Over the past 2 decades, dairy producers and veterinarians have become aware of an emerging syndrome in dairy cattle that is characterized clinically by a sudden onset of abdominal crisis and rapid death associated with devitalization of the small intestine, particularly the jejunum. Postmortem examination of affected cows reveals devitalization of the proximal portion of the small intestine, primarily the jejunum, associated with frank hemorrhage into the lumen with immediate clotting that results in physical blockage. The condition was first reported in 1991. Multiple descriptive names have been proposed for this condition, including hemorrhagic bowel syndrome, acute hemorrhagic enteritis, bloody gut, or JHS. Interestingly, the syndrome was actually documented as early as 1966. The prevalence was usually sporadic and involved individual animals on different dairy operations with few cases reported in the 1970s and 1980s; however, during the last few years, there has been a marked increase in the number of reported cases. Herd outbreaks involving approximately 10% of the cows on a given dairy farm have been reported. The prognosis for affected animals is poor, and the case fatality rate for cattle with JHS is reported to exceed 85%. The cause of JHS is uncertain and the pathogenesis poorly understood, but Clostridium perfringens type A has been strongly suggested as a primary etiologic agent, with CPA having an important role. Other authors, however, have reported an association between JHS and infection with Aspergillus fumigatus. In a retrospective study including 22 clinical cases of JHS in Colorado, C perfringens was isolated from 17 of 20 fecal samples obtained from clinically affected cows. In the same study, the genotyping of C perfringens was carried out on 10 of the 17 isolates. Alpha toxin–producing C perfringens type A was detected in 5 cows, and CPA and beta 2 toxin–producing C perfringens type A were identified in the remaining 5 cows. Jejunal hemorrhage syndrome (JHS) is an acute, highly fatal enterotoxemic disorder in dairy cattle that has been reported during the last few decades. No specific cause of this syndrome has been identified; however, several studies have revealed a strong association between JHS and infection with Clostridium perfringens type A. A common mold, Aspergillus fumigatus, has also been implicated as a potential causative agent in this disease syndrome. Clinical signs of JHS (including sudden decreases in feed intake and milk production, rapid loss of condition, a right-sided ping audible during simultaneous auscultation and percussion of the abdomen, abdominal distension, and melena or bloody feces) usually develop early during lactation when cattle receive rations that are high in energy and low in fiber. Appropriate preventive strategies have not yet been determined, and intensive medical management with or without surgical intervention is rarely successful. The use of commercially available vaccines that are directed against C perfringens types C and D is of questionable efficacy and not likely to be helpful as a preventative measure. This article highlights the potential etiologic and risk factors, describes common clinical signs, outlines relevant diagnostic testing, and summarizes treatment options and their outcomes.
the organism in tissue samples collected from 7 of 8 clinical cases in Italy, from which 3 isolates were identified as *C perfringens* type A and 4 isolates were identified as *C perfringens* type A with the beta 2 toxin gene.

Recently, a research team has found that the rate at which *C perfringens* type A is isolated from multiple sites in the intestinal tract of cows with JHS is significantly higher than that in herd mates that have left-displaced abomasum but do not have JHS. In addition, intraluminal toxin production has been detected at various sites of intestinal tract of cows with JHS but not in the intestinal tract of control herd mates with left-displaced abomasum.

Although the findings of those clinical studies are compelling, the hypothesis that *C perfringens* is the exclusive causative agent of this syndrome was challenged when experimental inoculation of a pure culture of *C perfringens* type A, isolated from clinical cases, into the proximal portion of the jejunum of 12 adult nonlactating dairy cows failed to induce the syndrome. *Clostridium perfringens* is ubiquitous in nature and a component of the normal intestinal microflora of livestock. It is known to rapidly proliferate in high numbers in the intestines, invade the intestinal wall, and contribute to the postpartum putrefaction process; as a result, quantitative bacterial analysis and isolation of the organism via bacterial culture of tissue samples from dead animals is of refutable diagnostic importance. It has been suggested that the antemortem enteric proliferation of *C perfringens* type A and the accompanying intraluminal toxin production in animals with JHS are components of a multifactorial process that could develop secondary to 1 or more initial triggering factors.

The gene-encoding alpha toxin is present in all strains of *C perfringens*, and the purified CPA has been found to be zinc-containing metalloprotein possessing phospholipase C activity. *Clostridium perfringens* alpha toxin is preferentially active against cell membrane phospholipids and is the key virulence factor in myonecrosis caused by *C perfringens*. In fact, the organism is unable to induce myonecrosis without this toxin.

*Clostridium perfringens* type A was found to produce CPA when grown in a synthetic medium containing zinc. In a zinc-deficient medium, the organism produces protein similar to CPA in an amount comparable to that of CPA produced in the zinc-containing medium, but this protein is biologically inactive and unstable and rapidly disintegrates. *Clostridium perfringens* type A produces at least 3 distinct proteases in a synthetic medium containing calcium. Alpha toxin, being a zinc-containing metalloenzyme, is moderately resistant to the proteases, but toxin produced in a zinc-deficient or zinc-free medium is highly sensitive. By adding zinc, the toxin may have been converted to the zinc-containing metalloprotein that is resistant to proteases. This may explain why CPA activity increases progressively when *C perfringens* type A is grown in a zinc-containing medium despite the simultaneous production of potent proteases and disintegrates rapidly when *C perfringens* type A is grown in a zinc-deficient medium.

The bioavailability of zinc in the intestinal tract, primarily the small intestine, during the multiplication of the *C perfringens* type A is highly important for the stability, the subsequent destructive properties of CPA, and the initiation of the disease process. This fact might elucidate the poorly understood pathogenesis of the JHS. The production of CPA leads to cleavage of the cell membrane phospholipids and the outer layer of the host cell membrane, which is rich in phosphatidylycholine and sphingomyelin, both of which are preferred substrates of CPA. Cells treated with CPA respond by producing arachidonic acid, and activation of the arachidonic acid cascade results in the production of thromboxanes, leukotrienes, and prostaglandins. This cascade likely initiates a local inflammatory response, disrupts the integrity of intestinal microvasculature, and results in uncontrollable bleeding into the intestinal lumen. The disrupted integrity of the small intestine and the consequent loss of selective mucosal permeability result in diffusion of lipopolysaccharides from naturally existing gram-negative bacteria and CPA from the intestinal lumen to the bloodstream, resulting in severe toxemia. Furthermore, tissue damage products absorbed into the bloodstream accentuate the toxemia. Functional or mechanical obstruction of the intestinal tract results in auto-intoxication because of prolonged intestinal transit time with subsequent absorption of toxic amines and phenols into the systemic circulation.

However, a potential association between the common mold, *Aspergillus fumigatus*, and JHS has also been suggested. Some scholars maintain that infection of dairy cattle by *A fumigatus* is the causative agent, an assumption that is based on 2 factors. First, there is a similarity between hemorrhagic conditions in cows with JHS and those in immunocompromised people with enteric hemorrhagic diseases caused by *A fumigatus*. In addition, *A fumigatus* DNA can be detected in samples of blood and intestinal contents obtained from cows with JHS but not in samples obtained from cows without JHS. In 2004, investigators conducted a survey of 25 cows that died as a result of various gastrointestinal tract diseases, including JHS. Blood and tissue samples were assayed for pathogens including *Salmonella* spp, bovine viral diarrhea virus, and *C perfringens* type A. Detection of *A fumigatus* DNA in blood and tissue samples was also undertaken with a quantitative PCR assay. Although *C perfringens* type A was isolated from a high percentage of cows that died of JHS or other gastrointestinal tract disorders, *A fumigatus* was associated only with cows that had died of JHS, not those that had died of other gastrointestinal tract diseases. However, it remains unclear whether the fungus is the primary insulting agent or if the fungal toxins impair a cow’s immune system, thereby facilitating a concurrent disease process.

*Aspergillus fumigatus* is a fairly common mold found in both hay and corn silage. Worldwide, approximately 25% of crops are affected by mycotoxins annually, and mycotoxins are frequently present in a variety of feedstuffs that are routinely fed to animals. It is hypothesized that in animals with mycoses, mycotoxins produced by the invading fungi can compromise immunity, thereby augmenting the infectivity of the fungus. *Aspergillus fumigatus*-contaminated silage may contain gliotoxin, tremorgens, fumigaclavine, and several furutremorgens, which are toxic to cattle.
Developing JHS. Bovine somatotropin has been shown to uniformly increase energy content in their TMR throughout the day. Whereas cows that were not on pasture received more ration, the nonpasture portion of the nation for this finding is that to enable cows to achieve their production potential, the high-energy, low-fiber ration would have been exceptionally high in calories, reducing target cell lysis. It is conceivable that gliotoxin restrains host defense mechanisms and encourages fungus virulence, ultimately resulting in JHS.

Risk Factors for Development of JHS

Cases of JHS in dairies in all regions in the United States and some European countries have been reported. A higher incidence in fall and winter months has been documented. In addition, approximately 60% of the cases occur within the first 100 days of lactation, and another 20% of the cases occur during midlactation. More than 90% of reported cases occur during the second lactation and in older cows. The high incidence early during lactation when a cow’s milk production and feed intake are both relatively high could be associated with nutritional factors because feeding a high-energy, low-fiber ration has been found to increase the risk of developing JHS. Although the precise mechanism of association is unclear, it may arise from situations where an inadequate rumen fiber raft or high dietary levels of rapidly available carbohydrate result in an overgrowth of excessive quantities of carbohydrates into a cow’s small intestine. This could provide the necessary environment for rapid multiplication and production of toxins by clostridial organisms that are natural inhabitants in the intestinal tract. An association between subacute rumen acidosis and JHS in dairy cattle has also been reported, adding weight to the notion that a high-energy, low-fiber ration is a crucial factor in initiating the disease process.

Pasture consumption has been associated with decreased risk of JHS development in dairy cattle. The mechanism for this decreased risk is unclear. Previous reports have suggested that JHS may develop less frequently during the pasture-rich seasons of spring and summer. Conversely, operations having rolling herd average milk production > 9,000 kg (20,000 lb) and that allow their cows to graze on pasture have greater risk of JHS development than do operations that do not allow lactating cows access to pasture. A conceivable explanation for this finding is that to enable cows to achieve their production potential, the nonpasture portion of the ration would have been exceptionally high in calories, whereas cows that were not on pasture received more uniform energy content in their TMR throughout the day. In dairy cattle, the use of bST increases their risk of developing JHS. Bovine somatotropin has been shown to increase the dry matter intake of treated cows and provides the greatest increase in milk yield. Thus, operations that use bST may generally feed rations that are more energy dense and treated cows are expected to consume more feed.

The quality and quantity of the protein mix that is added to the TMR may influence the risk of JHS development. It has been documented that dryage–derived proteins contain an unidentified factor that stimulates rapid growth and gas production by C perfringens type A in the intestinal tract. Adjustment of either protein quality or quantity in the ration of a dairy herd is highly crucial to enable cows to attain their maximum production limit. Assessment of MUN concentration in dairy cows has been recommended as an aid in monitoring the protein content of fed rations. Operations that routinely undertake MUN concentration monitoring have more reported cases of JHS, compared with findings for operations that never use MUN concentration monitoring. This could be attributed to the repeated alterations or modification of the ration with regard to protein quality or quantity undertaken by operations that routinely use MUN concentration monitoring.

Herd size is significantly associated with development of JHS. As the size of a herd increases, the likelihood of having at least 1 cow with clinical signs consistent with JHS increases. Thus, the risk factors for development of JHS in dairy cattle appear to be multifactorial. Any high-producing dairy cow that is in its second lactation and in the first 3-month period after calving and that is receiving a high-energy TMR and bST is an ideal candidate for development of JHS.

Clinical Findings Associated With JHS

The clinical signs and physical examination findings of JHS in cattle are highly reflective of the acute nature of the disease and the resultant gastrointestinal tract compromise (Table 1). The clinical signs in cows with JHS are rapidly progressive, and affected animals may be found either dead or dying. Because of the combined effects of patho-

Table 1—Clinical findings in cattle with JHS.

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>Frequency (No. of animals with clinical sign/total No. of animals with JHS [%])</th>
</tr>
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<tbody>
<tr>
<td>Signs of depression</td>
<td>101/107 (94)</td>
</tr>
<tr>
<td>Decrease in milk production</td>
<td>25/40 (62)</td>
</tr>
<tr>
<td>Decrease in feed intake</td>
<td>85/105 (81)</td>
</tr>
<tr>
<td>Decrease in rumen motility</td>
<td>82/98 (84)</td>
</tr>
<tr>
<td>Scant or reduced amount of feces</td>
<td>78/99 (79)</td>
</tr>
<tr>
<td>Melena</td>
<td>48/85 (56)</td>
</tr>
<tr>
<td>Bloody feces (blood clot)</td>
<td>21/97 (22)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>38/107 (36)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>30/100 (30)</td>
</tr>
<tr>
<td>Right-sided ping audible during percussion of the abdomen</td>
<td>66/88 (75)</td>
</tr>
<tr>
<td>Audible fluid splashing sound detected via ballottement of the right side of the abdomen</td>
<td>60/74 (81)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>71/106 (67)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>30/41 (73)</td>
</tr>
<tr>
<td>Pale mucous membranes</td>
<td>35/88 (40)</td>
</tr>
<tr>
<td>Muscle fasciculation</td>
<td>27/102 (26)</td>
</tr>
<tr>
<td>Distended loop of intestine palpable per rectum</td>
<td>48/100 (48)</td>
</tr>
<tr>
<td>Recumbency</td>
<td>09/100 (9)</td>
</tr>
</tbody>
</table>
logical changes in the intestines, massive hemorrhage into the small intestine, and severe toxemia (enterotoxemia), affected cows usually have sudden onset of signs of profound depression, anorexia, and decreased milk production. The extremities of affected animals are often cool, and rectal temperature is frequently abnormally low. In some instances, muscle fasciculations and recumbency have been recorded.6–8,45

With the onset of intestinal vasculature rhexis and the resultant blood suffusion within the affected segments of the intestinal tract, the intestines often become obstructed, causing some cows to develop abdominal distension, abdominal discomfort characterized by teeth grinding, dehydration, tachycardia, reduced fecal output, and melena or dark clotted blood in the feces. Decreased frequency and amplitude of rumen motility and audible fluid splashing sounds on ballottement of the right aspect of the abdomen and pinging during the simultaneous auscultation and percussion over the right middle portion of the abdomen are often detected. Clostridium perfringens type A is a gas-producing organism, and the aggressive multiplication of the organism produces large amount of gases in the proximal portion of the small intestine.46 The retrograde flow of these gases through the duodenum to the abomasum could ultimately result in abomasal dilation. This might explain the right-sided ping detected in 75% of cases6–8 and clarify why cows that eventually receive a diagnosis of JHS are often initially referred for management of a possible right-displaced abomasum. Transrectal palpation may reveal distended loops of the small intestine, an inflated cecum, a dilated colon, and a distended, firm rumen.6,7,45 However, in many instances, a rectal examination does not reveal distended loops of intestine because the blood-filled intestinal segments sink into the ventral portion of the abdomen and remain beyond the reach of the examiner.29 In advanced cases, intestinal necrosis takes place with subsequent peritonitis and finally toxic shock. Death of affected cattle occurs within several hours or may take up to 2 days following the onset of clinical signs.59

**Clinicopathologic Changes Associated With JHS**

The hematologic and serum biochemical abnormalities detected in cows with JHS are largely reflective of the acute nature of the disease and the resultant gastrointestinal tract stasis.6–8,45 Leukocytosis and neutrophilia with or without left shift are common he-

**Ultrasonographic Findings Associated With JHS**

Diagnostic ultrasonography with either a 5.0-MHz linear probe or 3.5-MHz convex transducer may be a reliable procedure for preliminary diagnosis of JHS in standing or recumbent cows. The ultrasonographic findings that are common in cows with JHS are dilation of the small intestine, usually the proximal portion of the jejunum, with thickening of the intestinal wall (Figure 1).5,46 The intestinal content is mostly echoic to hypoechoic, with or without localized hyperechoic masses that are consistent with blood clots (Figures 2 and 3). The blood clots in the intestinal lumen are specific findings of JHS but are seen in only 19.0% of affected cows.57

In animals with JHS, intestinal motility is absent or remarkably reduced and often accompanied with accumulation of fluid between the loops of intestine.56 Fibrin accumulation within the peritoneal fluid may also be observed in some cows, which indicates probable damage and perforation of the intestines, thereby allowing leakage of intestinal contents and ultimate-
matologic findings in cows with JHS. These findings may be attributed to the release of inflammatory cytokines and the subsequent release of neutrophils from the bone marrow or to stress-dependent alterations induced by the disease process. Serum biochemical analysis frequently reveals hypokalemia, hypochloremic metabolic alkalosis. These metabolic derangements are a direct result of the sequesetered abomasal secretions as well as the ongoing mechanical and functional proximal bowel obstruction.

Hyperglycemia is a common finding in cows with JHS. It has been a consistent finding in ruminants with clostridial-related enterotoxemia and is most likely due to a stress-dependent response and epinephrine release. Hypocalcemia, hypermagnesemia, and hyperglyceridemia have been reported, but these findings are not fully understood.

An increase in BUN concentration without a concurrent increase in serum creatinine concentration is frequently detected in dairy cattle with JHS. This finding has been used to suggest rumen stasis and gastrointestinal tract bleeding. Ruminants have unique rumen microflora that can assimilate BUN into amino acids. Furthermore, the microbial and enzymatic degradation of blood from gastrointestinal tract bleeding increases the intestinal concentration of ammonia; the ammonia is then delivered to the liver and converted to urea, contributing to the increase of BUN concentration without increasing serum creatinine concentration.

High serum activities of aspartate aminotransferase, sorbitol dehydrogenase, γ-glutamyl-transferase, and lactate dehydrogenase are frequently detected in cows with JHS. The increases in these enzyme activities are most likely a result of acute liver insult associated with proximal gastrointestinal tract obstruction or stasis and subsequent absorption of bacteria and toxins from areas of intestinal damage. High serum creatine kinase activity is also commonly observed, most likely a result of the recumbency and accompanying ischemic myodegeneration that affects many cows with JHS. In most affected cows, hypercholesterolemia and hypertriglyceridemia have been reported, but these findings are not fully understood.

**Exploratory Laparotomy and Necropsy Findings Associated With JHS**

In cattle with JHS, a common finding during exploratory surgery or necropsy examination is severe distention of the small intestine. Also common is devitalization of the proximal portion of the small intestine (mostly the jejunum and rarely the duodenum), the serosal surface of which develops a dark red to purple discoloration. In addition, frank blood is usually found in the intestinal lumen with or without blood clots and sloughed intestinal mucosa. In advanced cases, the affected segments of intestine are friable, turgid, and impacted with gelatin-like clotted blood casts and fibrin strands on the serosal surface of the jejunum.

The most prominent histopathologic finding is severe segmental submucosal hemorrhage and edema of the small intestine, especially the jejunum. This is often accompanied by a mixed segmental necrosis, ulceration, or complete epithelial sloughing with inflammatory cellular infiltration consisting primarily of neutrophils and gram-positive rods. In severe cases, total destruction of the mucosa with severe hemorrhages and hematomas in the submucosa, tunica muscularis, and serosa is frequently seen.

**Treatment of Cattle With JHS**

Early diagnosis and prompt intervention are important for treatment success in affected cattle. Medical management usually includes administration of fluids, analgesic agents, and anti-inflammatory drugs. Antimicrobials, most commonly penicillin G procaine administered SC at a dosage of 22,000 U/kg (10,000 U/lb) every 8 hours, are thought to be of value in addition to the administration of *C perfringens* types C and D antitoxin. Unfortunately, there is no specific antitoxin for CPA, but there may be some limited cross protection provided by the antitoxin of *C perfringens* types C and D.

Surgical intervention early in the course of the disease can be effective. Successful treatment has been achieved by opening the intestinal tract to remove the blood clots and any devitalized segments. Manual
clot dissolution without an enterotomy can also be attempted. However, in advanced cases, surgery is highly challenging. The involvement of multiple segments of jejunum or ileum is frequently found, which renders the option for intestinal resection and anastomosis unwieldy. Furthermore, intestinal perforation during surgical manipulation can easily occur; if this happens, development of diffuse septic peritonitis is inevitable. In many such situations, the cow is euthanatized intraoperatively.

In 2 studies examining outcomes of surgical intervention, a right paralumbar celiotomy was performed in 65 cows believed to be affected by JHS. Twenty-six cows were euthanatized intraoperatively because of grave prognosis, clot dissolution was carried out manually without an enterotomy in 29 cows, blood clot removal with enterotomy was attempted in 5 cows, and intestinal resection with anastomosis was performed in 9 cows. The results of these studies indicated that only 23 of the 65 cows survived following surgery, although no details were provided as to duration of survival. In another study involving 11 cows with JHS, of which 7 underwent surgery, neither medical nor surgical treatments were advantageous; 1 cow died and 10 were euthanatized as a result of grave prognosis.

**Strategies for Prevention of JHS**

Appropriate preventive strategies have not yet been determined, mainly because the exact etiology of JHS has not been defined. Dairy practitioners have begun to recommend certain approaches such as vaccinations, use of feed additives, and nutritional management to decrease the incidence of the disease on problematic farms. Although *Clostridium perfringens* type A infection has been strongly suggested as a potential cause of JHS in cattle, currently available vaccinations do not prevent development of JHS. As documented in a survey by the National Herd Monitoring System, most cows that develop JHS have been vaccinated against *Clostridium perfringens* in the preceding 12 months. The commonly used vaccines are only directed against *Clostridium perfringens* types C and D and may not provide satisfactory cross protection against type A toxins. Furthermore, increasing the use of these clostridial vaccines in operations where cattle have developed JHS is not likely to be helpful in preventing additional cases. The efficacy of a commercially available toxoid directed solely against *Clostridium perfringens* type A has not yet been established, and anecdotal reports are available for its efficacy.

Recently, practitioners have become more interested in the development of autogenous vaccines (bacterin-toxoids) against *Clostridium perfringens* type A isolates from affected herds. To be effective, products must be made from fermentation processes maximized for growth and toxin production of a genotypically appropriate *Clostridium perfringens* type A.

The average milk production per cow during lactation has increased significantly during the last 2 decades. To achieve this level of production, the energy in a dairy ration is maintained at the highest possible level to allow cows to maximize their production potential. The use of highly concentrated feeds to achieve maximal productivity must be tempered to avoid development of disorders commonly associated with rumen acidosis. Although JHS is an infrequent and mostly sporadic disease syndrome, an association between subacute rumen acidosis and JHS has been reported. Therefore, operations that have had cases of JHS should monitor and control subacute ruminal acidosis, investigate ration fermentable carbohydrate and fiber levels, adjust ration particle size, and manage bunk space to minimize sorting by the cows. The ration should be balanced to provide an adequate level of effective fiber to maintain good rumen health and integrity of the rumen raft. Problematic operations should discontinue feeding poorly ensiled feedstuffs as well as work with nutritionists to evaluate forages with regard to component nutrients, moisture, temperature, and pH, in addition to monitoring for mycotoxins. Recently, a mold inhibitor has been added to the feed in some dairy operations to reduce the incidence of JHS. Consumption of the product has been demonstrated to improve certain indicators of leukocyte immune function in immunosuppressed sheep.

**References**


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*a.* *Clostridium perfringens* type A toxoid, Novartis Animal Health US Inc, Greensboro, NC.

*b.* Omnigen AF, Prince Agri Products Inc, Quincy, Ill.