"Steer"-ing in the Right Direction

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Introduction:

Bovine respiratory disease (BRD), also known as shipping fever, is the most common cause of sickness and death in beef cattle in the United States (11). Bovine respiratory disease affects cattle most commonly within the first 60 days after arrival at a feedlot or farm due to their exposure to a wide range of pathogens combined with a multitude of stressors(9). This is most commonly due to a primary infection with one or more respiratory viruses that is then followed by a secondary infection with one or more respiratory bacteria (10). Information pertaining to the prevalence and antimicrobial resistance of these bacterial pathogens is crucial to choosing antibiotics for the treatment and control of BRD (9). Commonly, producers use multiple antimicrobials in their herd in an effort to treat disease in a herd, leading to a development of antimicrobial resistance that could make BRD refractory to treatment (11). A study by Dr. Brandi Karisch and Dr. Amelia Woolums, along with other researchers in the Mississippi State University College of Agriculture and Dairy Science, Department of Pathobiology, and Department of Population Medicine, is currently in progress to determine how the percentage of steers shedding multidrug resistant (MDR) *Manheimia haemolytica* in combination with the effect of different numbers of steers being placed in pens affects morbidity and mortality of the herds due to BRD over a 60 day period. This information can also be extrapolated to determine if antimicrobial resistance is causing current treatments to be ineffective for BRD treatment, as well as seeing how pen size is affecting the spread of BRD. During my food animal rotation, I was able to assist in multiple days of sample collection for the study, inspiring this discussion of BRD. Due to the lack of final results in the study, as well as the current unpublished status of the research, the following will be presented as an example case presentation using a singular steer from a previous similar study as a specific example of BRD (4).

History and Presentation:

The cattle in the study were Angus cross steers weighing between approximately 400 and 500 lbs. These steers were purchased from local auction markets and then randomly assigned to treatment groups. They came from different locations across the southeastern United States. There was no information provided about history of the cattle prior to purchase for the study. Upon arrival they received vaccines including MLV 5-way viral and 8-way clostridial bacterin-toxoid. They also were dewormed with levamisole at 8 mg/kg orally and fenbendazole at 10 mg/kg orally. These cattle were then checked daily for signs of BRD or other illness using a standardized scoring system based on the severity of their BRD signs. The cattle were monitored for alertness and willingness to move, respiratory rate, rumen fill, nasal discharge, coughing, depression, muscle weakness, increased abdominal effort while breathing, and for more severe versions of these signs. In addition to being monitored for illness, they were also treated for clinical signs with up to three different antibiotics.

For purposes of this case study, a more severe case from a similar previously published research study will be used as an example (4). This steer had a fever of 104.2° F upon arrival. It later presented with clinical signs 9 days after arrival with a BRD clinical signs score of 2 with these signs including moderate depression, mild muscle weakness, moderate decrease in rumen fill, increased abdominal effort while breathing, repeated coughing, serous nasal discharge, and a fever of 106.8° F.

Pathophysiology:

This disease presents typically in a recently transported or stressed group of calves or cattle (10). The predisposing stressors can include environmental factors, host factors, or pathogens (3). Environmental factors such as weaning, commingling, or transport serve as stressors that weaken the immune system (3). Transport is the most accepted non-infectious risk factor for BRD with the segmented nature of cattle production in the United States ensuring that all cattle will likely be transported at least once in their lifetime (8). These stress events then lead to a primary infection with one or more respiratory viruses that is followed by a secondary infection with one or more respiratory bacteria (10).

Viral pathogens include infectious bovine rhinotracheitis (IBR) (or bovine herpesvirus-1 (BHV-1)), bovine viral diarrhea virus (BVDV), Bovine parainfluenza virus 3, and bovine respiratory syncytial virus (BRSV) (1,6). Viruses are believed to predispose to bacterial infection in two distinct ways (8). The first of these is that viral agents can cause direct damage to the respiratory clearance mechanisms and lung parenchyma, leading to bacterial entry from the upper respiratory tract into the compromised lung (8). Secondly, the viral infection inhibits the immune system's ability to respond to the bacterial infection (8). Many of these viral infections are self-limiting and serve a primary purpose of promoting a secondary bacterial infection with host susceptibility playing an important role in eliminating the viral infection (6).

There are four bacteria most commonly associated with bronchopneumonia or pleuropneumonia in cattle including *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni*, and *Mycoplasma bovis* (10). These bacteria are commensals that likely exist in healthy cattle as biofilms (6). When membrane damage occurs, the bacteria disperse from the biofilm and invade the deeper lung (6). Once established in the lung, the bacteria cause inflammation and bronchopneumonia, due to a variety of virulence factors and also the host response to these factors (6). *M. haemolytica* produces a leukotoxin that kills ruminant white blood cells while also producing endotoxin (10). *P. multocida* produces endotoxin while *H. somni* produces lipo-oligosaccharide similar to LPS, another endotoxin (10). *Mycoplasma bovis* has variable surface proteins and impairs host defense by decreasing the oxygen radical production by leukocytes with some strains producing a cytotoxin that contributes to caseous necrosis in the lung (6,10).

Diagnostic Approach/Considerations:

The steers were observed daily by animal caretakers trained by project senior investigators for clinical signs of disease and were assigned a score based on a standardized scoring system. The scoring system used for BRD severity in individuals within the herd was as follows:

0	Clinically Normal - Calf is alert and watches approaching examiner, may actively move toward or away from examiner when approached closely - Respiratory rate normal for environmental conditions - Rumen fill normal
1	Mild BRD including one or more of the following signs: - elevated respiratory rate for the environmental conditions - nasal discharge: clear, cloudy, white, or yellow - mild decrease in rumen fill - coughs occasionally (no more than twice per observation period)
2	Moderate BRD including one or more of the following signs: - mild or moderate depression o lethargic, but may look alert when approached o head carriage lower than normal, but may return to normal when approached - mild to moderate muscle weakness o mild incoordination and/or o cross stepping and/or o floppy ear carriage - moderate decrease in rumen fill - breathing with mild to moderately increased abdominal effort - coughs repeatedly (more than twice per observation period) Cattle with a score of 2 may also have nasal discharge and increased respiratory rate for the environmental conditions
3	Severe BRD including one or more of the following signs: - severe depression o lethargic and does not look more alert when approached o low head carriage, does not return to normal when approached o does not move away from examiner as fast or as far as expected when closely approached - breathing with effort o open mouth breathing o moderately to markedly increased abdominal effort

	Cattle with a score of 3 may also have elevated respiratory rate, nasal discharge, and/or moderate to marked decrease in rumen fill
4	Moribund - recumbent and does not rise when approached or directly stimulated OR - standing but does not move unless directly stimulated: if the animal moves, it is very weak: drags feet, sways, stumbles - eyes may be very sunken, abdomen may be very gaunt Moribund animals may also have other signs described for score of 1,2, or 3

Any cattle meeting the requirement for treatment, a score of 1 or 2 with a temperature of 104° F or higher OR a score of 3 or 4 with any temperature, received an antibiotic. They were then monitored and treated for up to three antibiotics, with restrictions on frequency of administration. Throughout the experiment, the cattle were weighed every 2 weeks, and nasopharyngeal swabs werecollected on day 0, d. 12, and d. 60. These nasopharyngeal swabs were then sent for aerobic culture and sensitivity.

Treatment and Management:

Ideally upon diagnosis using clinical signs, antibiotics should be administered for 3-7 days past resolution of all clinical signs, which usually indicates a treatment time of 7-28 days depending on severity of clinical signs (10). In commercial settings, this protocol is not practical and set antibiotic protocols are developed for ease of administration and treatment. For purposes of this paper, a more severe case from the previously published research study will be used as an example. As mentioned previously, this steer (#91) had a fever of 104.2° F upon arrival and first presented with clinical signs 9 days after arrival with a BRD clinical signs score of 2 and fever of 106.8° F. The steer was then treated with ceftiofur crystalline free acid. Then, 10 days later, it was noted that the steer was not showing signs of improvement with a continued score of 2 with a fever of 107.4° F; he was thus treated with florefenicol. Approximately 6 days later, the steer presented with a score of 3 with a fever of 107.2° F and was treated with oxytetracycline.

Overall the treatment protocol was as follows:

a. First treatment: Ceftiofur crystalline free acid (Excede®, Zoetis) at 6.6 mg/kg SC
    a. Clinical signs persisting 7 days or more post first treatment warranted second treatment
b. Second treatment: Florfenicol (Nuflor® Injectable solution, Merck Animal Health) at 40 mg/kg SC
    a. Clinical signs persisting 4 days or more or more post second treatment warranted third treatment
c. Third treatment: Oxytetracycline (Noromycin®, Norbrook Laboratories) at 20 mg/kg SC
    a. Cattle with signs of BRD after third treatment were not eligible to receive additional antimicrobial therapy during the study but were monitored.

This treatment protocol is comparable if not the same as other bovine respiratory disease treatment protocols seen in many beef operations around the country.

Management is equally important as treatment if not more important than treatment when it comes to BRD. It has been repeatedly shown that cattle arriving at a new farm are at the greatest risk for BRD, likely resulting from exposure to pathogens as well as increased stress during episodes of transit (8). Other factors associated specifically with sale barn cattle have been shown to increase BRD incidence including commingling, age, and weight (8). Commingling by buying calves from one or more sale barns and combining through an order buyer has been shown to increase the risk of BRD (7). Yearling cattle are reported to have a lower incidence of morbidity and mortality than calves (8). There have also been multiple studies that show lighter weight calves are at a greater risk than heavier ones (8). Therefore, a case can be made for recommending purchasing cattle directly from a farm or ranch. Also, if a purchase does need to be made through an order buyer, effort should be made to purchase those at a higher weight and older age to decrease risk of BRD.

Vaccinations for BRD are an important aspect of managing a beef cattle herd. Commonly vaccinations against BRD pathogens are administered at weaning with a booster 30 days later, often at feedlot entry (5). One study found that vaccinating before these stressful events resulted in increased plasma concentrations of antibodies against *M. haemolytica* and BVD at feedlot entry and increased average daily gain (ADG) during feedlot when compared to vaccinations being administered at the same time or after these stressful events (5). This shows that vaccines are more effective when administered prior to stressful events.

Another aspect of management is preconditioning calves before transport. Preconditioning includes weaning, castrating, dehorning, and administering vaccines well in advance of transport (10). One common preconditioning program known as VAC-45 requires a 45 day post weaning phase with a buyer specific nutritional program and health program, possibly including dehorning, castrating, and bunk feed training (2). Calves castrated after purchase have been found to have an increased risk of BRD as well as decreased average daily gain compared to calves castrated prior to arrival (8). Preconditioned calves are healthier, with a stronger immune system, and are more valuable to feeder cattle buyers (2).

Case Outcome:

Ultimately, the steer was euthanized 3 days post last treatment due to lack of improvement and poor prognosis. A necropsy was then performed. Upon necropsy, the following respiratory lesions were seen:

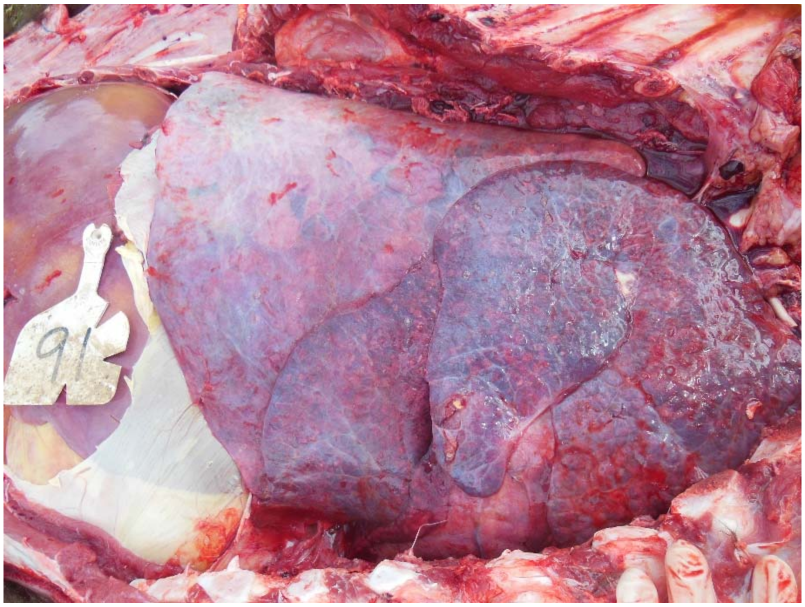

Fig 1. The image on the left shows pulmonary lesions seen on necropsy. This image is courtesy of Dr. Amelia Woolums and Dr. Courtney Griffin.

The image in Fig 1. shows the right lung lobes on necropsy of steer # 91 after euthanasia during the study. There is mild fibrin formation on the cranial and middle lung lobes. The fibrinous bronchopneumonia is focused in the ventral cranial, middle, and caudal lung lobes with only a small amount of normal lung present in the caudal dorsal lung.

Portions of the lung tissue were submitted for aerobic culture and sensitivity. The lung showed moderate growth of both *Trueperella pyogenes* and *Histophilus somni*. Both *T. pyogenes* and *H. somni* were found to be sensitive to ceftiofur but resistant to both florfenicol and tetracycline.

Conclusion:

Bovine respiratory disease is the most economically devastating disease of beef cattle in North America and has a variety of physical and physiological factors predisposing cattle to pneumonia (8). Cattle purchased through market channels are at risk for BRD with potential exposure to multiple pathogens during the commingling of cattle from many sources, in addition to stressors such as weaning and transportation (4). Many methods and treatments can be used to manage or prevent BRD including preconditioning, vaccinations, and antimicrobial use. The example seen in this case study was a particularly severe case of BRD and is not typical for the disease but does show how the disease can progress and the pathology that can be seen on necropsy of severe cases. With the results of the culture and sensitivity showing bacterial growth that was sensitive to our first treatment, but resistant to our second and third treatments, multiple theories can explain the lack of response to treatment. One theory is that the first treatment successfully treated the bacterial populations present at the time of the first treatment, but after that treatment other resistant populations, namely *H. somni* and *T. pyogenes*, began to flourish in the lung tissues. Another theory is that the bacterial populations were not successfully treated with the first treatment consisting of the sensitive antibiotic, ceftiofur, but would have responded if the treatment was continued for more than a 7 day period.

Manheimia haemolytica is traditionally one of the most common bacterial isolates seen in BRD and antimicrobial resistance has become a major concern (8). The study from which this case presentation was originally inspired is still in progress. Its overall purpose is to determine whether changing the number of cattle in a pen can affect the spread of MDR *M. haemolytica* and affect the morbidity and mortality of the cattle in that pen. It is important to see how antimicrobial use is affecting drug resistance in this very prominent disease in order to reduce its prevalence and the effects it has economically on the cattle industry. By researching the connections between the spread of antimicrobial resistance and herd size we are “steer”-ing in the right direction of more effective BRD management and treatment.

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