Bovine Respiratory Disease Management in Cow Calf Operations: A Practical Guide for Veterinarians

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This guide outlines the scientific evidence for the prevention of bovine respiratory disease with a focus on cow-calf operations.

Bovine respiratory disease (BRD) *is a multi-factorial disease complex involving interactions between the environment, the host, and pathogens. Environmental risk factors include ambient temperature, humidity, ventilation, dust, ammonia, and overcrowding, while host determinants are age, sex, weight, nutrition, breed, genetics, immune status, hydration status, and concurrent disease.* [1-3] *Pathogens often associated with BRD include Bovine Herpesvirus-1 (BHV-1, IBR), Bovine Respiratory Syncytial Virus (BRSV), Parainfluenza Virus 3 (PI-3), Bovine Viral Diarrhea Virus (BVDV), and Bovine Coronavirus, as well as the bacterial species Pasteurella multocida, Mannheimia haemolytica, Histophilus somni, and Mycoplasma bovis.* [4, 5] *In addition to the risk factors above, weaning, commingling, processing, and transportation (shipping) are stressors that commonly influence BRD.* [6]

DIAGNOSIS

In the field, diagnoses based on clinical signs are most commonly used to come to individual treatment decisions, although the sensitivity and specificity of clinical signs for the diagnosis of BRD in weaned cattle have been estimated to be moderate, at approximately 62%. [7] The clinical signs most frequently used to diagnose a case of BRD are depression; anorexia; respiratory signs, such as tachypnea or nasal discharge; and elevated rectal temperature. Because most of these signs are non-specific (e.g. heat stress can lead to elevated rectal temperature and increased respiratory rate, GI diseases can lead to anorexia and depression), cattle displaying these signs are frequently misdiagnosed as having BRD. Submission of carcasses or tissues to a diagnostic lab to determine the pathogens involved in an outbreak can guide treatments and changes to vaccination protocols. Talk to your diagnostic lab about specific samples to submit; at a minimum, submit lung, heart, liver, kidney, and any tissues with lesions. If *H. somni* is suspected as a causative agent, brain may be important to submit as well. Additional tissues submitted may aid in ruling out systemic or septicemic conditions which may manifest with respiratory signs.

PREVENTION

The research into prevention of BRD in beef cattle is heavily focused on the arrival period at the feedlot as a high-risk period for this disease. Studies on BRD in cow-calf operations are sparse or evaluate practices associated with weaning stress before transport to the next step in the production cycle. Findings may therefore not be completely applicable to the cow-calf sector, but many of the same principles still apply.

Herd management

The scientific literature identified risk factors associated with BRD in cattle herds, which may help guide potential herd management changes that may lower those risks:

Testing and removing calves persistently infected (PI) with BVD may reduce BRD morbidity.[8-10] Testing can be done via submission of ear notches for antigen detection at birth or at branding; contact the diagnostic lab for sample requirements including storage requirements and whether pooling of samples is recommended.

Bulls castrated at the feedlot are at higher risk of BRD than steers.[11, 12] The effect of timing of castration on BRD outcomes at the cow-calf operation has not been studied, but early castration has been recommended by the Beef Quality Assurance program and may provide health benefits.

The **physiological stress response associated with transportation** has been observed to occur within the first 30 - 60 minutes with no further increases up to 150 minutes; and, transportation distance was not associated with BRD in one study but shrink (body weight loss during transport) was in other studies, particularly for lighter cattle.[13-16] The effect of distance traveled may be mediated by other contributing factors, such as warmer ambient temperatures, which may lead to higher shrink.[17, 18] Greater temperature fluctuations may also result in increased BRD risk.[15, 19]

Fine particulate matter or dust levels have been associated with lung consolidation or BRD, and wildfire smoke has been anecdotally associated with an increase in BRD cases in beef cattle and other livestock. [20-22] Reducing cattle's exposure to high levels of dust (e.g. by hosing down surfaces before processing) may be a way to minimize its impact on BRD.

Dehydration is a stressor that alters composition of respiratory secretions and may enhance the risk for BRD. [23]

Animal characteristics

Male calves have been observed to be at higher risk for BRD following transportation compared with heifers. [16, 24-26]

Lower expression of pro-resolvin mediators, which help to maintain cellular homeostasis during inflammation, has been associated with BRD. [27] Vitamin E metabolites can induce expression of genes involved in the production of resolvins and have been suggested as adjunct metaphylactic therapy—*see information on nutritional supplements below.*

Disease Control

Antimicrobial therapy may be necessary for the control of BRD in a herd. Antimicrobial control, also referred to as metaphylaxis, is the administration of antimicrobials to reduce the number of animals affected by a disease in a herd that already has some infected animals. [28] For an individual animal, metaphylaxis means the use of antimicrobials to decrease the risk of a subclinical infection resulting in clinical signs of disease, to reduce shedding of infectious bacteria, and to minimize chances of disease transmission. [29] Caution should be used when considering use of antimicrobials to control disease due to the risk of antibiotic resistance from antimicrobial administration to a population with unknown individual disease status.

According to the Food and Drug Administration's Guidance for Industry #209, when considering antimicrobial therapy for disease control, veterinarians should "examine several important factors such as determining the medical rationale for such use, and that such use is appropriately targeted at a specific etiologic agent and appropriately timed relative to the disease." Medically important antimicrobial drugs (MIADs) should also not be used based solely on an animal's age, weight, life stage, or event. Rather, the veterinarian should use clinical judgement to determine if sufficient factors indicating elevated risk are present.

The use of metaphylactic treatment to reduce the incidence of BRD during an outbreak has been studied in the feedlot receiving scenario and, to a much lesser degree, in grazing cattle. Several review papers and meta-analyses are available on the topic. [30-34] The efficacy of metaphylactic treatment to reduce the total number of calves developing BRD after entering the feedlot has been thoroughly investigated, but concern remains about the use of mass medication of cattle with medically important antimicrobials. Many options for treatment are available, and criteria for choosing an antimicrobial could include cost, antimicrobial stewardship considerations, prior diagnostic test results, availability of and results reported in antibiograms, drug availability, withdrawal times, ease, safety, efficacy in research trials, and anecdotal efficacy in the same or a similar herd. Whenever possible, the etiologic agent of BRD should be identified prior to antibiotic administration to ensure a bacterial cause.

Considerations for the use of metaphylaxis:

- There is increasing concern surrounding antimicrobial resistance in livestock.
- Metaphylaxis has demonstrated consistent reduction of morbidity and mortality of clinical BRD in cattle, while other interventions (vaccination and nutrition) have shown limited benefit. [33]
- On average, only 20% of cattle benefit from metaphylactic treatment.
- Lowered morbidity and mortality can improve animal welfare in affected herds. [35]
- Mass treatment is costly and adds more stress to cattle, although may be warranted during outbreaks resulting from unexpected events such as smoke exposure, severe weather events, or commingling during an evacuation. The decision to treat due to an inciting incident should fall under veterinary discretion and consider a holistic view of the disease process.
- Field diagnostics have poor sensitivity, so cases are missed that may be more refractory to treatment once clinical disease becomes apparent.
    - The California BRD scoring system is a useful diagnostic tool for preweaned dairy calves but has not been validated for use in beef herds, which may have a different pathogen profile than dairy calves. [36]
- In extensive management situations, individual treatment options may be limited once clinical signs appear.
- A case of bacterial bronchopneumonia is poorly distinguishable from primary viral cases. Metaphylaxis is usually conducted without knowledge of inciting pathogen(s) or microbial sensitivity, which makes targeted therapy difficult. [32]

- Vaccination history of the herd should be taken into consideration, in addition to other risk factors, since a well-designed vaccination protocol may reduce the need for metaphylaxis. For example, are calves vaccinated at birth with an intranasal vaccine for BRD pathogens? Have they received parenteral vaccination for BRD pathogens and had enough time to mount an immune response? Is the vaccination history of herd additions, or any other cattle arriving onto a premises, known? Did their vaccination program include bacterins for both *M. haemolytica* and *P. multocida*, as well as viral vaccination?
- A comprehensive plan to accurately identify sick animals and those at increased risk for BRD could include:

Training of caretakers to identify and manage sick animals

Keeping accurate records that include stressful events, such as travel history, commingling with other herds, gathering and processing, and weather events, to identify risk factors for BRD justifying metaphylactic treatment

Assessing the farm's treatment success for clinical BRD to evaluate the efficacy of established protocols

- Successful and judicious use of a metaphylaxis program could include:

A set threshold for metaphylactic treatment; for example, medicate the herd/pen when a predetermined proportion (X%) of animals have been pulled and treated, based on current scientific publications

Risk assessments, such as whether incoming stockers have gone through preconditioning programs, to determine the need for metaphylaxis

Adequate nutrition, water, and shelter, which can reduce factors contributing to the need for metaphylaxis

A farm crew trained in proper timing of treatment, drug selection, dose, and handling to ensure no human-associated treatment failure

VACCINATION

When developing vaccination schedules for cow calf operations, keep in mind that no matter what the disease challenges are, no vaccine is always safe, no vaccine is always protective, and no vaccine is always indicated. Colostral antibodies are protective to the neonate. Therefore, good colostrum management in the form of vaccinating the pregnant dam 4 - 6 weeks prior to calving, and ensuring colostrum intake, can reduce the need for other prevention measures. Stress reduction, through good stockmanship, good nutrition, and preconditioning at weaning, further ensures that vaccines are efficacious when given. Avoid endotoxin stacking, which occurs when multiple vaccines for Gram negative bacteria are given simultaneously (i.e. *Mannheimia, Pasteurella, Histophilus, Salmonella, Moraxella, E. coli* K99 (recently renamed as F-5)).

Vaccines for viruses

Vaccination for viral respiratory pathogens, many of which can also contribute to reproductive loss, are considered core vaccines because the benefit of vaccination outweighs the risks and should be part of all herd-health plans. [37] The choice of vaccine (killed, modified live, intranasal, parenteral) depends on factors such as reproductive status of cattle to be vaccinated, interference of maternal antibodies in early calfhood, prior vaccination status for modified live vaccines in pregnant animals, or presence of unvaccinated dams when vaccinating calves with modified live virus. A meta-analysis of effectiveness of commercial viral vaccines for the mitigation of BRD evaluating the results of 88 trials in 31 studies found evidence for lower morbidity risk in vaccinated cattle but cautioned against overinterpretation because most trials used experimental challenge, which differs in many ways from natural exposure. [38]

When developing vaccine protocols, the following should be considered:

For vaccines to be most effective:

- Cattle need to be on a good plane of nutrition (adequate energy, protein, Vitamins A, D, E, copper, zinc, selenium)
- At the time of administration, cattle should not be stressed due to parasites, transportation, or environmental conditions such as heat stress [39]

Intranasal vaccines:

- Stimulate faster immune response
- Effective in the face of maternal antibodies
- May result in PCR positive animals

Modified live vaccines:

- May lead to reproductive adverse events if given too close to breeding, or to pregnant cattle without the proper prior exposure to a modified live vaccine, or to suckling calves of unvaccinated dams

Killed vaccines:

- Pose lower risk of reproductive adverse events than modified live vaccines
- In general, confer shorter duration of immunity than modified live vaccines, depending on adjuvant

Vaccines for bacteria

Vaccines for bacterial BRD agents are not considered core vaccines. The decision to add bacterins to a vaccination protocol for respiratory pathogens should be based on whether specific bacterial pathogens pose a documented problem in the herd. The addition of antigens or vaccines comes at a cost to the animal, and adverse events are more common when multiple vaccines for Gram negative bacteria are given simultaneously due to endotoxin stacking. As an example, reduced growth has been observed in backgrounded cattle given vaccines for respiratory pathogens, including *M. haemolytica.* [40]

- Vaccines are available as bacterins or leukotoxoids
- Efficacy of available vaccines is modest for bacterial pathogens

Nutritional supplements and trace minerals to reduce BRD incidence

The field of study of the microbiome is developing and may lead to improved health outcomes through proper nutrition and supplementation. Results on studies with specific products thus far are limited and have led to mixed results, indicating that no "silver bullet" is available. Further research may improve the understanding of how to utilize nutritional supplementation or manipulation of the microbiome to improve health outcomes. There is some evidence to support that vitamin and mineral supplementation or yeast products may have benefits in improving immune function or modulate an immune response. A review article on the interaction of cattle health/immunity and nutrition details the available literature until 1999. [41] The following examples show isolated studies and should not be considered to be as strong of evidence as systematic reviews and meta-analyses, but do provide interesting leads.

- Adding a yeast product to a receiving diet alone did not reduce morbidity but did so when given in combination with florfenicol metaphylaxis, compared to the same florfenicol metaphylaxis protocol alone. [42]
- Supplementation with Vitamin E did not lead to changes in morbidity in feedlot steers but led to a slower decline in BVDV1 antibody titers and increased activity of superoxide dismutase, which is part of the endogenous antioxidant defense system. [43]

- A study with an injectable trace mineral product led to higher BVDV1a antibody titers in treatment steers, although production and health outcomes were not different in this study. [44] In a study where injectable trace minerals were given to dairy calves, lower incidences of diarrhea and a combination of otitis and pneumonia were observed in those that received the trace mineral product. [45]
- Selenium supplementation (1 mg selenite / day) did not affect health or performance outcomes in newly received feedlot heifers over a 28-day period. [46]
- Feedlot steers supplemented with zinc methionine and challenged with IBR virus had lower mean rectal temperatures and less of a decrease in dry mater intake than controls. [47]

Miscellaneous interventions and risk factors

Nitric oxide releasing substance (NORS) has been studied as an alternative to metaphylaxis. Nitric oxide has been shown to have antimicrobial and immunological properties as a primary signaling molecule for growth and activity of immune cells. [48] Studies delivering NORS via an intranasal spray to cattle at feedlot entry led to mixed results. NORS proved to be non-inferior to tilmicosin treatment at feedlot entry in cattle at low to moderate risk for BRD, while it was inferior to tilmicosin in cattle at high risk for BRD. Inferiority in the latter trial was attributed to NORS' inability to prevent the colonization of the nasopharynx by *Pasteurellaceae.* [49, 50] No commercial product is available at present, although there is opportunity for future research.

Timing of growth implant on day 0, 14 or 28 after receiving of stocker cattle had no effect on morbidity or BVDV1a antibody titer, indicating no benefit in delaying growth implants after transportation. [51]

Oral meloxicam, a non-steroidal anti-inflammatory, given to feedlot cattle either pre-transport or at arrival had no effect on BRD morbidity or severity of disease over the course of a 42-day period. [52]

The data on the efficacy of i**mmunostimulants** is sparse. Immunostimulants are products that present pathogen-associated molecular patterns (PAMPs), such as bacterial cell wall fragments or non-coding bacterial DNA, to cells of the innate immune system. Once bound to PAMPs, innate immune cells are activated and, in turn, signal to cells of the adaptive immune response. Lipopolysaccharide, or endotoxin, is a naturally occurring PAMP. A small study with a commercial immunostimulant (Zelnate©) found that, in Holstein steers challenged with *M. haemolytica,* there was reduced mortality in the treatment group, as well as less lung consolidation. [53] A challenge study in Holstein calves with an experimental intranasal immunostimulant in the form of a liposome-toll-like-receptor complex showed reduced clinical signs and disease-associated euthanasia rates in the treatment group. [54] Field studies with natural exposure to respiratory pathogens are needed to confirm preliminary results.

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