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## Hemorrhagic Bowel Syndrome: An Update

David C. Van Metre, DVM, DACVIM

### Introduction

Hemorrhagic Bowel Syndrome (HBS) is a newly emerging, highly fatal intestinal disease that has been recognized most frequently in adult dairy cows in the United States<sup>1-7</sup> Recently, reports of HBS in Canadian dairy and beef cattle have been published.<sup>8,9</sup> Other names given to HBS include Jejunal Hemorrhage Syndrome, bloody gut, dead gut, and clostridial enteritis. Hemorrhagic bowel syndrome 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 areas of the intestine become necrotic, and affected cows appear to suffer from the combined effects of blood loss, intestinal obstruction, and devitalization of bowel. The disease is seen most commonly in adult dairy cows early in lactation, although cases occasionally occur in late lactation or the dry period. 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. The financial impact of HBS can be significant, owing to the high case fatality rate.

### Clinical Signs

Affected cows are rapidly debilitated by the combined effects of sudden and massive hemorrhage into the small intestine. As a result, affected cows may simply be found dead or dying. A rapid pulse and rapid respiratory rate are commonly found in affected animals, and the mucous membranes are pale. The cow’s extremities are often cool and the rectal temperature is often below normal; the loss of blood into the intestine and the resulting shock contribute to these findings. In this sense, affected cows can resemble milk fever cases. Unlike milk fever, however, the feces of affected cows are dark, tar-like, and may contain dark red to black clots of digested blood. As clots form in the affected segments of the intestine, the intestine often becomes obstructed, causing some cows to show abdominal distension, reduced fecal output, and signs of colic. Glucose can often be detected in the urine of affected cows, indicating a severe stress response.

When viewed from behind, the abdominal contour is typically round or pear-shaped in the standing animal. Noticeable distension is often appreciated in the lower right abdomen, presumably resulting from accumulation of multiple loops of blood-filled small intestine in the ventral abdominal cavity. Scattered, low-pitched “pings” may be evident in the lower right abdomen. Occasionally, motility is reduced throughout the gastrointestinal tract, and affected cows can appear bloated. In the author’s experience, rectal examination often does not reveal distended loops of intestine because the blood-filled segments of intestine seem to sink to the ventral abdomen, thereby becoming beyond the reach of the examiner. However, small intestinal distension was palpable per rectum in 6 of 8 cows in a Canadian study.<sup>8</sup>

Ultrasonography can be used to visualize intestinal distension and clot formation within loops of affected bowel.<sup>6</sup> A 3.5 or 5.0 MHz, sector- or linear-array probe is placed on the abdominal wall at the lower aspect of the right side. Dilated loops of intestine can often be seen, and on occasion, material consistent with the appearance of clotted blood can be seen within the distended loops. Differential diagnoses include intussusception, intestinal volvulus, enteritis, and abomasal ulceration. Differentiation of HBS from intussusception requires exploratory surgery.

### Treatment

Successful treatment of this disease is difficult. Occasional, anecdotal reports exist of successful treatment with fluids, laxatives, anti-inflammatory drugs, and antibiotics; however, it appears that such treatment successes are quite rare. Cows treated with medical support alone almost inevitably develop ileus, intestinal necrosis (tissue death) with subsequent peritonitis and shock. Death of affected cattle occurs within several hours to 1-2 days after the onset of clinical signs.<sup>6,8</sup>

At surgery, multiple inflamed segments of jejunum, ileum, or rarely, duodenum are found. The serosal surface of affected segments is often dark purple to black in color. The affected segments of intestine are turgid with luminal blood, and the casts of clotted blood within the lumen of the intestine impart a gelatin-like feel to the affected bowel. Involvement of multiple segments of jejunum and/or ileum is frequently found, which eliminates the option for intestinal resection and anastomosis. Techniques for surgical management of HBS cases to date include manipulation of the affected intestine so as to break down the obstructing clots, enterotomy and removal of the offending clots, and resection and anastomosis of affected segments. Common reasons for poor surgical outcome include discovery of multiple segments of non-viable bowel and/or septic peritonitis. Also, if the initial surgical procedure is completed successfully, affected cows may develop repeated clotting and recurrent obstruction of the intestine after surgery. Of 22 cows affected with HBS presented to the CSU Veterinary Teaching Hospital over a 3-year period, only 5 (23%) survived; four of these survivors were treated surgically.<sup>6</sup> Since publication of that case series, our success rate in treating HBS with surgery, medical management, or both has remained poor, similar to that reported in other studies.<sup>2,8,9</sup>

#### Pathogenesis

The cause of HBS is currently unknown, and no consistent predisposing factor has been identified. The majority of HBS cases seen at the CSU VTH occur during the first 3 months postpartum,<sup>6</sup> a trend evident in other reports.<sup>1,2,10</sup> In a large survey of American dairy producers, the median parity for cows affected by HBS was reported to be the third lactation, and the median days in milk for affected cows was 104 days.<sup>10</sup> During this time period, dairy cows experience significant physiologic stress associated with peak milk yield. In addition, the rations fed during this stage of production are rich in energy and protein and fiber-depleted relative to rations fed later in lactation. These factors have been proposed to place cows at greater risk for HBS, but the events that lead up to the development of this disease remain undetermined.<sup>1-10</sup>

The gross and histologic features of HBS have been described in a few reports.<sup>6,8,9</sup> Gross lesions are usually segmental or multifocal in distribution in the small intestine, primarily in the jejunum with occasional involvement of the duodenum or ileum. Affected segments show purple or red discoloration of the intestinal wall, with distension of affected segments caused by intraluminal casts or clots of blood. The intestine oral to these lesions may be distended with fluid and gas, indicating obstruction of affected segments. Fibrin accumulation on the surface of affected intestine may be evident, and affected segments may rupture ante- or postmortem. The blood clot in affected segments is often tenaciously attached to the mucosa, and manual removal of the clot often results in "peeling off" of the surrounding mucosa. On histologic examination of affected bowel, HBS appears to be a segmental, necrohemorrhagic enteritis, with submucosal edema, mucosal ulceration, transmural hemorrhage, and neutrophil accumulation evident in affected areas. Sloughing of mucosa in affected areas may also be present.

Several reports indicate an association between *Clostridium perfringens* type A and HBS.<sup>1-8</sup> This association is based on the following observations: (1) Affected cows have positive fecal cultures for this organism, (2) *C. perfringens* type A can be readily isolated from blood clots in the jejunum of affected cows, (3) there is microscopic evidence of intestinal necrosis associated with heavy

intraluminal growth of *C. perfringens* type A, and (4) other enteric pathogens associated with hemorrhagic enteritis are rarely identified in tissues or enteric contents of affected cows.<sup>2,4-6</sup> In addition, based on anecdotal evidence, reduced monthly incidence of HBS has occurred following administration of 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, this disease.

*Clostridium perfringens* is a large, Gram-positive, anaerobic bacillus that is considered to be ubiquitous in the environment and in the gastrointestinal tract of most mammals.<sup>11-14</sup> The rate of isolation of the organism from the gastrointestinal tract of cattle may be enhanced by high grain diets.<sup>15,16</sup> There are five defined types of *C. perfringens* (A, B, C, D, and E), which are identified based on the lethal toxins that they produce. These toxins are named alpha, beta, beta<sub>2</sub>, iota, epsilon, and enterotoxin.<sup>11-14,17,18</sup> Genetic classification of *C. perfringens* is performed by multiplex polymerase chain reaction (mPCR).<sup>19,20</sup> Type A usually produces alpha toxin, although different isolates may produce different quantities of this toxin.<sup>21,22</sup> Alpha toxin is a calcium-dependent phospholipase that is capable of cleaving phosphatidylcholine in eukaryotic cell membranes.<sup>23</sup> Additionally, the recently discovered beta<sub>2</sub> toxin may be produced by any of these types.<sup>18,19</sup> Beta<sub>2</sub> toxin is also a lethal toxin,<sup>18</sup> and strains of *C. perfringens* with the *cpb2* gene produce variable amounts of beta<sub>2</sub> toxin in vitro.<sup>24</sup>

In two studies, *Clostridium perfringens* type A and/or type A + beta<sub>2</sub> was isolated from feces and / or intestinal contents of 28 of 32 cows with HBS seen at Colorado State University.<sup>3,6</sup> These bacteriologic findings are concordant with those of other studies.<sup>2,4,5,8</sup> In the past, veterinary microbiologists have been reluctant to consider *C. perfringens* type A as an important disease-causing pathogen of livestock because this organism is part of the normal flora of the cow's intestine.<sup>7</sup> Furthermore, this organism proliferates rapidly in the intestine after death, making isolation from necropsy specimens of questionable diagnostic significance.<sup>7,15,25,26</sup> Because *C. perfringens* types A and A + beta<sub>2</sub> can be isolated from the gastrointestinal tract of apparently healthy animals, the diagnostic significance of isolation of these organisms from animals with enteric disease is increased if the corresponding toxins can be detected in gastrointestinal contents or blood.<sup>25,27</sup> Recently, the author's research team has found that *Clostridium perfringens* types A and A+B<sub>2</sub> 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).<sup>3</sup> In addition, intraluminal toxin production can be demonstrated in the intestine of HBS cows, but not in the intestine of control herd mates with LDA.<sup>3</sup>

It is unclear at present whether enteric proliferation of, and intraluminal toxin production by *C. perfringens* type A occurs as part of the primary insult to the intestine, or if these processes occur secondary to another disease or triggering factor. Hemorrhage into the intestine from another cause could, in theory, initiate secondary proliferation of the ubiquitous *C. perfringens*, as this organism is likely to rapidly multiply when large quantities of soluble protein or carbohydrate is presented to the intestine.<sup>25</sup> 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. This destruction of the intestinal wall in sections of the gut affected by HBS is likely to contribute to the subsequent shock and peritonitis that is evident in so many affected cows.

Efforts to experimentally reproduce enteric disease with *C. perfringens* type A have produced varied results.<sup>28-30</sup> In light of these findings, it is apparent that yet unidentified microorganisms and/or host and environmental factors may be involved in the pathogenesis of HBS.<sup>7</sup> A limited number of HBS cases have been fully investigated for enteric pathogens. Pathogens capable of inducing intraluminal hemorrhage, such as *Salmonella* spp. and bovine viral diarrhea virus, have been identified in very few

HBS cases.<sup>2,3,6,31</sup> However, the gross and histological lesions of HBS do not resemble those classically attributed to these agents.

Investigators at Oregon State University have focused on characterizing the role of *Aspergillus fumigatus*, a mold (fungus) that can be found in livestock feeds.<sup>31,32</sup> Genetic material of this fungal agent can be detected in the blood and intestine of affected cattle. 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.<sup>31</sup> 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 GI disease. However, because *C. perfringens* type A was isolated from cows of both groups, 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. *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.<sup>33,34</sup> 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. This product has recently been demonstrated to improve certain indicators of immune function in the white blood cells taken from immunosuppressed sheep.<sup>35</sup>

## Prevention

Preventive strategies for HBS remain somewhat speculative at present, given the lack of understanding about the pathogenesis of this disease. In addition, controlled studies on particular preventive measures are currently pending. 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, and 3) deciding upon which specific corrective measure(s) might be most justified for a particular dairy.

To begin, the author currently recommends 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 should be considered carefully,

with the costs of the proposed interventions and their potential efficacy weighed against the costs of the disease.

### Future Research

Our current research at CSU centers upon a comparison of the characteristics of *C. perfringens* isolated from HBS cows with characteristics of the same organism isolated from normal cows. Preliminary genetic analysis of isolates taken from HBS cases indicates that these organisms are not all descendants of a single “superbug,” that is, these bacteria are not all derived from a single strain. They appear to be genetically diverse. However, preliminary data from our laboratory does indicate that toxin production is greater in *C. perfringens* isolated from animals with HBS than in the same organism isolated from herd mates without HBS.<sup>36</sup> What induces these changes in *C. perfringens* in cows with HBS? Is it the presence of blood in the intestine? A feed change? Or is it a signal from *A. fumigatus*?

### Summary

It is apparent that both *Aspergillus fumigatus* and *Clostridium perfringens* types A and A+beta2 can be demonstrated in the tissues and/or blood of cows affected with HBS. A lot of unanswered questions about this disease remain, particularly in regard to the factor(s) that trigger its onset. Do these bacterial and fungal agents act together or independently? These questions are under investigation, and hopefully, greater insight into the pathogenesis of this troublesome disease is forthcoming.

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