Management of bovine respiratory disease in beef stocker calves – an overview of current evidence and recommendations

Brent Credille, DVM, PhD, DACVIM (Large Animal)

College of Veterinary Medicine, University of Georgia
Athens, GA 30606

Bovine respiratory disease and the North American cattle industry

Prevalence

Bovine respiratory disease (BRD) is one of the most common and costly diseases affecting beef and dairy cattle of all age groups and production classes in North America. Recent studies have shown that BRD affects nursing beef calves on more than 20% of cow-calf operations in the United States and is responsible for more than 90% of all morbidity and mortality on stocker operations.[1-3] In feedlots, BRD affects nearly 20% of all animals on feed and is responsible for approximately 75% of all morbidity and 50% of all mortality. Similarly, BRD is estimated to affect more than 22% of all nursing dairy calves and is responsible for approximately 20% of all deaths that occur in this population.[4] Moreover, BRD is the leading cause of morbidity and mortality in weaned dairy heifers and this single disease syndrome is responsible for nearly 60% of all producer reported deaths in this age group.

Economic impact

The economic impacts of BRD can be significant, as demonstrated by losses of more than $260 million in cow-calf and $2 billion in stocker and feedlot operations annually.[5] Indeed, the Texas A&M Ranch to Rail studies conducted from 1992-2001 found that cattle diagnosed with BRD were worth $50-150 less than cattle that remained healthy.[5] In nursing dairy calves, the short-term and long-term costs of BRD have been estimated to exceed $42 and $280 per affected animal, respectively.[4] Direct costs associated with losses due to BRD come from pharmaceuticals and biologics (antimicrobials, anti-inflammatories, vaccines, etc.) used for disease prevention, treatment and control, as well as reductions in animal performance (reduced average daily gain, poorer carcass quality, longer days on feed, lower lifetime milk production, etc.).[6] In addition, cattle that succumb to BRD bear production costs incurred up to the time of death, the opportunity cost of failure to market the animal or failure of the animal to enter future stages of production (lactation, feeding, etc.), and the costs of carcass disposal.[6]

Emerging Issues

An increasing prevalence of antimicrobial resistance (AMR) in bacterial respiratory pathogens and the negative impacts of BRD on animal welfare are two of the most significant issues facing the cattle industry as it relates to BRD. While BRD is a multifactorial disease syndrome with numerous risk factors, bacteria are ultimately responsible for the clinical signs observed in affected cattle. For this reason, antimicrobials are a mainstay of BRD treatment and control; however, antimicrobial resistance is an emerging issue in common bacterial BRD pathogens and isolation of multi-drug resistant (MDR) strains harboring integrative conjugative elements (ICE) has become a more frequent occurrence.[7-11] The emergence of MDR bacterial strains could complicate the treatment of animals with clinical BRD, making some animals less likely to respond to antimicrobial administration, a factor that perpetuates the negative economic impact of BRD. In addition, the use of antimicrobials in production animal agriculture has come under intense scrutiny by consumers, human health professionals and regulatory organizations. Driven by concerns that overuse of antimicrobials in animal agriculture contributes to antimicrobial resistance challenges being faced in human medicine, numerous new regulations have been implemented that affect both the use and availability of commonly used, medically important antimicrobial agents. Moreover, consumer demand for antibiotic-free, all-natural, and organic animal products continues to increase and will further serve to place pressure on cattle producers and veterinarians to reevaluate their antimicrobial use and prescribing habits.

As it relates to animal welfare, it is important to recognize that welfare plays an increasingly important role in the public perception of animal agriculture and consumer purchasing decisions. Additionally, veterinarians are ethically bound to recognize and respond to impaired animal welfare as part of the veterinary oath. Thus, it is imperative that welfare be at the forefront of all considerations and discussions regarding management of cattle health so that our social license to operate can be maintained. In the case of BRD, many risk factors for disease development are known, and numerous studies have shown that common management practices (weaning, vaccination, deworming, adaptation to feed bunks and water troughs, provision of shade, increasing nutritional plane, etc.) can be used to reduce disease prevalence. Nevertheless, these practices are not commonly adopted and, despite decades of research and the widespread availability of effective vaccines and pharmaceutical agents, neither the prevalence nor impact of BRD have changed over time. Instead, deleterious management practices remain commonplace, complicating our best efforts to mitigate the impact of this complex disease syndrome. For example, less than 40% of U.S. cow-calf producers vaccinate calves against common viral respiratory pathogens between birth and weaning and fewer than 60% of bull calves are castrated prior to sale. In addition, more than 40% of cow-calf producers sell calves the same day they are weaned and, of those that do keep calves on farm after weaning, less than 70% keep calves for the recommended 45-day preconditioning period. Moreover, feeder calves are often transported in small spaces over long distances without regular access to feed or water and commingled with cattle from many different operations, factors that result in increased levels of psychological and physiologic stress. There is also an increasing amount of evidence suggesting that BRD can be associated with significant pain and discomfort. Over the long term, addressing these issues will require forward-thinking leadership, honest and open discussions amongst all industry stakeholders, sincere effort and financial incentives.

Beef stocker industry – structure, function and challenges

Although often seen as a single entity, the North American beef industry is divided into multiple distinct segments that operate with different management focuses and end goals in mind. One critically important segment of the beef industry is the stocker segment, as stockers represent a link between cow-calf producers and cattle feeders. In the US, between 2/3 and 3/4 of calves spend some amount of time in a stocker-type facility before entering a feedlot. One of the reasons for this is that cow-calf operations market calves on a semi-seasonal schedule with most calves being marketed in the early to late fall. Cattle feeding, however, is constant throughout the course of the year so that industry and consumer needs can be effectively met. Stocker operations play a critical role in managing this seasonal and irregular supply of feeder cattle, buffering both excess and inadequate animal availability.

More importantly, however, cultural and economic factors often result in North American cow-calf producers marketing calves before they are adequately prepared for finishing. As a result, stocker facilities often purchase cattle in small lots and the cattle in these lots are usually lightweight, in poor nutritional status, recently weaned, of unknown health status (i.e., unvaccinated, not dewormed), and males often remain intact. These cattle are then commingled with cattle from multiple other sources to build larger groups. Dehydration and negative energy balance are also common due to long transport distances and limited access to water and feed being a part of this process. Ultimately, stocker enterprises function to improve the health and well-being of mismanaged calves, with a particular focus on improving immune status, adding weight and sorting cattle into groups of uniform size, weight and color. These practices allow stocker calves to be marketed to cattle feeders as a value-added product. Without this industry segment, many North American cow-calf producers would have little to no potential to market their cattle in a cost-effective manner. As a result, stocker operators provide a way for small-scale cow-calf producers to remain viable and competitive in the modern beef industry. Thus, the stocker segment is a significant contributor to the US agricultural economy and the sustainability of the U.S. beef industry.

Unfortunately, the very factors that make stocker operations an integral component of the beef industry also increase the risk that BRD will develop in a high proportion of calves. The inherent structure of the beef cattle marketing system and procedures commonly performed at the time of initial animal processing impose a significant amount of stress on the animal's normal homeostatic mechanisms. Indeed, the processes of weaning, marketing, transportation, and adapting to high energy density feedlot rations likely represent the most challenging experiences a calf will ever face. These stresses can be manifested in several ways and include: 1) disruption of the hypothalamic-pituitary-adrenal (HPA) axis; 2) alterations in energy and protein metabolism; 3) decreases in appetite and growth rate; 4) changes in immunologic function; and 5) compromised rumen function. In the end, these different factors interact to increase susceptibility of stocker calves to infection with viral and bacterial pathogens ubiquitous in their environment and negatively affect health, well-being, productivity, and profitability. Therefore, the goals of these proceedings are to describe how stresses imposed upon stocker cattle affect physiologic and immunologic function and use this information to provide recommendations for the design of practical, evidence-based receiving programs with a particular focus on arrival facility design, vaccines, immunostimulants and metaphylaxis.

Stress – definition, purpose, physiology and pathologic effects

Definition and purpose

Simply defined as the non-specific response of the body to change, stress represents the psychological, emotional, or physiologic strain imposed by exposure to adverse circumstances.[12,13] Stress responses are mediated through an interaction of body systems that activate the sympathetic-adrenomedullar (SAM) axis, the HPA axis, and immune system. Stress responses allow the body to adapt to internal or external challenges faced by an animal, with the ultimate goals being removal of the animal from a stressful environment, prevention or attenuation of tissue damage, and restoration of psychologic and physiologic homeostasis. Nevertheless, when a specific stress or series of stressors are overly intense, repetitive, or prolonged, stress responses become maladaptive and can be detrimental to host physiology. These types of stresses cause anxiety, alter appetite, stimulate mobilization of muscle and fat, and precipitate the mounting of dysfunctional, and potentially harmful, immune responses.

Physiology

There are 2 affective systems in the brain that drive an animal's psychological and physiologic responses to stressful situations.[14] The first, the fear system, is localized to the amygdala and, when stimulated, promotes activation of the autonomic nervous system and secretion of both catecholamines and cortisol from the adrenal gland. The second, the separation distress system, is in the stria terminalis of the thalamus and is activated when youngstock are separated from their dam, single animals are separated from their herd mates, and when animals are placed into novel social structures.[14] Like the effects of fear system activation, stimulation of the separation distress system increases secretions from the adrenal gland.

Once the fear and/or separation distress systems have been activated, stress responses are initiated. There are 2 components to the stress response: 1) A fast response mediated by the SPA axis and 2) a slow response mediated by the HPA axis. Activation of the fast response results in increased secretion of epinephrine and norepinephrine from the adrenal medulla. These hormones function to increase blood pressure and heart rate, as well as stimulate gluconeogenesis and lipolysis. In addition, intestinal motility is reduced, bronchioles are dilated, and behavioral changes such as arousal, agitation and alertness occur. Activation of the slow response causes release of cortisol into the circulation. Cortisol and other steroid hormones function to enhance catecholamine release and upregulate the expression of catecholamine receptors, antagonize the effects of insulin, mobilize body energy stores, stimulate the resorption of water and electrolytes in the kidney and, ideally, reduce the magnitude of inflammatory response. In the end, these responses are designed to conserve and maintain energy supply, sustain fluid and electrolyte homeostasis, reduce inflammation, and remove unnecessary or malfunctioning cellular components to support the physiologic functions needed to adequately manage stressful situations.

Pathologic effects

Role of stress in the development of BRD

In both people and mice, a link between respiratory infections and common stressors has been suggested. Numerous epidemiologic studies have found that, when people are exposed to psychological stressors, the incidence and severity of respiratory infections increases. Indeed, when experimentally challenged with a laboratory strain of Influenza A, people experiencing higher levels of psychological stress had increased plasma concentrations of IL-6 and greater clinical symptom scores than those with lower levels of stress. In mice, the effects of stress on respiratory infections are more nuanced.[15-17] For example, restraint stress imposed prior to experimental infection with Influenza A was found to reduce both the production of pro-inflammatory cytokines and infiltration of immune cells into the lung.[18] Additional work found that administration of RU486, a selective glucocorticoid receptor antagonist, resulted in enhanced pro-inflammatory responses and increased mouse mortality, a finding that confirmed corticosteroid hormones were responsible for the disease modifying effects of restraint. In contrast, stress imposed through social reorganization was found to increase cellular infiltration into the lung, as well as disease severity and mortality following Influenza A challenge.[16] Interestingly, the increased mortality seen in this study was found to correlate with a state of corticosteroid insensitivity induced by high concentrations of nerve growth factor (NGF).[15] Thus, it appears as though that the nature and type of the stressor imposed upon the animal can have conflicting effects on the immune response to subsequent infection and contribute to the marked differences seen across different studies.

Stocker calves are exposed to considerable amounts of stress and encounter a wide variety of stressors during the weaning, marketing and transportation processes. Of these stressors, weaning and disruption of established social structures are likely the most significant. Previous work has shown that weaning and disruption of social structure cause significant increases in epinephrine and norepinephrine.[19] Also, weaning and social disruption, when combined with transport, result in increased serum cortisol concentrations, as well as alterations in protein and fatty acid metabolism/excretion. More recent work, however, has shown that the effects of weaning and transport stress on serum cortisol concentrations, when evaluated serially with more clinically relevant stress models, might be more complex than previously described. A study by Hudson et al found that peak serum cortisol concentrations in stressed calves were nearly 30% lower than peak cortisol concentrations in control calves.[20] Moreover, concentrations of cortisol measured serially in the serum of stressed steers were approximately 50% lower than what was measured in control steers.[20] Another study evaluating a model of weaning stress combined with experimental challenge with both bovine herpesvirus-1 (BHV-1) and *M. haemolytica* (*Mh*) found that patterns of serum cortisol secretion mimicked that of Hudson et al, with stressed calves having lower peak cortisol concentrations and reduced cortisol persistence.[21] In fact, the duration of hypercortisolaemia in stressed calves was less than half that of the control calves.[21]

In addition to stimulation of stress responses, weaning and social reorganization have profound impacts on local and systemic immune responses. Historically, it has been assumed that the increase in catecholamines and cortisol seen in traditional stress models had an immunosuppressive effect. New evidence, however, has begun to challenge this assumption. Studies performed using isolated populations of neutrophils and eosinophils have shown that both epinephrine and norepinephrine increase the production of reactive oxygen species and the expression of CD11b, molecules responsible for pathogen killing, facilitation of leukocyte migration and pathogen phagocytosis.[22] Also, serum concentrations of haptoglobin have been found to increase more than 3-fold in stressed calves when compared to unstressed calves.[20,21] Work performed by researchers in the UK evaluating immune responses associated with weaning stress found that weaning stress increased the expression of genes for the pro-inflammatory cytokines IL-1β, IL-8, IFN- , and TNF-α, as well as the receptor for endotoxin, TLR4.[23,24] Additionally, there was decreased expression of genes encoding glucocorticoid receptors. This same group, using RNA-Seq technology, found that expression of genes encoding pro-inflammatory cytokines, chemokines, and integrins was consistently upregulated in calves subjected to weaning stress and these responses were maintained for up to 7 days following weaning.[24] Studies from researchers at Mississippi State University evaluating the transcriptomic profile of cattle arriving at a stocker research facility found that genes promoting immune activation were upregulated in the blood of auction market derived calves when compared to unstressed, single-source controls. More specifically, auction market derived calves had increased expression of genes associated with enhanced innate immune responses and microbial killing, interferon production, and TLR4.[25-27] Stressed calves were also found to have a decrease in expression of genes associated with mediation of inflammatory responses. This change was found to involve a decrease in the expression of genes for pro-resolvin mediators and endogenous metabolism of angiotensinogen.[27]

Stress-pathogen synergy and BRD

While the development of BRD has been linked to weaning stress and social reorganization, severe and fatal cases are most often seen when a primary viral infection allows for colonization of the lungs with bacterial pathogens. Viral infections of the bovine respiratory tract damage epithelial cells and the function of neutrophils and macrophages within the airway.[28,29] Additionally, common viral pathogens, namely bovine respiratory syncytial virus (BRSV) and coronavirus, have been shown to upregulate the expression of various receptors that allow for pathogenic bacteria to adhere to respiratory epithelial cells and invade the lower airway. Also, it has been shown that coinfection of isolated lung cell cultures with BRSV and *P. multocida* (*Pm*) results in an increase in the expression of numerous pro-inflammatory cytokines. In a study evaluating a model of weaning stress combined with experimental challenge with both bovine herpesvirus-1 (BHV-1) and *M. haemolytica* (*Mh*) concentrations of the proinflammatory molecules haptoglobin, IFN-γ, and TNF-αin the serum of stressed calves were significantly higher than in control calves following challenge.[21] Moreover, expression of genes encoding CD14 and TLR4 in isolated populations of peripheral blood mononuclear cells was also significantly higher in stressed than control calves.[21] In the end, stressed calves had a mortality risk (80%) more than double that of control calves (40%).[21] From this work, it appears as though stressors, viruses, and bacteria interact synergistically with one another to enhance the inflammatory response caused by infection of the lower respiratory tract with common pathogens. Much of this enhanced inflammatory response seems to be mediated by a combination of elevations in epinephrine/norepinephrine, reduced cortisol peak/persistence and viral infection of the respiratory tract, factors that results in increased production of pro-inflammatory molecules, decreased production of anti-inflammatory molecules, and enhanced attachment of bacterial pathogens to the respiratory epithelium.

Thus, the relationship between stress, BRD, and pulmonary pathology is complex, involving multiple body systems and exposure to pathogenic microorganisms. Nevertheless, the common stressors imposed upon the typical stocker calf seem to promote inflammation rather than dampen it. In other words, in the same way that acute stress responses prepare an animal to mount an effective and efficient fight-or-flight response, it also prepares the immune system for challenges commonly encountered as part of the stressful event. In summary, data would suggest that when calves are provided a period of adaptation prior to a stressful event (i.e., preconditioning), are spared significant social disruptions, or have health managed appropriately, cortisol concentrations rise and persist at appropriate levels until the stressor is removed. This adaptive response likely allows the animal to shunt metabolic resources to tissues needing them most and successfully dampen deleterious pro-inflammatory immune responses to preserve physiologic homeostasis following exposure to infectious agents. However, when a stressful episode is prolonged or severe, episodes are repetitive, or no prior period of adaptation is provided (i.e., abrupt weaning combined with long distance transport and social reorganization) prior to the event, stress responses become dysregulated. This likely results from disruption of the HPA axis, hypocortisolaemia, and/or glucocorticoid resistance. These factors, combined with exposure to novel respiratory viruses and pathogenic bacteria, prevent the animal from controlling wayward immune responses and lung pathology is subsequently enhanced.

Managing high-risk calf health – arrival facility design, vaccination, metaphylaxis and immunostimulants

Overview

Because of the effects that stress, pathogen exposure and immune dysfunction have on the health of high-risk calves, they are put into stocker production systems to most efficiently address challenges associated with the increased risk of BRD commonly seen in these populations. As a result, veterinarians consulting with stocker operations spend a large part of their time developing arrival health programs. Volumes of scientific information regarding the design of effective arrival protocols have been published and practitioners often combine these data with personal observations, clinical experience and knowledge of different production systems to develop protocols tailored to individual operations. Nevertheless, no one protocol is appropriate for all operations and there is tremendous opportunity to refine health protocols using rational, evidence-based and sustainable decision-making principles.

Of the various tools used to mitigate the impact of BRD of stocker calves at the time of arrival processing, the use of vaccines, metaphylaxis and immunostimulants has received the most consistent and well-researched attention. While pharmaceuticals and biologics are considered the standards for management of BRD risk in stocker facilities, arrival facility design and considerations related to animal flow are often overlooked. Proper facility design allows for the development of efficient and effective biocontainment and biosecurity protocols. It also assists with management of environmental extremes and facilitation of recovery from transportation events by allowing for the provision of high-quality feedstuffs, clean water and comfortable resting areas. Surveys have shown that nearly 100% of calves classified as high-risk will receive at least 1 vaccine at arrival processing and another 53% will be revaccinated between 14 and 21 days on feed. These same surveys also found that nearly 100% of consultants recommend the use of metaphylaxis to control BRD. Unfortunately, results of trials evaluating the use of modified-live vaccines in stocker calves at the time of arrival processing have been conflicting and some data would suggest that this practice might be more harmful than it is beneficial. Also, not all antimicrobials labeled for metaphylactic use have equivalent efficacies and the emergence of MDR bacterial pathogens following metaphylaxis is a threat to the long-term sustainability of this practice. While the use of immunostimulants has not been evaluated to the same extent, several recent studies have evaluated their impact on morbidity, mortality and performance in experimental and commercial settings and the results of these trials, while somewhat limited, show promise. With these things in mind, the remainder of these proceedings will focus on how the rational implementation of these tools can be used to improve stocker calf health and welfare, as well as to enhance operational productivity and profitability.

Arrival facility design

It has been the author's observation that facilities designed to receive cattle are poorly designed and inadequately utilized. Facilities are often too small for their intended use, and this necessitates regrouping and resorting arrival cohorts, factors that further increase social stresses experienced by stocker calves. Also, the size of the carryover population (i.e., processed calves that remain in the receiving facilities as new groups arrive) can be substantial on some operations and this allows for carryover of pathogens from one group to the next. In addition, receiving areas are often unshaded, poorly ventilated and, in some cases, have substantial amounts of mud/manure accumulation. Poor management of these areas can lead to increased nutritional demands, reduced performance, decreased comfort, and higher levels of morbidity and mortality.

As a general practice, receiving pens should be managed on an all in-all out basis and resident cattle populations should never be kept in or near the arrival barn to reduce sharing of pathogens among groups. They should also be designed so that each calf has least 14-20 sq ft of space and, at times of the year when heat is of concern, a minimum of $2m^2$ of shaded area/calf (natural or artificial) should be provided. Because newly received cattle will often walk the periphery of their enclosure, feed bunks and water troughs should be placed along fencelines and oriented perpendicularly to the long axis of the fence to force cattle to run into them. There should be 18-24 linear inches of feed bunk space and 2 linear inches of water trough space per calf to provide enough space for all cattle to eat and drink without antagonistic social interactions. It is often recommended that feed be placed in bunks prior to arrival and that this feed be top-dressed with high-quality grass hay to stimulate feed intake and reinvigorate rumen microbes. Waterers should be allowed to overflow so that the sounds of running water are recreated and water flow should be such that it allows the consumption of up to 15L water/100 kg of BW/day during hotter times of the year.

Vaccination

Vaccination against common viral and bacterial respiratory pathogens is a frequently used and almost universally preferred approach for controlling BRD in almost all cattle populations and studies have shown that nearly all North American stocker calves are given a vaccine at the time of arrival processing. Even though the use of vaccines is common, there is very little evidence to available to support this practice. In fact, a recently published systematic review and network meta-analysis showed no evidence to suggest that the use of viral or bacterial vaccines at or near arrival reduced the incidence of BRD in feedlot cattle.[30] Moreover, results of recent trials would suggest that arrival viral vaccination might, in certain situations, even serve to enhance BRD-associated BRD morbidity and mortality. Indeed, a meta-analysis recently published by our group found that vaccination (arrival or delayed) had no impact on morbidity but showed that delaying vaccination by 2-4 weeks reduced mortality by nearly 20%.[31] As a result, there has been an increasing amount of focus given to delaying vaccination for 14-30 days to allow stress responses and immune function to return to a homeostatic state. This work has shown that delaying viral vaccination by 2-4 weeks can improve performance, reduce relapse risk, decrease mortality, and increase profit per heifer sold when compared to arrival vaccination or no vaccination at all.[31-33]

In one study that evaluated the effect of arrival vs. delayed viral vaccination, 528 high-risk calves were assigned to either an arrival vaccination or delayed vaccination (14-days after arrival) group.[34] Calves in the delayed vaccination group had improved performance and numerically less BRD-associated morbidity and mortality. Another study that enrolled nearly 5200 auction market derived heifers found that calves receiving their first viral vaccine 30 days following arrival had a reduced risk of second treatment and numerically lower risks of overall morbidity, total mortality and BRD-associated mortality than calves vaccinated at arrival.[33] In another trial that evaluated the impact of arrival vaccination on BRD morbidity and mortality, 80 auction market derived calves were assigned to receive either an arrival viral vaccine or no vaccine at all. In the calves that received an arrival vaccine, BRD-associated morbidity and mortality were 3.2 and 8.3 times higher, respectively, than in calves that did not receive a vaccine.[35] In a study that enrolled 370 high-risk calves and evaluated the effects of arrival viral vaccination, delayed viral vaccination or no vaccination, calves in the delayed vaccination group had significantly higher average daily gain and a lower risk of relapse than calves assigned to the 2 other treatment groups.[36] In another trial in which 2,600 high-risk heifers were enrolled to evaluate the effect of 3 different vaccine programs on health and performance, overall mortality and case fatality risk were lower, while profit/heifer sold was $10-20 higher in the delayed vaccination group than in the 2 arrival vaccination groups.[32]

In contrast to viral vaccines, the use of vaccines labeled control of BRD associated with bacterial pathogens show more promise, specifically those products commonly used for reduction in disease prevalence and severity associated with *Mh*. Currently available vaccines contain either modified live *Mh* and/or *Pm*, inactivated bacteria, leukotoxin, or leukotoxin and other bacterial products. A meta-analysis published in 2012 evaluating the available published research found that *Mh* vaccines significantly decreased BRD morbidity and tended to reduce crude mortality in feedlot cattle and beef and dairy calves.[37] In fact, this study showed that morbidity and mortality associated with BRD in cattle were reduced by 7% and 24%, respectively, in vaccinated cattle.[37] Nevertheless, a more recently published meta-analysis found that there were too few published trials using bacterial vaccines in comparable populations to perform a formal statistical analysis.[38] Therefore, while the use of these products for reducing disease prevalence and severity is intriguing, more data derived from well-designed clinical trials are needed before their ultimate benefit can be fully assessed.

Metaphylaxis

Despite decades of research, the risk of morbidity and mortality associated with BRD has remained relatively unchanged and common interventions (i.e., vaccination) have been shown to have little impact on its incidence. However, the use of antimicrobial metaphylaxis in animals considered to be high-risk for the development of clinical BRD has been shown to reduce morbidity and mortality significantly when compared to controls. Work recently published by our group showed that cattle receiving metaphylactic tulathromycin were 78% less likely to be treated for BRD than cattle given saline.[3] Similarly, Crosby et al found that cattle given tulathromycin at the time of arrival processing were 3 times less likely to be treated for BRD than untreated controls.[8] Additionally, these same trials showed significant improvements in animal performance with cattle receiving metaphylaxis gaining 0.15-0.32 kg/day more than cattle that not treated.[3,8] In the end, it has been estimated that the use of metaphylaxis in fed cattle has a direct net return of more than $530 million and that eliminating metaphylaxis would result in nearly $2 billion in surplus losses to beef producers.[39]

Today, multiple antimicrobials are labeled for metaphylactic use and the decision to use a specific antimicrobial is often based on combinations of label approvals, efficacy (real or perceived), cost-effectiveness, and familiarity.[40] What is most important to the clinician prescribing antimicrobials for metaphylactic use, however; is clinical efficacy. Choosing metaphylactic antimicrobials with greater efficacy has the potential to enhance economic returns to the operation by reducing morbidity, retreatment, and case fatality risks, as well as enhancing performance. In the ideal world, conclusions related to efficacy are based on evidence from well-designed, randomized, controlled clinical trials. Fortunately, multiple clinical trials have been performed to investigate the comparative efficacy of the various antimicrobials commonly used for metaphylaxis and, in recent years, several meta-analyses have been published to summarize the results of these trials. A meta-analysis is a statistical representation and summary of the results of multiple studies. These types of studies provide a combined effect size of a specific intervention across multiple studies and provide the results in a single location. The results of one meta-analysis showed that macrolide antimicrobials, specifically tulathromycin, tilmicosin and gamithromycin, were more efficacious than other antimicrobials evaluated.[41] A mixed-treatment meta-analysis published in 2020 showed similar results, with macrolide antimicrobials, namely tulathromycin and gamithromycin, ranking consistently higher than all other antimicrobial classes.[42] In addition to meta-analyses, the NNT statistic has been used to evaluate antimicrobial efficacy.[43] The NNT is the reciprocal of the attributable risk reduction (ARR), a parameter that describes the difference in the probabilities of an event occurring in control and treatment groups.[43] Compared to the ARR, the NNT is more straightforward to interpret and is defined as the number of treatments needed to make a difference in the outcome of 1 patient. The use of NNT, by expressing the effect of the drug relative to the likelihood of recovery of untreated controls, has the added benefit of incorporating the severity of the disease challenge into the estimate of drug effect.[43] When efficacy is evaluated using the NNT statistic, the NNT for macrolides ranges from 2-3 while the NNT for other antimicrobial agents ranges from 7 to more than 10.[43]

Historically, the efficacy of metaphylaxis was rooted in the effect of the antimicrobial effect of the administered drug on pathogenic bacterial populations. While some of the numerous benefits of metaphylaxis are certainly related to treatment of animals with subclinical disease at the time of drug administration, it is likely that metaphylaxis also modifies the epidemiologic parameters associated with BRD outbreaks in high-risk cattle populations.[44] More specifically, metaphylactic antimicrobial administration reduces the susceptibility of animals to BRD by reducing bacterial burdens to a level that is below a threshold sufficient to cause clinical disease. During this time, stress responses dissipate, and protective immune responses are mounted. Once therapeutic antimicrobial concentrations are no longer present, specific immunity is at such level that calves remain healthy in the face of additional challenge.[44]

In addition to their disease modifying effects, the macrolides have been shown to have potent immunomodulatory properties.[45-47] Work performed with this class of antimicrobials in both cattle and swine has shown that these drugs reduce the secretion of IL-8 from activated immune cells, decrease the production of reactive oxygen species, induce apoptosis in activated neutrophils, and enhance macrophage-mediated clearance of necrotic cells.[46,47] Also, tulathromycin has been shown to prevent alterations in neutrophil phagocytic function caused by infection with viral respiratory pathogens. In live animals, these immunomodulatory effects have been shown to reduce pulmonary damage and progression of existing pulmonary lesions. Thus, the macrolides, in addition to their antimicrobial activity, dampen pro-inflammatory immune responses and have pro-resolving effects that are likely responsible for their clinical effects. Therefore, metaphylaxis effectively functions as a modifier of the disease reproduction factor (R_0) by forcing a temporary change in the susceptible population that allows animals to move permanently to a resolved/resistant state through a combination of pathogen burden reduction, promotion of specific immunity, and modulation of inflammatory responses.

While the use of metaphylaxis has significant benefits for the stocker producer, this practice is not without its detriments. Recent trials have shown an association between the use of metaphylaxis and the emergence of MDR bacterial isolates in high-risk calves.[8] In addition, metaphylaxis has been shown to increase total antimicrobial use relative to the use of a pull-and-treat strategy.[3] With the public perception of antimicrobial use in animal agriculture being what it is, it is necessary to revisit the approaches taken when deciding whether metaphylaxis is justified in a specific population. Additionally, economic analyses have shown that identifying and focusing metaphylactic therapy on only those groups of animals with the highest likelihood of BRD development has the highest potential for economic payback, a factor that becomes increasingly important as animal prices, feed costs and cost of gain increase.[48] It has been shown in one clinical trial that selective metaphylaxis with florfenicol in only calves with elevated rectal temperature was not significantly different from metaphylaxis of the entire group when considering clinical, pathological, and productivity outcomes. Another more recent trial using 216 lightweight beef steers found that the use of random metaphylaxis with tildipirosin in just 66% of calves was not different than medicating 100% of animals when considering health outcomes. Moreover, this trial showed that production outcomes were maintained, total antimicrobial use was reduced, and medication costs per steer were decreased. Thus, the use of a precision medicine approach will become more important in the future and allow for treating animals selectively at the herd level. Taking a targeted, precision-oriented approach will allow producers to benefit from the numerous benefits of metaphylaxis, while also having the net effect of dissociating it from the negative connotations that come with mass medication. Unfortunately, large scale data on when metaphylaxis can be selectively initiated are lacking. The lack of validated diagnostic tests that have acceptable sensitivity and specificity is a major limitation to such a strategy. Nevertheless, radio frequency identification (RFID) technologies, chuteside blood leukocyte differentials, and other precision technologies are under investigation and hold promise for the future.

Immunostimulants

Immunologic dysfunction is common in high-risk stocker calves and modulation of these dysfunctional responses has the potential to be leveraged to improve outcomes in BRD-affected cattle. One of the best studied immunostimulants is Zelnate, a product containing non-coding DNA in a cationic lipid matrix. This product is intended to modulate immune responses through activation of the innate immune system. *In vitro* work has shown that Zelnate activates IRF3 in innate immune cells via GAS-STING pathway.[49] Activation of this pathway leads to the production of type I interferons and, while type I interferons are known primarily for their antiviral activity, they have also been shown to have potent anti-inflammatory effects. Work has shown that this interferon subtype increases concentration of the anti-inflammatory cytokine IL-10 in response to LPS exposure or viral infection. In addition, increased concentrations of type I interferons suppress the activity of the pro-inflammatory cytokines IFN- , TNF-α,IL-8, and IL-17. Also, type I interferons promote the differentiation and proliferation of regulatory T cells, suppress inflammasome activity, and stimulate lymphocyte apoptosis. Thus, stimulation of type I interferon production could lead to a wide array of beneficial immunomodulatory functions in animals at risk for BRD.

In an experimental challenge model, Zelnate was found to be safe for use and reduced both lung lesion severity (36% reduction) and mortality (5% vs. 20%) in treated animals.[50] In a study evaluating delayed viral respiratory vaccination and immunostimulant inclusion in an arrival protocol, the addition of Zelnate was found to reduce the number of cattle requiring 3 treatments, BRD case fatality risk, BRD mortality, and overall mortality.[33] In fact, cattle receiving Zelnate and subsequently diagnosed with BRD were 22% less likely to die than cattle not receiving treatment.[33] In another trial comparing on-arrival treatment with tulathromycin or the combination of tulathromycin and Zelnate, cattle given the combination treatment had a reduction in BRD-associated morbidity, BRD case fatality, and BRD-associated mortality.[51] More recent work performed in 64 single-source, recently weaned, cross-bred beef calves found that calves treated with Zelnate had a tendency for improved performance (higher ADG and feed:gain) than control calves.[52] In addition, cytokine expression profiles in mononuclear cells isolated from treated calves were different than those of control calves, with calves given Zelnate having higher levels of IFN- and lower levels of IL-4 and TNF-α.[52] These data suggest that Zelnate promoted the development of robust Th-1 immune responses and Th-1 responses are known to be important for protection against viral and extracellular bacterial infections. Interestingly, there was an outbreak of BRD that occurred during the trial and 6 of the 63 cattle included in the study died. Of the 6 that died, 5 were in the control group and only 1 was in the treatment group.[52] While these numbers are too small to make definitive conclusions, they do suggest that inclusion of Zelnate in a receiving protocol might have had a benefit on reducing mortality in the recently weaned steers included in this study. Therefore, there is evidence to suggest that the use of Zelnate has the potential to improve performance, decrease the number of cattle requiring multiple antimicrobial treatments, reduce disease severity, and improve survival through restoration of immune homeostasis through modulation of immune responses.

References

1. Hanzlicek GA, Renter DR, White BJ, et al. Management practices associated with the rate of respiratory tract disease among preweaned beef calves in cow-calf operations in the United States. *J Am Vet Med Assoc* 2013;242:1271-1278.

2. Woolums AR, Berghaus RD, Smith DR, et al. Case-control study to determine herd-level risk factors for bovine respiratory disease in nursing beef calves on cow-calf operations. *J Am Vet Med Assoc* 2018;252:989-994.

3. Credille B, Berghaus RD, Jane Miller E, et al. Antimicrobial metaphylaxis and its impact on health, performance, antimicrobial resistance, and contextual antimicrobial use in high-risk beef stocker calves. *J Anim Sci* 2024;102.

4. Overton MW. Economics of respiratory disease in dairy replacement heifers. *Anim Health Res Rev* 2020;21:143-148.

5. Smith RA. North American cattle marketing and bovine respiratory disease (BRD). *Anim Health Res Rev* 2009;10:105-108.

6. Jim K. Impact of bovine respiratory disease (BRD) from the perspective of the Canadian beef producer. *Anim Health Res Rev* 2009;10:109-110.

7. Crosby S, Credille B, Giguère S, et al. Comparative efficacy of enrofloxacin to that of tulathromycin for the control of bovine respiratory disease and prevalence of antimicrobial resistance in *Mannheimia haemolytica* in calves at high risk of developing bovine respiratory disease. *J Anim Sci* 2018;96:1259-1267.

8. Crosby WB, Karisch BB, Hiott LM, et al. Tulathromycin metaphylaxis increases nasopharyngeal isolation of multidrug resistant *Mannheimia haemolytica* in stocker heifers. *Front Vet Sci* 2023;10:1256997.

9. Snyder E, Credille B, Berghaus R, et al. Prevalence of multi drug antimicrobial resistance in isolated from high-risk stocker cattle at arrival and two weeks after processing. *J Anim Sci* 2017;95:1124-1131.

10. Snyder ER, Alvarez-Narvaez S, Credille BC. Genetic characterization of susceptible and multi-drug resistant *Mannheimia haemolytica* isolated from high-risk stocker calves prior to and after antimicrobial metaphylaxis. *Vet Microbiol* 2019;235:110-117.

11. Woolums AR, Karisch BB, Frye JG, et al. Multidrug resistant *Mannheimia haemolytica* isolated from high-risk beef stocker cattle after antimicrobial metaphylaxis and treatment for bovine respiratory disease. *Vet Microbiol* 2018;221:143-152.

12. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. *Immunol Res* 2014;58:193-210.

13. Dhabhar FS. The short-term stress response - Mother Nature's mechanism for enhancing protection and performance under conditions of threat, challenge, and opportunity. *Front Neuroendocrinol* 2018;49:175-192.

14. Grandin T, Shivley C. How farm animals react and perceive stressful situations such as handling, restraint, and transport. *Animals (Basel)* 2015;5:1233-1251.

15. Hermann G, Beck FM, Sheridan JF. Stress-induced glucocorticoid response modulates mononuclear cell trafficking during an experimental influenza viral infection. *J Neuroimmunol* 1995;56:179-186.

16. Hermann G, Tovar CA, Beck FM, et al. Restraint stress differentially affects the pathogenesis of an experimental influenza viral infection in three inbred strains of mice. *J Neuroimmunol* 1993;47:83-94.

17. Hermann G, Tovar CA, Beck FM, et al. Kinetics of glucocorticoid response to restraint stress and/or experimental influenza viral infection in two inbred strains of mice. *J Neuroimmunol* 1994;49:25-33.

18. Sheridan JF, Stark JL, Avitsur R, et al. Social disruption, immunity, and susceptibility to viral infection. Role of glucocorticoid insensitivity and NGF. *Ann N Y Acad Sci* 2000;917:894-905.

19. Hickey MC, Drennan M, Earley B. The effect of abrupt weaning of suckler calves on the plasma concentrations of cortisol, catecholamines, leukocytes, acute-phase proteins and in vitro interferon-gamma production. *J Anim Sci* 2003;81:2847-2855.

20. Hudson RE, Tomczak DJ, Kaufman EL, et al. Immune responses and performance are influenced by respiratory vaccine antigen type and stress in beef calves. *Animals (Basel)* 2020;10.

21. Hodgson PD, Aich P, Stookey J, et al. Stress significantly increases mortality following a secondary bacterial respiratory infection. *Vet Res* 2012;43:21.

22. Howell A, Arsic N, Griebel P. Resting and activated bovine neutrophils and eosinophils differ in their responses to adrenergic agonists. *Vet Immunol Immunopathol* 2024;272:110758.

23. O'Loughlin A, McGee M, Waters SM, et al. Examination of the bovine leukocyte environment using immunogenetic biomarkers to assess immunocompetence following exposure to weaning stress. *BMC Vet Res* 2011;7:45.

24. O'Loughlin A, Lynn DJ, McGee M, et al. Transcriptomic analysis of the stress response to weaning at housing in bovine leukocytes using RNA-seq technology. *BMC Genomics* 2012;13:250.

25. Scott MA, Woolums AR, Swiderski CE, et al. Hematological and gene co-expression network analyses of high-risk beef cattle defines immunological mechanisms and biological complexes involved in bovine respiratory disease and weight gain. *PLoS One* 2022;17:e0277033.

26. Scott MA, Woolums AR, Swiderski CE, et al. Whole blood transcriptomic analysis of beef cattle at arrival identifies potential predictive molecules and mechanisms that indicate animals that naturally resist bovine respiratory disease. *PLoS One* 2020;15:e0227507.

27. Scott MA, Woolums AR, Swiderski CE, et al. Use of nCounter mRNA profiling to identify at-arrival gene expression patterns for predicting bovine respiratory disease in beef cattle. *BMC Vet Res* 2022;18:77.

28. Rivera-Rivas JJ, Kisiela D, Czuprynski CJ. Bovine herpesvirus type 1 infection of bovine bronchial epithelial cells increases neutrophil adhesion and activation. *Vet Immunol Immunopathol* 2009;131:167-176.

29. Leite F, Kuckleburg C, Atapattu D, et al. BHV-1 infection and inflammatory cytokines amplify the interaction of *Mannheimia haemolytica* leukotoxin with bovine peripheral blood mononuclear cells in vitro. *Vet Immunol Immunopathol* 2004;99:193-202.

30. O'Connor AM, Hu D, Totton SC, et al. A systematic review and network meta-analysis of bacterial and viral vaccines, administered at or near arrival at the feedlot, for control of bovine respiratory disease in beef cattle. *Anim Health Res Rev* 2019;20:143-162.

31. Snyder ER, Credille BC, Heins BD. Systematic review and meta-analysis comparing arrival versus delayed vaccination of high-risk beef cattle with 5-way modified-live viral vaccines against BHV-1, BRSV, PI3, and BVD types 1 and 2. *Bov Pract* 2019;53:1-7.

32. Hagenmaier J, Terhaar BLB, Blue K, Hoffman BW, Fox JT, Theurer ME. A Comparison of three vaccine programs on the health, growth performance, and carcass characteristics of high-risk feedlot heifers procured from auction-markets. *Bov Pract* 2018;52:120-130.

33. Rogers KCM, Miles DG, Renter D, Sears JE, Woodruff JL. Effects of delayed respiratory viral vaccine and/or inclusion of an immunostimulant on feedlot health, performance, and carcass merits of auction-market derived feeder heifers. *Bov Pract* 2016;50.

34. Richeson JT, Kegley EB, Gadberry MS, et al. Effects of on-arrival versus delayed clostridial or modified live respiratory vaccinations on health, performance, bovine viral diarrhea virus Type I titers, and stress and immune measures of newly received beef calves. *J Anim Sci* 2009;87:2409-2418.

35. Griffin CM, Scott JA, Karisch BB, et al. A randomized controlled trial to test the effect of on-arrival vaccination and deworming on stocker cattle health and growth performance. *Bov Pract* 2018;52:26-33.

36. Richeson JTB, P. A.; Poe, K. D. Effects of administration of a modified-live virus respiratory vaccine and timing of vaccination on health and performance of high-risk beef stocker calves. *The Bovine Practitioner* 2015;49:37-42.

37. Larson RL, Step DL. Evidence-based effectiveness of vaccination against Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni in feedlot cattle for mitigating the incidence and effect of bovine respiratory disease complex. *Vet Clin North Am Food Anim Pract* 2012;28:97-106, 106e101-107, ix.

38. Capik SFM, Moberly HK, Larson RL. Systematic review of vaccine efficacy against *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni* in North American cattle. *Bov Pract* 2021;55:125-133.

39. Dennis EJ, Schroeder TC, Renter DG. Net return distributions when metaphylaxis is used to control bovine respiratory disease in high health-risk cattle. *Transl Anim Sci* 2020;4:txaa020.

40. Ives SE, Richeson JT. Use of antimicrobial metaphylaxis for the control of bovine respiratory disease in high-risk cattle. *Vet Clin North Am Food Anim Pract* 2015;31:341-350, v.

41. Abell KM, Theurer ME, Larson RL, et al. A mixed treatment comparison meta-analysis of metaphylaxis treatments for bovine respiratory disease in beef cattle. *J Anim Sci* 2017;95:626-635.

42. O'Connor AM, Hu D, Totton SC, et al. A systematic review and network meta-analysis of injectable antibiotic options for the control of bovine respiratory disease in the first 45 days post arrival at the feedlot. *Anim Health Res Rev* 2019;20:163-181.

43. DeDonder KD, Apley MD. A review of the expected effects of antimicrobials in bovine respiratory disease treatment and control using outcomes from published randomized clinical trials with negative controls. *Vet Clin North Am Food Anim Pract* 2015;31:97-111, vi.

44. Ley BV. Understanding the mechanism of metaphylaxis from an epidemiologic perspective. American Association of Bovine Practitioners 2019.

45. Chin AC, Lee WD, Murrin KA, et al. Tilmicosin induces apoptosis in bovine peripheral neutrophils in the presence or in the absence of Pasteurella haemolytica and promotes neutrophil phagocytosis by macrophages. *Antimicrob Agents Chemother* 2000;44:2465-2470.

46. Fischer CD, Beatty JK, Duquette SC, et al. Direct and indirect anti-inflammatory effects of tulathromycin in bovine macrophages: inhibition of CXCL-8 secretion, induction of apoptosis, and promotion of efferocytosis. *Antimicrob Agents Chemother* 2013;57:1385-1393.

47. Fischer CD, Beatty JK, Zvaigzne CG, et al. Anti-Inflammatory benefits of antibiotic-induced neutrophil apoptosis: tulathromycin induces caspase-3-dependent neutrophil programmed cell death and inhibits NF-kappaB signaling and CXCL8 transcription. *Antimicrob Agents Chemother* 2011;55:338-348.

48. Kopp DJ, Larson RL, Lancaster PA, et al. Determining the economically optimum metaphylactic strategy for cattle cohorts of varied demographic characteristics. *Animals (Basel)* 2024;14.

49. Ilg T. Investigations on the molecular mode of action of the novel immunostimulator ZelNate: Activation of the cGAS-STING pathway in mammalian cells. *Mol Immunol* 2017;90:182-189.

50. Nickell JSK, Keil DJ, Settje TL, Lechtenberg KF., Singu V. Efficacy and safety of a novel DNA immunostimulant in cattle. *Bov Pract* 2016;50:9-20.

51. Van Donkersgoed JH, Hendrick S, Hofstede T. Efficacy of a DNA immunostimulant for on-arrival control of bovine respiratory disease in fall-placed feedlot calves. *Bov Pract* 2018;52:141-145.

52. Woolums AR, Karisch BB, Parish JA, et al. Effect of a DNA-based immunostimulant on growth, performance, and expression of inflammatory and immune mediators in beef calves abruptly weaned and introduced to a complete ration. *J Anim Sci* 2019;97:111-121.

