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The clinical syndrome of BRD: what it is and what it is not

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Abstract

The clinical syndrome of bovine respiratory disease (BRD) continues to be a major challenge in bovine production systems. We are challenged by our ability to predict morbidity in groups of cattle, our ability to accurately diagnose and provide a prognosis for individual cases, and our ability to evaluate the results of preventive and therapeutic interventions in the field when production system data are the sole basis for analysis. However, we are fortunate to have perhaps the highest quantity and quality of negative-controlled, prospective, randomized, and masked clinical trial data for any disease in veterinary medicine. It is nevertheless important to recognize that case definitions in these studies may not be consistent or necessarily externally relevant, and that production data in these studies are often missing.

Keywords: bovine respiratory disease, prognosis, diagnosis, treatment data.

Introduction

The clinical syndrome of bovine respiratory disease (BRD) continues to be a major challenge in bovine production systems. We are challenged by our ability to predict morbidity in groups of cattle, our ability to accurately diagnose and provide a prognosis for individual cases, and our ability to evaluate the results of preventive and therapeutic interventions in the field. We can agree that BRD is a complex disease, but after that the complexities of the disease syndrome make agreement on specifics more difficult. We are frustrated by the knowledge that much work is done by private entities and is not available in the literature; this work may include equivocal or negative studies which are not made available to balance the positive bias in the literature. This paper is not intended to provide an exhaustive review of the literature, but rather points to recent publications as a means of highlighting our continued efforts to better understand this disease.

BRD is not a disease with well-defined prognostic indicators

There are multiple definitions of high- and low-risk cattle, with some managers also including a medium risk category. These definitions are used to make decisions about issues such as purchase price differentiation, whether to treat for control of BRD, nutritional management options, and treatments to be included in the processing protocol. While many may feel they have these categories well defined, the literature gives us less confidence in the consistency of our prognostic ability for a group or individual.

Risk factors for BRD in calves still on the cow have been characterized by surveys of cow/calf producers (Hanzlicek *et al.*, 2013; Woolums *et al.*, 2013). There are general trends as to what predisposes cattle on a herd basis, but there are really no consistent approaches to identifying cattle at risk within the herd.

A review of predisposing factors for BRD in feedlot cattle concluded that the complexity of BRD makes it difficult to specifically characterize the involvement of individual factors (Taylor *et al.*, 2010). The authors cited specific risk factors such as purchasing from sale barns and commingling, but the impact of shipping, weather, arrival weight, gender, castration, and dehorning are less consistent when the whole of the literature is examined.

Bovine respiratory disease is not easily and consistently diagnosed

Put another way, diagnosis is easy if one is not going to be checked for accuracy. However, when diagnosis of BRD is checked against measurable outcomes, accuracy of diagnosis is usually revealed as marginal at best. Improvements in the validation of a case definition for BRD are needed, which would allow us to evaluate true morbidity as well as an accurate case fatality rate.

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Recent attempts at improving diagnostic precision in feedlot cattle have included lung biopsy (Burgess *et al.*, 2013), ultrasound (Abutarbush *et al.*, 2012), radio frequency identification (RFID)-associated thermography (Schaefer *et al.*, 2012), breath biomarkers and serum haptoglobin (Burciaga-Robles *et al.*, 2009), and rumen temperature boluses (Rose-Dye *et al.*, 2011). Pulmonary auscultation and rectal temperature have been demonstrated to have a correlation with clinical outcome in feedlot cattle (DeDonder *et al.*, 2010).

In neonatal cattle, evaluation of multiple scoring systems (Love *et al.*, 2014), and evaluation of scoring systems in relation to ultrasonography and auscultation (Buczinski *et al.*, 2014) have recently been published.

The treatment response to initial therapy (percent treated that require no further treatment) and case fatality rate (percent of those treated that die) can be too 'good'. One interpretation of exceptionally high first treatment response rates and low case fatality rates may be that a significant proportion of cattle are being treated which are not truly ill. This determination is dependent on the accuracy of our case definition for BRD.

It is hard to communicate to the public that we may have a target of losing a few cattle in order to avoid treating a high number of cattle that did not need treatment, but this is exactly the balance that is necessary. In fact, I think it would be rare to encounter a food animal veterinarian who is confident that with the proper application of chemical management we can avoid all death loss. In other words, to avoid putting antimicrobials into a large population that does not need them, perhaps we must accept that we will put antimicrobials into a small population of animals that are further into the disease process than we would like. This balance is elusive, and sure to bring about heated arguments involving the cost of treatment, conservation of animal resources, animal welfare, labor, and antimicrobial exposure in a population.

BRD does have a wide array of negative-control treatment data available for high-risk feedlot cattle

With all the caveats about prognosis and accuracy of the case definition, BRD is still the disease with arguably the most negative-control treatment outcome data of any veterinary disease, perhaps any disease in both veterinary and human medicine. Therefore, in high-risk cattle (begging a consistent definition for this term), we have an idea of treatment response rates and case fatality rates based on the case definitions for BRD used in these studies.

A good statistic for evaluating drug effects in a population is the number needed to treat (NNT). This is the number of animals that need to be treated with the drug to make a clinical outcome difference in one animal. The NNT is calculated using the attributable reduction in risk (ARR). For example, in a trial where 25% of the untreated controls were classified as treatment successes and 75% of the treated group was classified as treatment successes, the ARR is 50% (75 − 25%). If the only two outcome options are success or failure, it does not matter how you subtract, the difference is the same whether for the difference in successes or the difference in failures.

The NNT in this example would be 100%/50%, or two, indicating that you need to treat two animals to make a difference in one. Another way of looking at the example is that in every four treated animals there would be one response regardless of treatment (the 25% of untreated controls which are successes), one failure regardless of the treatment (the 25% of treated animals which were treatment failures), and two successes in the treated group which would have been failures in the control group (the ARR). Therefore, we made a difference in two out of four, or one out or two. We have to treat two to make a difference in one, an NNT of two.

The NNT therefore evaluates the effect of the drug in the context of a disease in a target population. The 'response rate' observed in production data is a combination of spontaneous recovery and the effect of the drug. Negative-control clinical trials allow separation of these two components of treatment response, isolating the effect of the drug in the population according to the success/failure case definitions used in the studies. The higher the response ('cure') rate in the control population, the less room there is for a treatment to make a difference.

Detailed tables of the available data on negatively controlled, prospective, randomized, masked clinical studies for BRD have been published (Apley, 2013). With few exceptions, these studies are pivotal dose finding and clinical efficacy approval studies conducted under good clinical practices (GCP) guidelines and accepted in the approval process by the Food and Drug Administration Center for Veterinary Medicine (FDA/CVM). These studies would predominantly represent high-risk calves. In my experience, the success/failure criteria used by the FDA/CVM result in a lower apparent clinical success rate than what would be observed in typical feedlot practice. However, the mortalities have a fairly constant definition, which even veterinarians might have difficulty debating. The extrapolation of these results to low-risk cattle would likely overestimate the effect of the antimicrobials due to an expected higher response rate in the untreated controls.

It must be admitted that these studies do not take into account the potential improved production performance of the successful cases in the treated group as opposed to the successful cases in the control group. However, practically speaking, clinical response is the basis for interpreting the effect of any treatment. In feedlot practice it is typical to evaluate treatment outcomes and to use these data to constantly monitor therapeutic 'efficacy'. How much of the monitored clinical outcomes are actually due to the drug administered?

The median NNT in 30 studies evaluating treatment of BRD with commercially available antimicrobials is two; for every two animals treated for BRD in the overall population of high-risk cattle, one animal became a treatment success which would have otherwise been a failure. Treatment success rates in untreated cattle in these studies ranged from 0 to 57%, with a median of 23.9%. This means that in these 30 studies, a median percentage of approximately 24% of the cattle meeting BRD case definitions were classified as treatment successes at the end of the placebo treatment regimen, and did not require treatment again during the study (these studies were not to closeout).

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In contrast, treated success rates in the treated cattle ranged from 51 to 92% with a median of 70.7%.

In 24 of these 30 trials, BRD mortality was also reported; this would be a case fatality rate because all cattle in the study were treated. In these studies, the median NNT for preventing BRD mortality is seven; for every seven animals treated for BRD in the overall population, one mortality was prevented in these study populations. The case fatality rates in the untreated controls fell within a range of 2.5–48% with a median of 17.0%. For treated cattle, the range was 0–23.0% with a median of 1.0%.

The authors of a meta-analysis of these and other treatment outcome data, as well as data related to antimicrobial comparison studies without negative controls, have classified antimicrobials used for BRD therapy as to their relative efficacy (O'Connor *et al.*, 2013). Using 194 trial arms from 93 trials, the authors were able to rank antimicrobials for comparative efficacy across the trials.

Conclusion

While we struggle with accuracy of diagnosis and prognosis, there are still data to help us evaluate diagnostic and prognostic methods, as well as treatment outcomes in some classes of cattle. Our glass is definitely half-full, with promising research on the horizon to advance our understanding.

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