Hemorrhagic bowel syndrome in cattle

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Abstract
Hemorrhagic bowel syndrome is relatively common disease in dairy and beef cattle which has high fatality rate. It is classified as acute, sporadic and necrohemorrhagic enteritis. It is commonly seen in highly productive dairy cattle. The cause of hemorrhagic bowel syndrome is unclear and the pathogenesis is not well-understood. As a primary etiologic agent Clostridium perfringens type A has been strongly proposed and its alpha and beta2 toxin are suggested to have an important role in occurrence of the disease. Disease especially observed in the first 3 months of lactation in lactating dairy cows. Ration is seem to be the most important predisposing factor in the development of hemorrhagic bowel syndrome. Severe toxemia (enterotoxemia) and intense hemorrhage in the small intestine cause pathological changes in the intestine. The blood clots in the intestinal lumen, a specific finding of hemorrhagic bowel syndrome can only be demonstrated in 19% of affected cows. Diagnosis is often based on the clinical, ultrasound and necropsy findings and also with differential diagnosis of other haemorrhagic enteritis caused by salmonellosis, Bovine Viral Diarrhea and coccidiosis etc. Prognosis is poor and fatality rate is nearly 100% despite intensive medical and surgical therapy. The use of feed additives, good nutritional management and vaccine administration are recommended for disease control.

Süçlarda hemorajik bağırık sendromu

ÖZ
Hemorajik bağırık sendromu, daha yaygın olarak suçu ve etçi suçlarda görülen ölüm oranı yüksek bir hastaluktur. Akut, sporadik ve nekrohemorajik enterit olarak sıralanabilir. Süt verimi yüksek suçlarda yaygın olarak görülür. Hemorajik bağırık sendromunun nedeni belirsizdir ve patogenezini tam olarak anlaşılamamıştır. Primer etiyolojik etkenin Clostridium perfringens tip A olduğu ağırlıklı bir şekilde öne sürülmüş olup, etkenin alfa ve beta2 toksininin, hastalığın oluşumunda önemli bir rolü olduğu düşünülmektedir. Hastalık, özellikle laktasyonu 3 aydan sonra görülür. Rasyon, hemorajik bağırık sendromu gelişiminde en önemli predispozan faktör olarak görülmektedir. Ince bağırıklardaki şiddetli toksemi (enterotoksemi) ve yoğun hemorajik, bağırıkçıklarda patolojik değişiklikler neden olur. Spesifik bir hemorajik bağırık sendromu bulgusu olan bağırık lumenindeki kan pıhtılaşması, sendromdan etkilenen ineklerin sadece %19’unda tespit edilebilir. Tedavi, genellikle klinik, ultrason ve nekropsi bulgularına dayanır ve teşhis, ayrıca salmonellosis, Bovine Viral Diarrhea ve koksidioz vb. kaynaklı diğer hemorajik enteritlerin aynı tanı ile olur. Prognoz kötüdür ve ölüm oranı, yoğun medikal ve şirurjikal tedaviyle %100’den fazladır. Hastalığın kontrolu için yemdeki maddelerin kullanımı, iyı beslenme yönetimi ve aşın uygulaması önemlidir.

Introduction
Hemorrhagic bowel syndrome (HBS), which is also designated as jejunal hematoma or jejunal hemorrhagic syndrome (JHS) is relatively common disease in and dairy cattle which has high fatality rate. It is defined as acute, sporadic and necrohemorrhagic enteritis (1). HBS is also called as dead gut, bloody gut and clostridial enteritis (2, 3). It is commonly seen in highly productive dairy cattle and its exact cause is still not well-established (4, 5). The disease is encountered often in adult dairy cows during early lactation although the disease can be seen seldom in the dry period or late lactation (3).

The disease is associated with haemorrhagic enteritis, mainly from the proximal part of small intestines often with blood clots present within the lumen (4, 5). HBS is presented with sudden, progressive, and sometimes massive hemorrhage into the small intestine. Obstruction occurs by recurrent occurrence of clots among the intestine (3).

Etiology
The etiology of the disease is unclear. However, Clostridium perfringens type A and its toxins has been found in the intestinal tissues of patients. Its pathogenic importance is obscure due to C. perfringens type A could be identified from intestines of non-sick cattle. Also the microorganism can be encountered after the animal dies. Therefore, it is not known whether the organism causes hemorrhagic jejunitis or not (2, 6).
The cause of HBS is unknown and the pathogenesis is not well-understood. As a main causative agent, *C. perfringens* type A has been strongly proposed and its alpha and beta2 toxin are suggested to have an important role in occurrence of the disease (6-8). On the other hand, some authors have suggested an association between HBS and infection with *Aspergillus fumigatus*. In animals infected with *A. fumigatus*, a potent immune suppressant and apoptogenic agent called gliotoxin has been explored (9). It is demonstrated to potentiate the virulence of *A. fumigatus* (10). It is shown that gliotoxin suppresses host defense mechanisms, supports fungus virulence and at last leads to HBS (6, 11).

HBS occurs in beef cattle after the animal eat food consists of several types of mycotoxigenic fungi (Mouldy feed) including *Fusarium poae*, *F. sporotrichioides*, *F. verticillioides*, *A. fumigatus* and *Penicillium roqueforti*. Mixtures of Shiga toxin-producing *Escherichia coli* (STECs) occupy in the hemorrhagic tissues. In beef cattle, HBS is related with mycotoxins, moulder feed and STECs colonization (12).

**Risk Factors**

Investigations of herds with HBS could not determine any trustworthy risk factors (13). Disease especially observed in the first 3 months of lactation in lactating dairy cows (2).

It has been reported that fall and winter months are risk factors and the incidence of the disease is very high in these months (11, 14). On the other hand, ration is seem to be the most important predisposing factor in the development of HBS (15). Total mixed ration (TMR) diets high in energy and protein with little structure have a predisposing effect (5, 15, 16). A high energy TMR feeding has been shown to rise the risk of developing HBS. Milk yield and feed intake are high in a cow at early lactation period and increased incidence of the disease during that time shows association of nutritional factors with the disease (13, 16). The exact mechanism of association is unknown, but an inadequate rumen fiber raft and excessive amounts of dietary levels of rapidly available carbohydrate could lead to overflow of excessive carbohydrates in the cow’s intestine. As a result, essential surrounding for production and rapid multiplication of toxins for clostridial organisms which are natural inhabitants of the gastrointestinal tract is provided. In dairy cattle, an association has been determined between HBS and subacute rumen acidosis suggesting that a high-energy and low-fiber ration are critical factors for the disease formation (11, 17). Otherwise, grazing on the pasture reported to reduce risk of HBS development in dairy cattle (11, 15).

The risk of HBS development can be effected by the quality and quantity of the protein added in to TMR. An unidentified factor in the dry legume-derived protein is suspected to stimulate rapid growth and gas production by *C. perfringens* type A in the intestinal tract (11).

However, in dairy cattle the elevated levels of milk production can rise the probability of occurring HBS. For entire risk factors raised consumption of a high energy diet appear to be the most possible common pathway (15).

One of the probably risk factor suggested is feeding rations rich in soluble carbohydrates which lead to ideal condition in intestine for *C. perfringens* type A to increase rapidly and secrete enterotoxins. Similarly, abomasitis, abomasal ulceration and hemorrhagic enteritis can occur in calves (2, 7, 18).

Administration of bovine somatotropin (bST) increases their probability of developing HBS in dairy cattle (15). It has been demonstrated that administration of bST increase the dry matter consumption (19) and maintain high milk yield in treated cows (20). Consequently, using bST often lead to feed more energy dense rations and cows that are treated are hoped to eat more feed (11).

Development of HBS is conspicuously increases with the herd size. The probability of the clinical symptoms of the disease to be seen even in one cow increases as the size of the herd enlarge (15).

**Pathogenesis**

Prominent hypothesis about the pathogenesis of the disease is protein overfeeding and overgrowth of bacteria, *C. perfringens* and as a result toxin production leads to cell damage and the production of inflammatory mediators and local inflammatory responses occurs. Inflammatory response disrupt the intestinal barrier which leads to secretion of the plasma proteins and growth factors into the intestinal lumen and contributes to bacterial overgrowth. Eventually, microorganisms and toxins easily diffuse into the tissues resulting in toxemia and death (5, 11).

The major finding of HBS is acute localized necrotizing hemorrhagic enteritis in the small intestine causing obstructive blood clot. Obstruction of the intestine lead to ischemic complications and devitalization of portions of the affected gut (7). The lesions in fast growing calves, lambs or piglets are identical to hemorrhagic enterotoxemia caused by *C. perfringens* (2, 21).

Pathological examinations demonstrate foci of necrosis and luminal obstruction caused by huge intramural hematomas. The affected mucosa separate from the intestinal wall. Hemorrhagic changes are not seen in the lumen. The mucosal layer which is not disturbed occasionally overlay the intramural hematomas. Intraluminal blood clots which is suggested before does not explain all pathological symptoms. Anti-Clostridium antibody positive short bacilli and gram positive bacilli are identified in hemorrhagic necrotic tissue. However, the normal flora of cattle consists of *Clostridium* spp. Therefore, it is unknown if there is a correlation between HBS and *Clostridium* spp. encountered in the disease (1).

Gastrointestinal stasis, intestinal gas and fluid accumulation occur in the proximal part of the obstructed intestine. As a result, hypochloremia, hypokalemia, varying degrees of anemia, dehydration and distension of intestinal loops can also be seen. Upper small intestine obstruction and accumulation of abomasal secretions leads to the serum biochemistry changes including hypokalemia and hypochoolemia. The hemorrhagic enteritis is a progressive disease leads to necrosis and ischemia through the intestinal wall and finally dehydration, electrolyte imbalance, prominent fibrinous peritonitis, toxemia and death.
Clinical Symptoms

In cows with HBS, the clinical symptoms are progressive and the animals can be encountered dead or die soon. Severe toxemia (enterotoxemia) and massive hemorrhage into the small intestine cause the pathological changes develop in the intestines. Affected animals generally have sudden onset of the disease with symptoms of anorexia, severe depression and decreased milk production. The extremities of affected cow are generally cool and rectal temperature is usually extremely low. Recumbency and muscle fasciculations have been also reported in these animals (11, 14, 22, 23). Dry scent feces or bloody to dark-red feces, abdominal distension, dehydration, weakness progressing to recumbency, vocalization, treading, bruxism, kicking at the abdomen and abdominal pain are other commonly seen findings in cows with HBS. Furthermore, pale mucous membranes, elevated respiratory and heart rate (over 90-120 beats/min) and atonic rumen are also reported other clinical findings in cows with HBS. By succession over the right abdomen fluidsplashing sounds can usually be heard. Sometimes a ping may be revealed over the right abdomen (2). Standing behind a cow the abdominal contour is observed characteristically round or pear shaped (8).

C. perfringens type A, one of the etiologic agent of HBS, produce gas and these gases accumulate in the proximal part of the small intestine and abomasal dilatation can be caused by these gases flow in a retrograde direction from duodenum to the abomasum (11). This could be the reason of ping recorded on the right part of the abdomen which can be observed in 75% of cases (13, 14, 22). It can also be the reason why cows with HBS are usually at first considered as right displaced abomasum, but finally given a diagnosis of HBS. Transrectal examination can identify a dilated colon, an inflamed cecum, a distended and firm rumen and distended loops of the small intestine (11, 14, 22, 23). As the disease progresses peritonitis, intestinal necrosis and subsequent septic shock occurs. Death may occur within several hours to 2 days after the beginning of the symptoms (8, 11). But, a sudden death without clinical symptoms has also been reported in cows with HBS (2, 7).

The duration of illness is generally 2-4 days. Despite intensive fluid and electrolyte treatment animals progressively worsened become weakened recumbent and die or euthanasia is selected (2).

Ultrasonographic Findings

In cows with HBS the recorded ultrasonographic findings include thickening of the intestinal wall and dilatation of the small intestine, generally the proximal part of the jejunum. The intestinal content is echogenic to varying degrees and can contain a hypechoic mass which represents the blood clot. The clotted blood in the intestinal lumen, a specific finding of HBS can only be demonstrated in 19% of affected cows (11, 13, 23). Intestinal motility is strikingly decreased or absent in animals with HBS and usually collection of fluid between the loops of intestine can be seen. In some cows, fibrin accumulation could be observed within the peritoneal fluid due to probable damage and perforation of the intestines which contribute to leakage of intestinal contents and finally peritonitis occur. In some affected cows, abomasal dilatation with hypoechoic material can be easily demonstrated and within the ingesta abomasal folds shown as echoic, sickle shaped structures. Although this imaging technique can provide valuable information, exact diagnosis of HBS can be made by using ultrasonography in only 20% of cases (11, 23, 24).

Clinical Pathology

Hematology

The hematologic findings are variable and not helpful for the diagnosis. Common blood parameters in cows with HBS include leukocytosis and neutrophilia with or without left shift. These findings can occur as a result of inflammatory cytokine and neutrophil release from the bone marrow or stress-dependent changes stimulated by the disease (2, 14).

Serum biochemistry

Serum biochemical analysis shows hypokalemic, hypochloremic metabolic alkalosis with compensatory respiratory acidosis. The reason of the metabolic disturbances is the sequestered abomasal secretions and continuous proximal bowel obstruction (2, 14, 22, 23).

Necropsy

Surgical exploration or post mortem examinations revealed that a frequent finding in cattle with HBS is intense distention of the small intestine. In addition, discoloration with a dark-red to purple occurs on the serosal surface and devitalization of proximal part of the small intestine, especially jejunum and less often duodenum is frequently seen. Blood with or without clot can be seen in the intestinal lumen and intestinal mucosa is sloughed. In more developed examples, swollen, friable intestine has gelatin-like blood clots and on the serosal surface of the jejunum there are fibrin strands (8, 11). Large intraluminal blood clots and segmental necrohemorrhagic enteritis of the small intestine can also be demonstrated at necropsy (2).

The most important histopathologic changes of the small intestine are intense edema and hemorrhage in the submucosa which is particularly encountered in the jejunum. Ulceration, necrosis, neutrophil rich inflammatory infiltrate which contribute to epithelial sloughing and gram-positive bacilli can also be seen. As the disease progresses, destruction of the mucosa is observed throughout the full thickness of bowel wall that is severe hemorrhages and hematomas are seen in the submucosa, tunica muscularis and serosa. C. perfringens type A has been found in the intestinal contents of sick animals, but its significance is uncertain (11).

Diagnosis and Differential Diagnosis

Diagnosis of HBS is based mainly on a combination of clinical symptoms, laboratory tests, digital rectal examination and transabdominal ultrasonography findings (7, 8, 13, 14, 22, 23).
With the transabdominal ultrasonography examination distention of the loops by gas or fluid can be identified. Also, ileus of the small intestine is confirmed by detecting increased echogenicity caused by clotted blood and hemorrhage within the lumen (13, 23).

The differential diagnosis must be evaluated carefully to rule out other possible reasons of acute functional or physical blockage of the small intestine which lead to dehydration, electrolyte imbalances, distended loops of intestine. Conditions to consider in the differential diagnosis include indigestion, cecal dilatation, enteritis, abomasal ulcer, volvulus, intussusception and diffuse peritonitis which lead to ileus. Distention of bowel loops can be determined by rectal examination in cows with ileal impaction (2, 8). On laparotomy finding the impaction rules out other abnormalities (8, 25). As a result of abomasal ulcer, melena can be seen. In cows hemorrhagic shock will contribute to serious hemorrhage. Fresh blood does not detected together with the melena. Increasing abdominal distension which is typical for HBS is seldom seen. Indigestion will not lead to melena, blood lost or shock. Especially, following treatment with fluids and calcium salts, large amounts of fecal excretion continue in cattle with enteritis, but it is not generally encountered in cattle with HBS. Exploratory laparotomy is performed to differentiate HBS from intestinal volvulus and intussusception (8).

Because of uncertain pathogenesis and lack of confirmed causative pathogen, the diagnosis of HBS remains difficult. Diagnosis is often based on the clinical, ultrasound and necropsy findings and also with differential diagnosis of other haemorrhagic enteritis caused by salmonellosis, Bovine Viral Diarrhea (26) and coccidiosis etc (5).

Prognosis

The treatment of HBS is often done surgically by resection of the affected intestinal segment or by massaging the blood clots. Alternative processes are treatment conservatively with antibiotics and prokinetics. There are no available published studies comparing different treatment protocols in cows with HBS. However, in the treatment studies, the mortality rate is reported to be about 85-100% in cows with HBS (7). Treatment is not economically justified in many cases because of high surgical and conservative treatment costs (5). Prognosis is poor and fatality rate is nearly 100% despite intensive medical and surgical therapy (2).

Treatment

Early diagnosis and rapid approach of treatment are necessary for successful treatment in affected animals. Medical administration generally includes fluids, analgesic drugs, laxatives, and anti-inflammatory agents (8, 11). In almost all cases treated only with medical support will lead to intestinal necrosis, ileus, peritonitis and shock. After the onset of clinical findings affected animals usually die within several hours to 1 to 2 days (8).

In addition to management of C. perfringens types C and D antitoxin, administration of antimicrobials can be valuable too. No specific antitoxin is available for C. perfringens type A, but antitoxin of C. perfringens types C and D can provide limited cross protection (13). The most suspicious causative agent for the disease is C. perfringens, therefore penicillin is the most appropriate antibiotic. Administration of C. perfringens types C and D antitoxin and penicillin G procaine administration (22,000 U/kg every 8 hours, SC) is valuable (11). For a more effective therapy, it is best to combine penicillin with an aminoglycoside (e.g., neomycin). Furthermore, a non-steroidal anti-inflammatory can also be used. This is necessary for pain relief (because, pain has a negative effect on gastrointestinal motility) and controlling inflammation in the gastrointestinal mucosa (5).

There are no prokinetics registered for use in beef cattle. Erythromycin supports the gastrointestinal tract motility. Erythromycin lactobionate (0.1 mg / kg, IV, or 1 mg/kg, IM) or erythromycin base (10 mg/kg, IM) can be used for gastrointestinal tract motility (5, 28). However, erythromycin administration does not allowed in lactating animals (5).

When a combine medical treatment and surgery applied the chances of success are quite high (8). Early surgery can be successful. Principles of surgical technique is opening the intestinal tract to remove blood clots and devitalized segments. As a result, satisfying treatment can be achieved (13). A number of surgical techniques can be applied to treat HBS. These are include break down the obstructing clots, enterotomy to remove blood clots, and resection and anastomosis of affected intestine (8). Diffuse septic peritonitis may occur during the surgery as a result of intestinal perforation. These animals with such a complication like diffuse peritonitis can be euthanatized (8, 11).

Prevention

The exact etiology of HBS has not been identified and thus convenient preventive programs have not yet been constituted. On the other hand, the use of feed additives, good nutritional management and vaccine administration are recommended for disease control (11, 27). But, vaccination against C. perfringens or autologus toxoid vaccines are reported to be insufficient to prevent HBS incidence (5, 11). Pen management and feed bunk have to be reviewed for providing appropriate feed intake. Attention should be given to ration preparation, storage and silage management to clarify if the mold formation and spoilage are appropriate or no. Mold growth should be prevented by using feed additives. In dairy cattle these additives can also have beneficial effect against other mycotoxicoses. Other potential supplements like prebiotics and probiotics should be examined in terms of increasing intestinal health (8).

CONCLUSION

Despite intensive and high cost of treatment, the prognosis for affected animals remains quite poor. Approaches to disease prevention and control include well-balanced diets with sufficient structure and no excess in protein. Ration formulation and its mixture should be carefully prepared. Soluble and fiber form of carbohydrate content and their potential dietary impact on intestinal microbiota should be...
considered. Vaccination against *C. perfringens* or autologous toxoid vaccines are insufficient to prevent HBS incidence. But, regular vaccination programs are still recommended to prevent clostridial infections.

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