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Inflammatory profiles of high risk cattle exposed to common management practices

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Bovine respiratory disease (BRD) is the leading cause of morbidity and mortality in beef cattle. Common management practices in addition to BRD have been shown previously to cause inflammation. The objectives of this study were: (1) characterize the inflammatory profiles as indicated by interleukin-1 beta (IL-1β) and haptoglobin concentrations; (2) evaluate the impact of on-arrival metaphylactic antimicrobial therapy on inflammatory profiles in high risk cattle; and (3) examine the relationship between inflammatory profile and BRD morbidity and mortality. Eighty sale barn heifers were purchased over a two-year period (n=160). At arrival, heifers were randomly assigned to either receive tulathromycin (Draxxin, META, n=40) or not (NO META, n=40). Inflammatory profiles remained increased for all groups through d70 (P = 0.028). Metaphylaxis did not affect haptoglobin concentration ($P > 0.10$). There was a significant increase in BRD cases from day 0 to 20 (P = 0.002). Morbidity (BRD vs no BRD) did not impact haptoglobin concentrations.

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CHAPTER I

INTRODUCTION

The United States is the world's largest producer of beef for domestic and export use. Over the years, beef production and numbers have decreased significantly (USDA National Agricultural Statistics Service). Researchers and farmers are looking for ways to increase profit and decrease labor while still caring for the health of the animal. There are two primary sectors of the beef cattle industry: cow-calf and fed cattle operations.

The stocker industry is critical to beef production because it allows time to develop immunity, overcome stress of weaning, and gain weight to prepare for the next phase of production. Eighty-one percent of the United States cow-calf operations have fewer than one hundred head of cattle, representing forty-six percent of the United States beef cow inventory (USDA, NASS 2012 Census of Agriculture). The weaned calves from these operations make their way to feedlots across the nation. Many of these calves are "stocked" onto pastures to prepare them to efficiently mature before reaching the feedlot. This provides farmers with a low overhead source of income based on forage (Rankins and Prevatt, 2013). The success of the stocker industry is driven by receiving high risk calves with unknown backgrounds which may have high rates of sickness and death. The stocker cattle sector adds value to these calves by marketing them as a uniform group of calves to cattle feeders.

Bovine respiratory disease (BRD) is the most common and deathly disease in the stocker industry accounting for approximately 75% of morbidity and 50% of mortality in U.S. feedlots

(Edwards, 1996; Smith, 1998). It is a multifactorial disease caused by different pathogens, irritants, and stressors such as a weakened immune system. One way to control BRD is by using a metaphylactic program which involved the administration of an antimicrobial to a group of cattle that are at risk of developing BRD. The goal of using this program is to improve the overall health and performance of the cattle (Nickell and White, 2010).

Difference in management practices affects the amount of stress put on the group of calves causing them to be at a higher risk level for disease. These cattle are considered "high risk" due to their unknown history before entering the stocker phase (Wilson et al., 2017; Taylor et. Al., 2010a). Calves are at risk due to several stressors such as transportation, comingling and timing of management practices. These management practices include things such as weaning, vaccination, castration, and dehorning. Timing of these practices is crucial as the calves are experiencing multiple inevitable stressors at the time of transport. Vaccination is a common practice that has been shown to increase inflammatory response, decrease feed intake, and cause tissue damage (Stokka et al., 1994).

These events that occur around weaning not only increases the incidence for disease but increases their risk of succumbing to infection or systemic inflammation which ultimately increases morbidity and mortality while decreasing performance (Woolums et al., 2018). BRD is frequently described by a viral infection combined with stress that ultimately suppresses the host's immune system which allows bacteria to infect the lung (Chitko-McKown et al., 2020). Inflammation is part of a normal immune response while excessive inflammation may be harmful or even fatal. Changes in the innate defense as well as the induction of pro-inflammatory cytokines is key in the pathology associated with BRD. There is limited knowledge on how to negate the impact of inflammation. Some studies show that by measuring levels of acute phase proteins such as haptoglobin or inflammatory cytokines such as IL-1β that are associated with inflammation, may indicate a calf that may be at risk of BRD prior to showing the clinical signs of this disease. Woolums and colleagues (2018) found that there is great variability in acute phase protein and inflammatory cytokine concentrations in calves due to weaning occurring even prior to additional transportation and treatment. Twenty-four hours after weaning, researchers found elevated serum concentrations of haptoglobin and IL-1β (Woolums et al., 2018). It is likely that cattle with high proinflammatory cytokines demonstrate negative performance.

Overall, these stressors can cause the immune system to fail which allows pathogens to enter the body within the respiratory tract and cause infection. Cattle that come from sale barns fall into the high risk category because they undergo these stress factors and are exposed to new pathogens when they are comingled with other calves from different areas (Taylor et al., 2010a). Various management strategies can mitigate the effects of these stressors resulting in healthier more uniform calves that increases profitability.

CHAPTER II

LITERATURE REVIEW

Introduction

Once cattle arrive to the stockering facility, multiple management practices can either improve or harm the health, growth, and overall profitability of the calves. The objective of this literature review is to 1) examine at the impact of bovine respiratory disease 2) evaluate the inflammatory response and 3) discuss management strategies to lessen the incidence of this disease on the stocker industry.

Bovine Respiratory Disease

Bovine Respiratory Disease (BRD) is the most significant health problem in newly weaned/received beef calves (Duff and Galyean, 2007) and is the leading cause of morbidity and mortality in U.S. feedlots (Woolums et al., 2015). This disease remains an extensive and costly problem for the beef industry as BRD deaths alone cost over $600 million annually (NASS, 2011). The impacts of BRD are both direct and indirect. Direct impacts are anything from treatment costs to death of these calves. A decrease in performance measures such as average daily gain (ADG) and feed intake are indirectly affected by BRD. These factors cost the beef industry more than $800-900 million annually (Chirase and Green, 2001).

Bovine Respiratory Disease is a multifactorial syndrome caused by a combination of various pathogens and stressors. This disease refers to any infection of the upper and lower respiratory tracts and is commonly associated with pneumonia in calves that have been weaned or recently arrived at the feedlot. BRD is most common during the first few weeks of arrival but can occur later. Any factor alone may be insufficient to trigger BRD, but together they can form an additive effect that can predispose the animal to the illness. Viral agents are considered precursors to, or occur simultaneously with, bacterial infection (Cusack et al., 2003). The viral components of this disease include infectious bovine rhinotracheitis virus (IBR), parainfluenza virus type 3 (PIV-3), bovine viral diarrhea virus (BVDV), and bovine respiratory syncytial virus (BRSV; Cusack et al., 2003). The bacterial agents most commonly associated with BRD are *Mannheimia haemolytica, Pasturella multicoda, Histophilus somni,* and *Mycoplasma bovis* (Taylor et al., 2010a). The most prominent of these is *M. haemolytica* (Fulton et al., 2002). When the innate immune system is weakened, bacteria enter the lower respiratory tract. The stress factors discussed earlier are another main component to this multifactorial disease. BRD is a very complex disease that is hard to vaccinate against due to the large variety of agents that are responsible for infection.

When stocker cattle are shipped or processed, this exposes them to an increase in predisposing causes as well as the environmental risk factors. Age, weight, and stressors such as weaning, castration, dehorning and nutritional changes are the main predisposing agents that cause the immune system to be compromised (Callan and Garry, 2002). A change in climate, ambient temperature, stocking density, ventilation as well as shipping distance are all environmental factors (Snowder et al., 2006). “Shipping fever” is caused by transportation stress which is the most widely known and accepted non-infectious stressor for BRD (Taylor et. Al., 2010a). There are many strategies that stocker operations implement to help mitigate these stressors. It is important to note that these stressors can never be fully eliminated.

The detection and diagnosis of bovine respiratory disease is highly subjective and potentially inaccurate (Galyean et al., 1999). The primary method of detection is by visual appraisal of people known as pen riders. These visual indicators are things such as: depression, lethargy, anorexia, labored breathing, coughing, and nasal or ocular discharge (Taylor et al., 2010b). Once cattle exhibit one or more of these signs, they are separated for further evaluation of sickness. There is some debate among researchers regarding the appropriate temperature to define BRD. Gallo et al. (1995) used a rectal temperature of >40.5°C to define cases of BRD. They found an overall morbidity relate of 23.0% during a 56 d receiving period. These calves were not treated metaphylactically but did receive respiratory and clostridial vaccination upon arrival. Recent research by Richeson and colleagues (2015) suggests that a rectal temperature ≥40.0°C should be used to determine which animals are sick and therefore require treatment. They found an overall morbidity of 34.7% with a 32.5% relapse rate. Another study by Rogers et al. (2016) stated the same thing and observed a 24.5% morbidity with a 41.8% relapse rate. It is important to note that in both studies, cattle received metaphylaxis upon arrival. These findings suggest that using a rectal temperature of ≥40°C is the most accurate and accepted parameter to be used when determining sick calves for treatment.

Along with the increased rectal temperature, producers can use a common BRD scoring system to determine the sickness level of these cattle in order to help what is known as a subjective measure maintain more of a quantitative diagnosis. The system ranges from 0-4 to determine the severity of sickness. When scoring, a 0 means the calf is normal while a 1 means they have mild BRD, 2 is for moderate, 3 is severe and 4 is moribund. A prompt and correct diagnosis of this disease is needed as cattle who are not treated in a timely manner will become worse. This clinical system provides a way to objectively make treatment decisions.

Immune Response and Inflammation

Diagnosis of BRD is often a subjective matter based on visual appraisal and clinical measurements such as rectal temperature, serum profiles and lung lesions (Galyean et al., 1999). Due to the subjectiveness of BRD diagnosis coupled with the animal's ability to mask the disease, it can be challenging for producers to accurately identify the disease (Noffsinger and Locatelli, 2004).

Immunity is the reaction of the animal's body to foreign microbes or pathogens regardless of the physiological or pathological result of such reaction (Abbas et al., 1991). Inflammation is part of the normal immune response; however, excessive inflammation may be harmful or even fatal. There are four categories of disease-causing microorganisms: viruses, bacteria, fungi, and parasites. We see that viruses kill cells by lysis, bacteria by toxins, pathogenic bacteria and fungi induce shock and sepsis, and some parasites form cysts. There are three strategies to deal with microbes: avoidance, resistance, tolerance.

Cellular immune responses are initiated when sensor cells detect inflammatory inducers. There are two types of immune responses that cattle experience. The first type is innate immunity which is a non-specific response to something that enters the body (virus, bacteria, etc.) or to tissue damage (Tizard et al., 2012). Second, the adaptive immune response which is specific for a single type of virus, bacteria, or other infectious agent.

Innate recognition receptors are encoded by a relatively small number of genes that remain constant over an individual's lifetime. These receptors can activate innate immune cells to produce various mediators that either act directly to destroy invading microbes or act on other cells to propagate the immune response. Dendritic cells may produce cytokine mediators that activate target tissues. Innate immune responses occur rapidly on exposure to an infectious organism. Lymphocytes express highly specialized antigen receptors that collectively possess a vast repertoire of specificity (Tizard et al., 2012). The adaptive immune system is enabled as it interacts with and relies on cells of the innate immune system for many of its functions (Baumann and Gauldie, 1999).

The three types of phagocytes in the immune system are macrophages, granulocytes, and dendritic cells. Macrophages are in almost all tissues and arise during embryonic development. There are many different responsibilities of the macrophage. One is to engulf invading microorganisms which is the first defense in innate immunity (Tizard et al., 2012). The second is to dispose of pathogens and infected cells. A third and crucial role is to orchestrate immune responses like inducing inflammation.

There are three types of granulocytes – neutrophils, eosinophils and basophils. Neutrophils are the most numerous and important in the innate response as they destroy organisms by phagocytosis. Eosinophils and basophils are less abundant but have granules containing a variety of enzymes and toxic proteins. Dendritic cells are a major class of sensor cells that trigger the production of mediators that activate other immune cells. They are the only cells that can activate naïve T-cells for the first time.

In vaccines, an adjuvant helps intensify the response to the immunizing antigen. Adjuvants are needed to activate innate receptors on various types of sensor cells to help activate T cells in the absence of an infection. Macrophage, neutrophils and dendritic cells are important classes of sensor cells that detect infection and initiate immune responses. These cells have different receptors to recognize pathogens or the damage that has been done.

Cytokines and chemokines act in a manner similar to hormones to convey important signals to other immune cells (Tizard et al., 2012). These are two important categories of inflammatory mediators. Cytokine is a term for any protein secreted by immune cells that affects the behavior of nearby cells bearing appropriate receptors. Cytokines mediate cell to cell communication. Chemokines are a specialized subgroup of secreted proteins that act as chemoattractants, attracting cells bearing chemokine receptors, such as neutrophils and monocytes (Tizard et al., 2012). Cytokines and chemokines recruit cells from the blood, which is part of the inflammatory response.

Inflammation is a process where the body's white blood cells protect against infection from bacteria and viruses. It increases the flow of lymph, which carries microbes or cells bearing their antigens from the infected tissue to nearby lymphoid tissues, where the adaptive immune response is initiated (Tizard et al., 2012). Endothelial cells produce cytokines in response to infection. The movement of cells into the tissue and their local actions account for pain. The main cell types seen in the initial phase of an inflammatory response are macrophages and neutrophils. They are known as inflammatory cells.

Cytokines are signaling proteins produced primarily by macrophages in response to infection, tissue injury or stress (Engen et al., 2013). Elevated serum concentration of the proinflammatory cytokines, haptoglobin and interleukin 1-beta, were found in the serum of calves 24 hours after weaning (Woolums et al., 2018). Haptoglobin, binds to free hemoglobin and reduces inflammation and oxidative stress. This is important because it helps to prevent hemoglobin-induced inflammation and oxidative tissue damage and suppress the overall production of inflammatory cytokines. Interleukin-1 beta is a proinflammatory cytokine that is an important mediator of the inflammatory response as it is essential for the host's response to pathogens. It is likely that cattle with high proinflammatory cytokines demonstrate a negative impact on performance. Cattle with high concentrations of serum haptoglobin are at increased risk for requiring multiple treatments for BRD (Holland et al., 22011). Vaccination is a common practice that has been shown to increase inflammatory response, decreased feed intake and cause tissue damage (Stokka et al., 1994).

The numerous risk factors that affect BRD can lead to an increased serum haptoglobin concentration after the arrival at the feedlot or stocker operation. In a study by Holland and colleagues (2011), the objective was to measure haptoglobin concentration in 360 heifer calves and 416 bull calves to assess the relationship between serum haptoglobin concentration and performance as well as BRD morbidity and mortality rates of calves. There were fewer significant differences than they hypothesized as there was no significant difference in serum concentration levels between the groups except for day one. Performance data was also analyzed for these calves and it was found that calves with a high haptoglobin concentration had lower average daily gains as well as dry matter intake. The research suggested that cattle with higher haptoglobin concentrations at arrival may have a more chronic disease state where antimicrobial treatment may be less effective. The authors proposed that earlier intervention targeted at cattle with higher haptoglobin concentrations upon arrival could lower the impacts of BRD on illness, death and performance losses in those cattle.

Management Practices

There are numerous management practices producers can use to protect their calves against BRD as well as other diseases. Vaccinating calves is important to stimulate the adaptive or acquired immune system to help the calf develop a memory response (Chase et al., 2008). When the calf encounters the pathogen in the future, the memory response is activated which allows the immune system to respond more rapidly. This does not necessarily prevent infection, however, it can reduce the severity of clinical signs. Some studies have shown that vaccinating upon arrival can impact the health and performance of cattle (Griffen et al., 2018). A study done by Griffen and colleagues (2018) showed that vaccination of calves at arrival is associated with increased BRD morbidity, mortality, and lower final weights. Their findings support the fact that vaccinating calves that have been recently exposed to stressors that cause BRD, may have an increase in their risk factors for sickness.

As previously discussed, a number of factors can lead to stress in these calves. Transportation, increase or decrease in temperature, as well as nutritional changes can all lead to calves becoming stressed (Damtew et al., 2018). Preconditioning calves after weaning is one of the most important practices that can take place to protect calves when stressed (Lalman et al., 2017). Commingling animals from different sources and backgrounds can cause stress and expose these animals to disease-causing agents. When this occurs, these calves are more likely to become sick. Even though a producer may use all of these practices, there are times when these calves will still become ill.

The use of antimicrobials in food animals is a hot topic that is facing scrutiny today. Even though most consumers agree that medicating sick animals is necessary, many disagree on the acceptable use of these antimicrobials (Landers et al., 2012). These antimicrobials are used to kill or inhibit the growth of bacteria that damage the productivity and health of livestock (Key and McBride, 2014). Research by the World Health Organization has shown the growing concerns that using antimicrobials in food animals for disease prevention could be linked to an increase in health risks as well as antimicrobial resistance in humans. Concerns like these have pushed legislators to increase regulation as well as veterinary oversight of the use of antimicrobials in food animal production (American Veterinary Medical Association, 2016; Food and Drug Administration, 2012).

Metaphylaxis has become a widely used aid in prevention of disease (Dennis et al., 2018). It is the mass treatment of cattle with antibiotics upon arrival. This practice is selectively used by 59% of U.S. feedlots on 20.5% of cattle that are placed on feed across all sectors of the cattle industry (U.S. Department of Agriculture, 2013). It is a management practice that administers antimicrobials to groups of high-risk animals to prevent or minimize the onset of disease (U.S. Department of Agriculture, 2013). Producers use this practice to reduce health risks when calves first arrive at stocker or feedlot facilities. Cattle producers are concerned that removing this widely used practice will be detrimental to the industry as metaphylaxis reduces the incidence of BRD (O'Conner et al., 2012; Abell et al., 2017). Numerous studies have evaluated the economic impact of BRD while little research has been done to determine the economics of metaphylactic antimicrobial use in cattle production.

Producers that do not use metaphylaxis practice what is known as the "pull-and-treat" method where they observe sick cattle and treat them as needed. In large stocker or feedlot operations, this method is costlier in high risk cattle. It has become more common to use this method alongside of metaphylactic treatment in order to decrease the number of treatments for sick cattle. As pull and treatment rates increase, medication costs rise as well as a decrease in carcass quality (Gifford et al., 2011). Dennis and colleagues (2018) found that by removing metaphylactic treatment, producers can loose $1.81 billion to $2.32 billion annually.

Conclusion

Calves that arrive at stocker operations are often immunocompromised and undergo a tremendous amount of stress. When calves are recently weaned, transported far distances, and are commingled, they are at a high risk for BRD. Bovine Respiratory Disease is the costliest disease in newly weaned and received calves regardless of management practices, antibiotics and vaccines (Galyean et al., 1999).

Preventing BRD by vaccination is not always achieved for producers when receiving high risk calves. Metaphylaxis is a way to mitigate the effects of stress caused by weaning, transport, and vaccination. It is important for producers to understand the best way to manage the health risk of these cattle to decrease the economic effects of BRD. By identifying the cytokine levels in calves upon arrival, we may be able to determine how management practices influence inflammatory responses in calves, and to determine what practices to implement to minimize harmful inflammation.

CHAPTER III

INFLAMMATORY PROFILES OF HIGH RISK CATTLE EXPOSED TO COMMON MANAGEMENT PRACTICES

Objectives

The objectives of this study were: (1) characterize the inflammatory profiles as indicated by serum interleukin-1 beta (IL-1β) and haptoglobin concentrations, at several time points after arrival in high risk cattle; (2) evaluate the impact of on-arrival metaphylactic antimicrobial therapy on inflammatory profiles in high risk cattle; and (3) examine the relationship between inflammatory profile and BRD morbidity and mortality in high risk cattle.

Materials and Methods

All procedures in this study were approved by the Institutional Animal Care and Use Committee at Mississippi State University (IACUC # 18-529).

Animals and Management

The 70 d trial was repeated over 2 years during the following dates: October 31, 2019 to January 9, 2020 and October 29, 2020 to January 7, 2021. A total of 170 black/black white face crossbred heifers (85 per study) averaging 228.95 and 228.74 kg respectively, were acquired from local auction markets and randomly assigned at arrival to treatment groups. In the fall of 2019, 2 heifers were removed by the research veterinarian due to toe tip necrosis. When serum was analyzed, there were 3 heifers with missing serum tubes. These heifers were removed from trial 1 bringing the total to 80. In the fall of 2020, one heifer removed by the research veterinarian due to health. When serum was analyzed, there were five heifers with missing serum tubes causing them to be removed from the study bringing the total of trial 2 to 81. Cattle were housed at the Mississippi Agricultural and Forestry Experiment Station H.H. Leveck Animal Research Center located in Mississippi State, MS.

The heifers either received the long-acting macrolide tulathromycin (Draxxin®, Zoetis Inc., Kalamazoo MI, META, n=40), or no metaphlaxis (NO METTA, n=40). Each group was housed on a 10-acre pasture where they were offered complete supplemental feed and free choice (Purina Animal Nutrition, Nashville, TN) mineral. Upon arrival, all heifers were identified, weighed, and a rectal temperature was obtained. Calves were ear notched for persistent BVD infection (PI) testing. Ear notches were sent to Mississippi Veterinary Research and Diagnostic Labratory for testing the next day. In both trials, no heifers tested positive for BVDV PI. Heifers were vaccinated with modified live virus vaccine containing BHV-1, PIV-3, BRSV, BVDV1, and BVDV2 (Pyramid 5®, Boehringer Ingelheim Animal Health USA Inc., Duluth, GA) and clostridial bacterin-toxoid (Vision 7® with SPUR®, Merck Animal Health, Madison NJ) and were dewormed with fenbendazole (Safe-Guard®, Merck Animal Health, Madison NJ) orally at 5 mg/kg as well as doramectin (Dectomax®, Zoetis Inc., Kalamazoo MI) by subcutaneous injection at 0.2 mg/kg. Blood was collected via jugular venipuncture into tubes containing no additive for separation of serum. The tubes were kept on ice during cattle sampling and taken back to the lab within 2 hours for processing.

Heifers were weighed, blood was drawn on d 0, 7, 14, 20, and 70 for trial one and d 0, 7, 14, 21, and 70 for trial two. After day 20/21, heifers were combined into one group and moved to a different pasture until d 70 where they were weighed, and blood was drawn for final analysis.

Trained pen riders observed cattle daily on horseback each morning for visual signs of BRD (e.g. nasal or ocular discharge, depression, lethargy, emaciated body condition, anorexia, labored breathing and cough). Cattle in the META group were not eligible for treatment for BRD for 7 days after metaphylaxis was administered, while cattle in the NO META group were eligible for BRD treatment beginning on study d 1. Once an animal met the criteria for BRD treatment (Appendix), it was treated with ceftiofur crystalline free acid (Excede®, Zoetic Inc., Kalamazoo MI) subcutaneously at the base of the ear. Once cattle were treated with ceftiofur, they were not eligible for treatment for BRD for 7 days. Cattle that required a second treatment for BRD were treated with florfenicol (Nuflor®, Merck Animal Health, Madison NJ) subcutaneously at a dose of 40mg/kg. Once cattle were treated with florfenicol they were not eligible for treatment for BRD for 4 days. Cattle that required a third treatment for BRD were treated with oxytetracycline (Noromycin 300 LA, Norbrook Inc., Overland Park KS). After a third treatment, cattle were not eligible for BRD treatment but cattle with signs of disease were evaluated by a project veterinarian to determine whether they met criteria for euthanasia.

To assess the systemic inflammatory response, serum concentrations of haptoglobin and interleukin-1 beta were measured at time points when blood was collected. Blood was collected by jugular venipuncture into tubes and allowed to clot. Serum was separated by centrifugation at 200 X g for 15 min at room temperature. Concentrations of haptoglobin and IL-1β were measured by a commercially available ELISA per kit instructions (Bovine haptoglobin ELISA Kit, E-10HPT, ICL Laboratories, Portland OR and Bovine IL-1β ELISA Kit, ESS0027, Thermo Fisher Scientific, Waltham MA). Serum samples were diluted as needed to keep the optical density value in the linear region of the standard curve. The concentration of haptoglobin or IL-1β was read off the standard curve, then multiplied by the dilution factor to determine the final concentration in ng/mL for haptoglobin and pg/mL for IL-1β. Arrival concentrations of haptoglobin and IL-1β were split into a "high" versus "low" groups. High haptoglobin concentrations at d 0 were considered anything ≥ 69968.27 ng/mL (mean concentration + standard deviation) while low concentrations were anything < 69968.27 ng/mL. High IL-1β concentrations at d 0 were considered anything ≥ 4383.739 pg/mL (mean concentration + standard deviation). Low and high concentrations were determined by using 0.5 standard deviations above and below the mean concentration as d 0 for both haptoglobin and IL-1β.

Statistical Analysis

All data was analyzed using SAS software version 9.4 (SAS Institute Inc., Cary, NC). Animal served as the experimental unit. The effects of arrival haptoglobin and IL-1β as well as BRD incidence on ADG for day 0 to 21 and 0 to 70, were evaluated in a multilevel linear regression model (PROC MIXED). The effects of d 0 haptoglobin, d 0 IL-1β and metaphylaxis on BRD incidence were evaluated by Poisson regression in a linear mixed model (PROC GLIMMIX). The changes in haptoglobin and IL-1β over time were analyzed by a repeated measures model (PRO MIXED). The variable year was treated as a random effect in the model to account for variation across years as it was not significant. Treatment means were estimated using LS-Means separated with the PDIFF option. All models accounted for year being random and significance was defined at $P \leq 0.05$ with trends being defined as $P < 0.10$.

Results and Discussion

BRD morbidity and mortality was not typical for high-risk stocker cattle as there were less treatments and deaths across each year when compared to normal studies. Cattle with higher haptoglobin levels upon arrival had a lower ADG from day 0 to 70 with no significant impact on health. BRD had a negative impact on ADG over the 70 day trial period but there was no interaction with cattle having higher inflammatory profiles upon arrival. Arrival haptoglobin and IL-1β levels were not different between the META groups but decreased in concentration over time as shown in Figure 1 and 2. Haptoglobin and IL-1β were high at arrival with a large amount of variation. This could be attributed to when the cattle went through the sale barn causing a lot of variety in the occurrence of stressful events. The variable year was treated as a random effect in the model to account for variation across years. Table 1 outlines descriptive statistics for performance and health by year.

Metaphylaxis

Performance

The use of antimicrobials administered by metaphylaxis is used widely by producers to inhibit the growth of bacteria that damages the performance and health of stocker calves (Key and McBride, 2014). Producers use this as a tool to reduce health risks when cattle first arrive at the stocker facility or feedlot (Dennis et al., 2018). In this study by Dennis and colleagues, they found that metaphylaxis is worth $532.18 million to the cattle feeding industry showing that if metaphylaxis was eliminated, net returns would decline by 0.92% annually in feedlot revenue. Previous research states that an increase in animal performance as a result of metaphylaxis could be due to decreased morbidity. Cattle that are not diagnosed with are expected to gain more rapidly than sick animals (Bateman et al., 1990; Morck et al., 1993; McCoy et al., 1994; Wittum et al., 1994). In a study by Wileman et al. (2009), the authors reported that cattle receiving metaphylactic treatment gained an additional 0.11 kg/d compared to those that did not receive metaphylaxis. This differs from the present study where treatment by metaphylaxis had no significant effect on ADG for d 0 to 21 ($P = 0.12$) or d 0 to 70 ($P = 0.17$). This difference could be due to the overall health of these cattle being better than most studies looking at high risk stocker calves.

Health

Several studies show the impact of injectable antibiotics by metaphylaxis and the success it has on decreasing the incidence of BRD. These antibiotics reduce clinical and subclinical morbidity and mortality cause by illness. Metaphylaxis is used to specifically treat groups of animals with elevated health risks (Dennis et al., 2018). In a study by Dennis et al., 2018, they found that morbidity in cattle is shown to decrease ADG. Oxytetracycline and sustained-release sulfadimethoxine reduced morbidity from 63.3% in control cattle to 7.1% in cattle treated upon arrival in a study by Lofgreen et al. (1983). The present study differed from this as treatment by metaphylaxis had no significant effect on BRD incidence ($P = 0.96$). When looking at relapse rate, there were no differences between the two treatment groups ($P = 0.18$). This difference could be attributed to the fact that the heifers in this study had lower overall morbidity (29%) compared to the 63.3% found in the study by Lofgreen and colleagues (1983).

Inflammation

There were no differences in haptoglobin ($P = 0.36$) and IL-1β ($P = 0.48$) concentrations between the two treatment groups at arrival ADD D 7. A study done by Chitko-McKown and colleagues (2020) showed similar results. They looked at 180 calves from different sale barns across the south east and found that there was no change in haptoglobin ($P = 0.19$) or IL-1β ($P = 0.20$) concentrations when looking at control versus metaphylatically treated calves over a 28 day study period.

BRD

Performance

Studies show that generally, there is a decrease in ADG as BRD incidence increases (Gardner et al., 1999). The effects of treatment for BRD on average daily gain is presented in Table 3. Average daily gain from day 0 to 21 was significantly lower ($P < 0.0001$) for those treated for BRD. There was also a significant decrease ($P = 0.0019$) in ADG from day 0 to 70 for those treated for BRD. These results are similar to those reported by Gardner et al. (1999) who found a 4% decrease in ADG and 1.7% decrease in final BW for steers treated for BRD. Holland et al. (2010) found a linear decrease ($P < 0.001$) in BW as the number of treatments for BRD increased over a 63 d preconditioning period.

Health

BRD has numerous impacts and is very expensive to treat. It has been estimated that 75% morbidity and 70% mortality is caused by BRD in feedlots (Edwards 1996; Galyean et al. 1999 and Lonergan et al. 2001). During a 63 d preconditioning phase evaluating 330 heifers, Holland and colleagues (2010) found a BRD morbidity of 57.6% and mortality of 8.3%. The present study differs from previous research. Of the 159 heifers, 50 (29%) were treated for BRD with 4 (2%) deaths. Four of the 159 heifers in this study died due to BRD and we found so significant differences between groups. Compared to previous studies, there were relatively low morbidity and mortality rates which could be the cause of no significant difference of metaphylactic treatment on BRD incidence.

Inflammation

Authors (Arthington et al. 2003 and Svensson et al. 2007) suggest that changes in acute-phase proteins through inflammation, could be useful to diagnose BRD in these high risk calves. Holland et al. (2010) categorized heifers into BRD risk groups based on arrival haptoglobin concentrations. There were no differences in arrival concentrations of haptoglobin ($P = 0.40$) and IL1-β ($P = 0.35$) for heifers that were treated for BRD and heifers that were not treated for BRD. In the same study mentioned earlier, similar results were seen, haptoglobin ($P = 0.34$) and IL1-β ($P = 0.95$) concentrations did not differ for calves that were healthy compared to those treated for BRD (Chitko-McKown et al., 2020). Holland and colleagues (2010) separated calves into groups based off of arrival haptoglobin concentrations (high, medium, and low). They found that there was no significant difference in haptoglobin concentrations upon arrival in heifers that were treated 1, 2, or 3 times for BRD.

Arrival Inflammation

Performance

Studies show that inflammation should decrease overall performance in these calves. Arrival haptoglobin concentration did not have a significant difference on ADG from day 0 to 21 ($P = 0.12$). There was a significant decrease ($P = 0.04$) in ADG from day 0 to 70 in calves that had a higher haptoglobin concentration upon arrival. When comparing levels of IL-1β at arrival to ADG from d 0 to 21 as well as d 0 to 70, we saw no differences between cattle with high and low concentration of IL-1β at arrival ($P = 0.66$, $P = 0.65$, respectively).

Health

Heifers with high concentrations of haptoglobin upon arrival had a morbidity rate of 27.2% while those with a low concentration, had a morbidity rate of 23.1%. There were no morbidity differences in heifers with a low (26.1%) or high (14.8%) concentrations of IL-1β ($P=0.42$). In the study by Chitko-McKown, they found that calves with higher haptoglobin levels on d 9 had an increased diagnosis of BRD. This could indicate that a lot of these calves were not exposed to pathogens prior to entry into the feedlot.

Inflammation over time

There was a wide range in concentrations for cattle within each group. Day had a significant effect ($P<0.0001$) but there was no time by treatment interaction ($P=0.48$). Serum concentrations decreased significantly from d 0 to 70 ($P<0.0001$), d 7 to 21 ($P=0.04$), d 7 to 70 ($P<0.0001$), d 14 to 70 ($P<0.0001$) and d 21 to 70 ($P<0.0001$). There was no significant effect of group ($P=0.42$) and no interaction between day and group ($P=0.51$) on serum concentrations for IL-1β. However, these concentrations decreased significantly from d 0 to 7, 14, 21 and 70 ($P<0.0001$) as well as from d 7 to 14, 21, and 70 ($P<0.0001$). These results are depicted in Figures 1 and 2. In the study by Chitko-McKown, in which haptoglobin concentrations were evaluated at multiple time points post arrival in 160 stocker calves, the authors also found a significant difference in haptoglobin ($P < 0.01$) and IL-1β ($P < 0.01$) concentrations over the 28 d study period. They found that arrival haptoglobin was the lowest at d 0 and peaked at d 9. In the present study, haptoglobin was high at d 0 but peaked by d 7 even though we saw no significant differences between the days.

Conclusion

This study showed that treatment with metaphylaxis upon arrival does not have a significant decrease or increase on ADG or morbidity in newly received stocker calves. This is different than most studies as we saw a lower overall morbidity and mortality throughout our trial when compared to other studies evaluating high risk cattle. Upon arrival, haptoglobin and IL-1β levels were not different between groups but decreased in concentration over the 70 day stockering period. This study showed that cattle with higher haptoglobin levels upon arrival had an overall lower ADG from day 0 to 70. We also found that BRD effected ADG over the 70 days even though it had no interaction with heifers who had higher inflammatory profiles upon arrival. This study showed that IL-1β levels were high at arrival with variation within the cattle. We hypothesized that inflammatory profiles would differ between healthy and sick cattle such that sick cattle will have elevated inflammatory markers. Even though we saw that higher haptoglobin levels has a detrimental effect on weight gain, we did not see it influence overall morbidity. Some of the results from this study do not match other results from several research articles as the heifers in this study remained healthier than normal over time. Ultimately more research should be done to confirm these findings.

Table 3.1 Descriptive statistics by year of health and performance data of newly received auction sourced high risk stocker calves during the 70 d receiving period

	Year	
Item	1	2
Initial BW, kg	229±18.3	228±16.3
Final BW, kg	256±31.6	277±31.7
ADG, kg/d		
0 to 21	1.42±1.3	-0.01±2.3
0 to 70	0.42±0.40	0.51±0.93
Morbidity, %	28.5	26.2
Mortality, %	0	0.04

Table 3.2 Effect of on arrival haptoglobin and IL-1β concentrations on growth for the 70 d receiving period in high risk stocker calves

	Haptoglobin			IL-1β		
ADG, kg	H	L	P-value	H	L	P-value
0-21	1.49±1.06	2.12±1.03	0.12	2.11±1.04	1.91±0.96	0.65
0-70	1.02±0.35[a]	1.31±0.33[b]	0.04	1.29±0.38	1.21±0.36	0.65

[a,b] Means within row with differing subscripts differ ($P < 0.05$)

Table 3.3 Effect of treatment by metaphylaxis and BRD incidence on growth for the 70 d receiving period in high risk stocker calves.

	META			BRD		
ADG, kg	Y	N	P-value	Y	N	P-value
0-21	1.71±1.00	1.20±1.0	0.12	0.56±1.03[a]	2.36±0.99[b]	<0.001
0-70	1.19±0.36	1.02±0.36	0.17	0.87±0.37[a]	1.33±0.35[b]	0.002

[a,b] Means within row with differing subscripts differ ($P < 0.05$)

Table 3.4 Effect of on arrival haptoglobin and IL-1β concentrations levels as well as treatment by metaphylaxis on health for the 70 d receiving period in high risk stocker calves.

	Haptoglobin			IL-1β			META		
Item	H	L	P-value	H	L	P-value	Y	N	P-value
Morbidity,%	27.2	23.1	0.47	14.8	26.1	0.42	23.4	25	0.96
Relapse rate,%	6.8	4.3	0.57	7.4	4.5	0.65	2.5	7.5	0.18

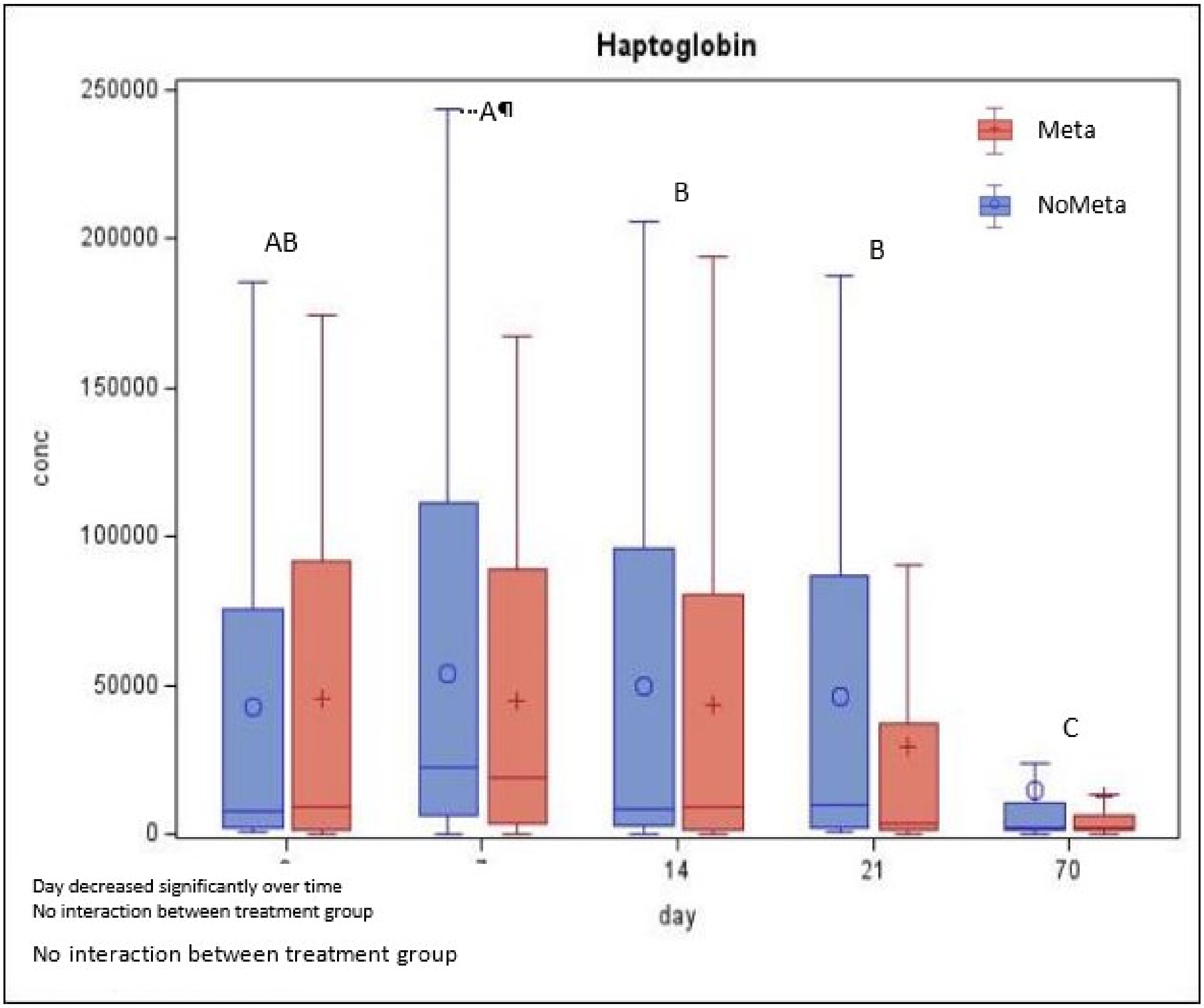

Figure 3.1 Serum haptoglobin concentration in metaphylactically treated stocker calves and controlled calves over the 70 d receiving period

[1]Haptoglobin concentrations measured at 7 day increments between the two treatment groups.
[2]META = treated with metaphylaxis, NOMETA = no metaphylaxis
[A,B.C] Means with differing superscripts differ ($P < 0.05$)

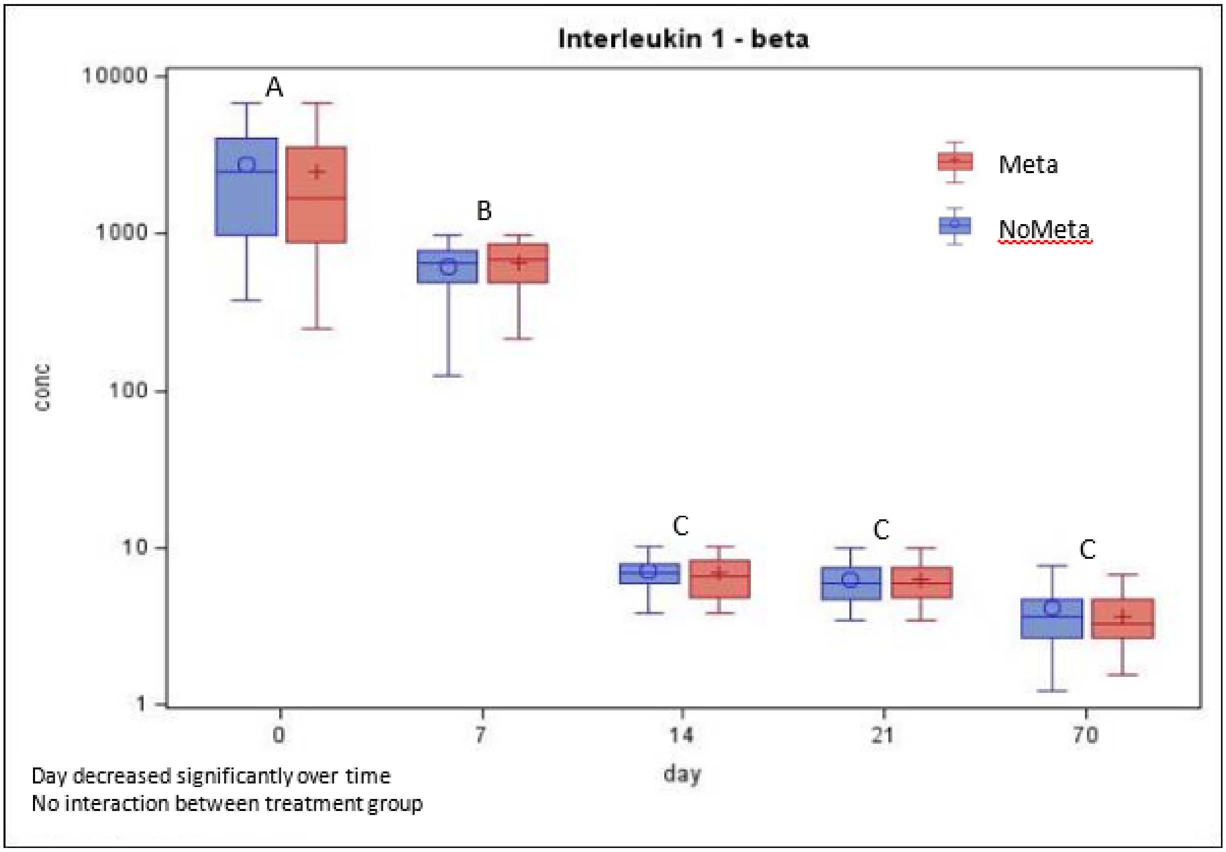

Figure 3.2 Serum IL-1β concentration in metaphylactically treated stocker calves and control calves over the 70 d receiving period

[1]IL-1β concentrations measured at 7 day increments between the two treatment groups.
[2]META = treated with metaphylaxis, NOMETA = no metaphylaxis
[A,B.C] Means with differing superscripts differ ($P < 0.05$)

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APPENDIX A

BOVINE RESPIRATORY DISEASE SCORING SYSTEM

BRD Scoring system

0 = Normal

1 = Mild BRD including one or more of the following signs:

- elevated respiratory rate for the environmental conditions
- mild to moderate gauntness
- mild depressed attitude: not as alert as expected when viewed from a distance

  becomes alert when animal sees human observer
- shallow or dry cough

Cattle with score of 1 may also have cloudy, white, or yellow nasal discharge.
Nasal discharge in the absence of any other abnormalities is not enough for a score of 1.

2 = Moderate BRD including one or more of the following signs:

- mild or moderate depression
  - lethargic, but may look alert when approached
  - head carriage lower than normal, but returns to normal when approached
  - hiding behavior: tends to stay behind other cattle, relative to the observer
- mild to moderate muscle weakness
  - stepping slowly when walking, or mild incoordination
  - droopy ears
- repeated coughing
- moderate gauntness
- breathing with mild to moderately increased abdominal effort

Cattle with a score of 2 may also have:
elevated respiratory rate for environmental conditions
clear, cloudy, white, or yellow nasal discharge.

3 = Severe BRD including one or more of the following signs:

- severe depression or weakness
  - lethargic and does not look more alert when approached
  - low head carriage, does not return to normal when approached
  - does not move away from examiner as expected when approached
  - cross stepping
- Repeated deep cough
- Severe breathing effort
  - open mouth breathing or panting
  - moderately to markedly increased abdominal effort

Cattle with a score of 3 may also have:
elevated respiratory rate for the environmental conditions
clear, cloudy, white, or yellow nasal discharge
and/or moderate to extreme gauntness.

4 = Moribund (near death)

- 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, falls down
- eyes may be very sunken, abdomen may be very gaunt

Moribund animals may also have signs described for score of 1, 2, or 3.
Coughing may be heard from animals with any score.

NOTE: sometimes animals near death may act aggressively, trying to charge an observer

BRD Case Definition

BRD score = 1 or 2 AND have a rectal temperature ≥104 ºF
OR
a BRD score ≥ 3 regardless of rectal temperature.
WITH
no other obvious signs of disease (lameness, diarrhea, swollen legs, strange behavior, etc.)