feeder's Association both have listed BRD as the number one disease problem of commercial beef production.[2] BRD causes economic losses through death loss, treatment costs and poor performance.

BRD in feedlot cattle refers to a syndrome that is multifactorial in origin, but results in a common end point of bacterial pneumonia. The classical lesion is that of a rapidly progressing fibrinous necrotic lobar pneumonia. The organism most commonly found in this lesion is *Pasteurella haemolytica* biotype A serotype 1.[3] While other organisms may be found in association with *P. haemolytica* A1, it is felt that this organism plays a unique, central role and that other organisms such as *Pasteurella multocida* or *Actinomyces pyogenes* are opportunistic invaders replicating in established lesions. The role of other bacterial agents such as *Mycoplasma bovis* in BRD is currently not well understood, but this agent has been cultured from cases of arthritis. Thus, it is difficult to direct antibiotic therapy against these mycoplasmal agents until their involvement is more clearly defined or documented in specific cases. *Haemophilus somnus* may also cause pneumonia as well as a number of other syndromes including myocarditis, arthritis, meningoencephalitis, pleuritis, and pericarditis. *Haemophilus somnus* and *Mycoplasma bovis* should be considered as possible differentials for fibrinous pneumonia due to *P. haemolytica* A 1 especially when symptoms of other organ involvement, such as arthritis, occur.

BRD produces disease with morbidity peaking in 1-3 weeks and mortality peaking in 2-4 weeks after entering the feedlot.[1,4] When an epidemic curve for BRD is constructed using fatal disease onset rather than mortality as the parameter, it can be seen that calves dying from BRD become ill within the first 2 weeks of entering the feedlot.[4] The fact that calves become ill so quickly after entering the feedlot obviously puts great emphasis on the type of animal and its recent history. This will be important in determining the morbidity and mortality which may occur. Fall placed calves going into feedlots in Canada and the northern United States will have higher morbidity and mortality than older calves. The morbidity and mortality of fall placed calves in the northern United States will be similar to that seen in stocker calves in southern United States. Both types of calves are young, multiorigin, long haul sale barn calves whose age and handling result in higher BRD morbidity and mortality.[5] Antimicrobial agents can be used in the feedlot in the traditional manner to control mortality and improve performance in sick calves experiencing BRD as well as prophylactically on arrival to limit both BRD morbidity and mortality.

Antibiotic Therapy to Treat BRD

The basic formulations of antimicrobial therapy for BRD are treat early enough, treat long enough and treat with the appropriate antimicrobial agent. Many presentations such as this conclude that treating early enough is far more important than what is used for therapy. It should be remembered that a major reason for treatment failure is the presence of a lesion that is too far advanced for successful therapy. The role of antimicrobial therapy in treating BRD is to control or stop bacterial replication. This will limit or prevent release of virulence factors from *P. haemolytica* A1 such as leukotoxin and endotoxin which are responsible for thrombosis, exudative edema, and necrosis. If this le-

sion becomes too far advanced, the antimicrobial agents will have difficulty reaching areas of necrosis and suppuration and the regenerative response will not be able to return this tissue to normal lung parenchyma.

Early detection relies on a systematic approach by trained personnel to identify cattle in pens which are subjectively different from pen mates.[6] Animals identified by this means should be removed from the pen and placed in a chute where body temperature can be determined. It is important that while this animal is being removed and taken to the restraint facility to be monitored closely for clinical signs to the respiratory system such as coughing, labored breathing, and nasal discharge, versus those which are referable to some other system such as ataxia, lameness, or abdominal distension. This, in effect is the physical examination which will then be used with the temperature by the feedlot personnel to make a decision as to whether to treat and for what condition. In general, cattle which are febrile without obvious symptomatology of other organ systems and with or without signs of respiratory system dysfunction are considered to have BRD (case definition). It is possible that in some cases cattle with *H. somnus* may produce similar symptoms. The peak in the epidemic curve of fatal disease onset is somewhat delayed for Haemophilosis versus BRD with the peak occuring at 4 weeks rather than 2 weeks for BRD.[4] For the individual animal being treated, this distinction would not allow sufficient differentiation to design specific treatment regimens. Post mortem examination of animals which die would be important to differentiate BRD treatment failure from haemophilosis (i.e. myocarditis or menigoencephalitis).

The precise temperature used to determine whether animals need treatment depends on the balance between the costs of overtreatment (drugs and labor) and undertreatment (treatment failures and mortality). In one study[7], greater cost-effectiveness was achieved when treatment was initiated at temperatures $\geq 39.5°C$ versus temperatures $\geq 40.0°C$. When outbreaks of respiratory disease occur, surveillance of the affected group must be increased to ensure early detection of diseased animals.

Although antibacterial agents for the treatment of BRD may reduce losses due to fatality and retarded growth, they do not serve as a substitute for preventative management practices; cattle requiring treatment do not perform as well as those that have not needed treatment.[7] In this study, it is interesting to note that if the calves receiving treatment are closely examined, those responding to initial therapy without relapse do end up with the same average daily gain as cattle not requiring therapy.[7] This further emphasizes the need for effective antimicrobial therapy for BRD as those having treatment failure (relapses and not responding) have decrease feedlot performance.

Treatment of sufficient duration can be achieved only if the response to therapy is monitored. Therapy should be continued for at least 48 hours after clinical signs of fever, dyspnea, and toxemia have abated. Frequently, antibiotics are evaluated over a standard 3 day treatment period with cases failing to provide a reduction in temperature being classified as non responders. Animals classified as non responders to the first line antibiotics may then be placed on an alternate antibiotic (second line antibiotic) for a set period of time (4 days).[7] It is important that the criteria used to define a favorable therapeutic response be closely adhered to. Determination of therapeutic response by evaluation of general appearance without regard to restoration of normal body temperature has been shown to result in high relapse rates.[8]

Selection of the appropriate antibiotic tends to be what most practitioners focus on when treating respiratory disease as this is the aspect of therapy over which they have the greatest control. Factors such as cost, route of administration, treatment interval, drug licensure, necessity of extra label doses, and withholding times quickly cull a number of antibiotics leaving a short list of suitable alternatives for use as first line antimicrobial agents. This list is then modified based on pharmacokinetic behavior and the minimum inhibitory concentration (MIC) of the organism being treated. More simply stated, the practitioner will have to have confidence that the antimicrobial agent can achieve lung tissue levels above the MIC of the organism being treated.

The practitioners may tend to rely on the manufacturers' recommendations for appropriate dose regimens, but numerous reviews are available which may also guide his/her selection in terms of plasma and tissue levels achieved for given antimicrobial agents.[9,10] Determining the MIC or sensitivity of the causative agent such as *P. haemolytica* A1 in the case of BRD is more difficult. In reviewing any MIC or sensitivity results it should be kept in mind that *P. haemolytica* can develop plasmid-mediated multiple antimicrobial resistance by bacterial conjugation so that for example exposure to oxytetracycline may induce resistance to oxytetracycline and penicillin.[11] Therefore, *P. haemolytica* A1 recovered from cattle treated with antibiotics will have a different sensitivity pattern from *P. haemolytica* A1 cultured from untreated cattle. This is especially important when reviewing publications of antimicrobial susceptibility of *P. haemolytica* isolates cultured at diagnostic laboratories[11-14] as these results will have a bias towards cases which have been treated with antimicrobial agents. The findings of these studies may be looked at as a worst case scenario demonstrating antimicrobial agents for which acquired resistance is rarely

or never a problem and those for which acquired antimicrobial resistance occurs commonly. In general few drugs with the possible exception of cetiofur, trimethoprin-sulfonamide combinations and to a lesser extent spectinomycin are found to have limited resistance in pasteurella isolates.

Sensitivity testing using isolates from the feedlot raises concerns over where to sample and from which cattle. Antibacterial sensitivities of isolates cultured from nasal swabs may not represent sensitivities of organisms causing pneumonia. This is strange, because pneumonia usually is preceded by multiplication of *P. haemolytica* in the upper respiratory tract,[15] and it is believed that the nasopharynx serves as the source of bacteria colonizing the lungs. Nevertheless, there are discrepancies between sensitivities of bacteria isolated from nasal swabs and clinical outcome.[8] Ideally, specimens for sensitivity testing should be collected from pneumonic lung, tracheal swabs or tracheobronchial aspirates from cattle prior to treatment. Unfortunately, this may not always be a practical alternative in the feedlot.

Susceptibility testing on bacterial isolates from field samples provide the most useful information if the MIC is determined. This allows a practitioner to make the decision himself as to whether it is possible to achieve the desired MIC in the pneumonic lung of the calves which are being treated. A knowledge of the dose given, the pharmacokinetic behavior and the tissue levels attained for a given drug greatly enhances this decision making. Mathematical formulas are available which can be used to modify the dose for an antimicrobial agent to achieve plasma levels above the desired MIC.[10] Such interpretation of results is not possible if the results are expressed as sensitive or resistant.

A final method of choosing a first line antimicrobial drug is reliance on published treatment trials.[7,8,16,17] These trials give comparisons between treatment response in cattle with naturally occurring BRD that have been treated with various antibiotics with the outcome expressed in both health and production parameters. These studies have shown no significant difference in post-treatment health parameters for calves treated with penicillin, oxytetracycline and trimethoprin - sulfadoxine[7] or a significant improvement in some health parameters in the trimethoprin-sulfadoxine treated calves.[8] In these studies, penicillin[7,8] and oxytetracycline[7] were given at extra label doses. Ceftiofur sodium was demonstrated to give a significant improvement in some health parameters when compared to trimethoprin-sulfadoxine in the treatment of undifferentiated BRD in one study[16], but showed no significant improvement in health parameters when compared to sulbactam-ampicillin in another clinical trial.[17]

When evaluating published treatment trials in cases of naturally occuring BRD, it is useful to realize that the results may not be applicable to the cattle and pathogens you deal with in your practice, but if the trial is well designed it should provide useful comparisons. To determine if the trial is well designed it should be controlled, random, use multiple experimental groups, and be statistically analyzed.

A controlled clinical trial will always involve a comparison group. This is best achieved when the study has a strict set of explicit criteria (case-definition) to allocate cases within treatment groups. Allocation of cases and controls should be random so that equal probability for each sampling unit is ensured. Furthermore, a case definition is necessary to avoid a misclassification bias which almost always skews the results toward no effect. Ideally, cases and controls are selected from a similar population within a given time frame. This increases the validity of the results and the degree to which these results may be generalized. The use of multiple comparison groups increases the power to detect differences in treatment effects, and again, improves the ability to generalize from the trial results. Another important issue in evaluating clinical trial data is whether the outcomes are adequately controlled for potential confounders (extraneous variables which affect both disease and treatment effects). The trials must be blinded in order to control biased outcome assessments. With these criteria in mind, one should carefully look at statistical analyses performed on the trials. The choice of correct methods to analyze results cannot be overemphasized. The analysis should test only the hypotheses which were set *a priori*.

Conventional wisdom has dictated that when treating cattle for acute diseases like BRD, use of medications designed for daily injection will give better results than products designed as long acting or sustained release. This belief is based on the assumption that daily treatment will ensure higher blood and tissue levels which are achieved more quickly and can be maintained at higher levels throughout the treatment period. The disadvantage of this method is that it requires hospitalization of the calf so that daily treatment can be accomplished. Concern has been expressed that animals placed in the hospital can result in animals being mixed in various stages of therapy which may create a negative effect or "hospital effect".[6] Use of long acting antibiotics although less than optimum pharmacologically may in fact give superior results as the calves can be treated and sent back to the home pen, eliminating the "hospital effect."

Antibiotics for prophylaxis of BRD

Antibiotics for on arrival mass medication of cattle to prevent BRD has been advocated in various forms

for many years. It is useful to examine the theoretical mechanisms of how prophylactic antibiotics may work in order to evaluate or choose a particular antimicrobial agent and the most suitable route of administration.

As part of its pathogenic mechanisms *P. haemolytica* A1 can proliferate in large numbers in the upper respiratory tract of cattle.[15] The exact site of replication is thought to be the tonsilar crypt;[18] this replication is a crucial phase in lesion development as large numbers of bacteria can be inhaled into the lung allowing colonization, proliferation and production of virulence factors. It is not clear whether all cattle carry *P. haemolytica* A1 in their tonsilar crypts or if only a small number do. If all cattle carry this organism and stress and viral infections allow selective proliferation then pneumonic pasteurellosis would not be considered a contagious disease. If, however, only a small number of calves carry this organism in their tonsilar crypts and following proliferation in the upper respiratory tract of these calves, other calves in contact also developed colonization of large numbers of *P. haemolytica* then there is a contagious component to this bacterial end point of BRD. Two epidemiologic studies have looked at BRD to determine if it is, or is not a contagious disease.[19,20] Both found some clustering or increased morbidity based on the source or truck load, but both investigators were unable to make any conclusion regarding whether or not BRD is a contagious disease. Regardless of its status as a contagious disease there is undoubtedly a short interval of time after arrival in the feedlot when cattle which will subsequently develop BRD have large numbers of *P. haemolytica* A1 present in their upper respiratory tract. Antimicrobial therapy timed to coincide with this event and designed to provide therapeutic levels could theoretically have a profound effect on BRD morbidity and mortality. This could be accomplished by reducing the numbered calves with *P. haemolytica* A1 colonizing their upper respiratory tract, by reducing the number of *P. haemolytica* A1 present in the upper respiratory tract of calves which remain colonized and by limiting colonization of the lung. Shoo in 1989 reported that long acting antibiotics could significantly alter the number of calves from which *P. haemolytica* could be cultured.[21]

An additional rational for mass medication of feedlot cattle on arrival with antimicrobial agents would be the fact that many of the calves dying from BRD are sick on arrival or get sick within days of arrival based on the epidemic curve of fatal disease onset for BRD.[4] Although mass medication through feed and water has been utilized for many years, the focus in recent years has shifted to mass medication using injectable antimicrobial agents. The ability of these drugs to reach therapeutic levels quickly in all animals gives them a clear advantage given the previously discussed rationale for BRD prophylaxis.

A number of trials have been published which examine various antimicrobial agents and their effectiveness for BRD prophylaxis. Most of these studies have examined both health and production parameters.[22-28] Tilmicosin given to calves on arrival at the feedlot was shown to reduce the treatment rate, extend the time from arrival to the onset of therapy and increase the average daily gain and feed efficiency over the trial period compared to non medicated control animals.[24] When long acting oxytetracycline was compared to trimethoprin-sufadoxine for prophylaxis of BRD, the long acting oxytetracycline reduced bovine respiratory disease morbidity as well as fatal fibrinous pneumonia mortality when compared to controls and trimethoprin-sulfadoxine treated animals.[25] This would indicate that there is an advantage to using long acting or sustained release formulations rather than products designed for daily injections. In a separate BRD prophylaxis study, tilmicosin treated calves, when compared to long acting oxytetracycline treated calves, showed lower morbidity and mortality attibutable to pneumonia, lower morbidity and mortality attributable to all causes and decreased case fatality.[27] The tilmicosin treated calves had significantly greater weight gains than the calves that received oxytetracycline. A long acting oxytetracycline product given subcutaneously was shown to have no significant difference from the same product given intramuscular in BRD treatment rates, BRD mortality rates, BRD case fatality rates or overall mortality rates when used for BRD prohylaxis.[28]

A paper recently published has used meta-analysis to examine antibiotics used for BRD prophylaxis.[26] Meta-analysis is the formal quantitative statistical review process that is used to synthesize the data from randomized field trials and draw conclusions concerning the efficacy of prophylactic mass medication for BRD.[26] Only 10 field trials out of 107 reviewed were ultimately included in this study. All other studies were excluded because they failed to meet the inclusionary criteria of being randomized, controlled field trials where mass medication was randomly allocated to the appropriate, independent, concurrent experimental units. Unfortunately, none of the studies involving mass medication in feed or water met these criteria and were not included in this study. It was concluded that long acting oxytetracycline and tilmicosin given parenterally on arrival at the feedlot would significantly reduce BRD morbidity rates.[26]

Conclusions

Antimicrobial agents play an important role in limiting losses due to BRD. It will be neces-

sary for the practitioner to have knowledge of both the susceptibility of the organism being treated as well as the pharmacokinetic behavior and attainable tissue levels for a range of possible drugs when choosing an antimicrobial agent for use as a first line drug. Alternately, a practitioner may choose to acquaint himself with a growing body of knowledge from statistically valid treatment trials to make a selection of first line antibiotics. Antimicrobial agents may play an even more important role when used as on arrival prophylaxis against BRD. In choosing these antibiotics, the same decision process is necessary as discussed for first line antimicrobial agents.

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