Western Dairy News
for the West, about the West, from the West
April 2005
Volume 5, No. 4

Research Progress in Hemorrhagic Bowel Syndrome

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HEMORRHAGIC Bowel Syndrome (HBS, also known as (Jejunal Hemorrhage Syndrome, bloody gut, or dead gut) is a newly emerging, highly fatal intestinal disease of adult dairy cows in the United States.

HBS is characterized by sudden, progressive, and occasionally massive hemorrhage into the small intestine, with subsequent formation of clots within the intestine that create obstruction. Affected segments almost inevitably die, causing release of toxins into the cow's bloodstream and abdominal cavity.

Successful treatment of HBS is difficult. Occasional, anecdotal reports exist of successful treatment with fluids, laxatives, anti-inflammatory drugs, antibiotics, and surgery; however, it appears that such treatment successes are quite rare. With or without treatment, death of affected cattle usually occurs within several hours or 1 to 2 days after the onset of clinical signs. At the Colorado State University Veterinary Teaching Hospital, only about 10 percent of cows affected with HBS have survived.

The disease is seen most commonly in adult dairy cows early in lactation. Thus, factors specific to fresh cow management, nutrition, or the physiologic stress of peak lactation could be playing a role in the development of this disease. Occasional cases occur in late lactation or the dry period, and heifers are rarely affected.

Although HBS usually occurs as a sporadic disease on most dairies, several cows in a herd may be affected in a relatively short period of time (i.e. "clusters" of cases can occur). Anecdotal reports exist of dairies that struggle with this disease on virtually a continual basis.

Research on Potential Causes

Clostridium perfringens type A is a bacterial organism that has been associated with HBS. This organism has been documented to cause disease in a variety of birds and mammals, including cattle. The primary virulence (disease-causing) factor for this organism is a potent, lethal toxin called alpha toxin. This toxin is released from the organism during rapid growth. The alpha toxin acts as an enzyme that destroys cell membranes. It is lethal to a variety of cells, including intestinal cells and red blood cells.

Based on anecdotal evidence, reduced monthly incidence of HBS has occurred after giving an autogenous *C. perfringens* vaccine to adult cows on certain dairies.

Some strains of *C. perfringens* type A also carry the beta2 toxin gene; these strains are designated as A+beta2. This gene codes for beta2 toxin which is also a lethal toxin for intestinal cells. The distribution of *C. perfringens* strains that carry this toxin gene is not well-described, but this strain has been identified in the intestine of both healthy and diseased cattle, horses, pigs, sheep, and goats. One or both of these organisms may be isolated from a cow with HBS. The association between these bacteria and HBS is based on the following observations:

1. Affected cows have positive fecal cultures for these organisms.
2. *C. perfringens* type A and/or type A+beta2 can be readily isolated from the affected segments of intestine in cows affected by HBS.
3. There is microscopic evidence of intestinal necrosis associated with heavy intestinal growth of one or both of these organisms.
4. Other enteric pathogens associated with hemorrhagic enteritis have, to date, been rarely identified in tissues or intestinal contents of affected cows.

In addition, based on anecdotal evidence, reduced monthly incidence of HBS has occurred after giving an autogenous *C. perfringens* vaccine to adult cows on certain dairies. At present, data from controlled studies are not available for evaluation of the effect of such vaccines on the incidence of, or survival rate for, HBS.

Sole Pathogen Unlikely

Despite these observations, there are many reasons why we hesitate to consider *C. perfringens* as the sole pathogen that could cause HBS.

C. perfringens is widely distributed in the environment and is considered to be a member of the normal bacterial flora of the gastrointestinal tract of most mammals. In

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the past, veterinary microbiologists have been reluctant to consider *C. perfringens* type A as an important disease-causing pathogen of livestock because it can be readily cultured from the intestine of healthy cattle.

Furthermore, this organism proliferates rapidly in the intestine after death, making isolation from necropsy specimens of questionable diagnostic significance. If the lethal toxins of *C. perfringens* can be demonstrated in gastrointestinal contents and/or blood of diseased animals, it is considered more likely that the organism is causing disease, rather than simply acting as a part of the normal gut flora.

Until recently, the toxins produced in vivo by *C. perfringens* in HBS cases had not been identified, and the genotype and density of colonization of *C. perfringens* isolated from HBS cows and normal dairy cows had not been compared.

Members of the Integrated Livestock Management Program have recently completed research that investigated these specific questions. We have found that *C. perfringens* types A and A+B2 can be isolated from multiple sites of the intestinal tract of HBS cows at a significantly higher rate than unaffected herd mates (cows with LDA). In addition, alpha and beta2 toxin production can be demonstrated in the intestine of HBS cows, but not control herd mates with LDA.

It is unclear at present whether proliferation of, and toxin production by, *C. perfringens* occurs as part of the primary insult to the intestine, or if proliferation occurs secondary to another disease process or triggering factor.

Hemorrhage into the intestine from another cause could, in theory, initiate secondary proliferation of the ubiquitous *C. perfringens*, as this organism multiplies rapidly when cattle ingest large quantities of soluble protein or carbohydrate.

In other words, blood certainly could act as a very rich culture medium for this organism. Once the organism proliferates, however, the toxins that it releases during rapid growth could contribute to the degradation of the intestinal wall that is so characteristic of HBS.

Fungus May Play Role

An alternate investigation of HBS, headed up by investigators at Oregon State University, has focused on characterizing the role of *Aspergillus fumigatus*, a mold (fungus) that can be found in livestock feeds. Genetic material of this fungal agent can be detected in the blood and intestine of affected cows.

A research project involving dairy cows with HBS and dairy cows that have died of other gastrointestinal diseases (the control group) is currently being conducted by investigators in Wisconsin, Minnesota, and Oregon. In this study, the rates of isolation of *C. perfringens*, Salmonella, and bovine viral diarrhea virus are being compared among cows of these two groups. In addition, the rate of detection of *Aspergillus fumigatus* DNA by polymerase chain reaction in the tissues is being compared among cows of the two groups.

Statistical analysis of preliminary data has revealed a significant association between HBS and the presence of *A. fumigatus* DNA in the tissues. In other words, the DNA of this fungal organism was present in the tissues of a significantly greater proportion of cows with HBS than of cows that died of another gastrointestinal disease.

However, because *C. perfringens* type A was isolated from cows of both groups, isolation of this organism was not significantly over-represented in HBS cows versus the control group. In other words, no statistical disparity was found among the two study groups for the presence of *C. perfringens*, although the authors indicated that future data may produce different results on this issue. To date, the BVD virus and Salmonella have been isolated from only a small fraction of cows affected with HBS.

Aspergillus fumigatus is clearly associated with HBS, and there are currently two hypotheses regarding its participation: 1) As a primary contributor to the intestinal lesion, or 2) as an agent that impairs the cow's immune system.

Aspergillus fumigatus is clearly associated with HBS, and there are currently two hypotheses regarding its participation in this disease:

1. As a primary contributor to the intestinal lesion, or
2. As an agent that impairs the cow's immune system, thereby facilitating or inciting whatever disease process triggers HBS.

Anecdotal reports suggest that the incidence of HBS can be reduced on dairies following the introduction of a feed supplement (Omnigen AF) into the ration. Controlled studies on the efficacy of this product for HBS prevention are pending. When fed to immunosuppressed sheep and cows, this product has recently been demonstrated to improve certain indicators of immune function in neutrophils, a type of white blood cell that plays a critical role in an animal's defense against infection.

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Prevention

Preventive strategies for HBS remain somewhat speculative, given that our understanding about the pathogenesis of this disease is incomplete at present. Nonetheless, potential risk factors for clostridial overgrowth in the intestine of ruminants have been identified in previous studies, and strategies to reduce those risks might, at least in theory, provide benefits in HBS control. Similarly, the potential role of pathogenic fungi in HBS warrants careful consideration when designing preventive strategies.

In short, until more refined information regarding the cause of HBS is published, it may be best to first consider all proposed causes or risk factors (e.g. bacteria, fungi, reduced host disease resistance) and take measures to mitigate these potential risk factors. In so doing, one should consider:

1. Identifying and correcting management and environmental factors that might impair cow immunity.
2. Performing a careful partial budget analysis of the cost of specific preventive measures.
3. Deciding upon which specific corrective measure(s) might be most justified for a particular dairy.

To begin, the authors currently recommend a thorough analysis of transition and fresh cow management to identify problems with cow comfort, nutrition, and disease control that might impact disease resistance during peak lactation.

Ration formulation and feed management should be reviewed as well, with due consideration given to such issues as effective fiber and soluble carbohydrate content to limit potential dietary influences on gut flora, assessment of feed bunk and pen management to maintain consistent feed and nutrient intake, and a review of commodity handling and silage management to limit spoilage and mold formation. Since these critical areas impact numerous facets of cow health other than HBS, identification and correction of problems in these areas will likely provide an overall benefit to cow health.

Lastly, potential use of feed additives or vaccines directed against specific, potential contributory pathogens (i.e. *Aspergillus* and *C. perfringens*) should be considered carefully, with the costs of the proposed interventions and their potential efficacy weighed against the costs of the disease.

Summary

It is apparent that both *Aspergillus fumigatus* and *C. perfringens* types A and A+beta2 can be demonstrated in the tissues and/or blood of cows affected with HBS. Do these bacterial and fungal agents act together or independently? These questions are under investigation, and, hopefully, greater understanding of the pathogenesis of this troublesome disease is forthcoming. Clearly, the funding provided to the ILM by dairy producers has helped us to make progress in our research on HBS, and the authors wish to express their sincere appreciation for that support.