“The Oncotic Adventure of Bo Luther”

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Introduction

Salmonella enterica is one of the most common causes of diarrhea in adult horses.[1] It can be spread by feco-oral transmission from subclinically or clinically infected animals.[2] Usually the onset of clinical disease is activated by stressful events, such as surgery, or more direct gastrointestinal insults that increase susceptibility of the intestinal mucosa to adherence and penetration by the microbe. Once the horse has been diagnosed with Salmonellosis using fecal culture, particularly when coupled with clinical signs of lethargy and foul-smelling diarrhea, isolation from the remainder of the herd is recommended to prevent further transmission of the pathogen.[3] Salmonellosis can progress to septicemia and eventual death.[2] The goals of therapy are to address pain, dehydration, toxemia, maintain colloid oncotic pressure and optimize mucosal healing. Laminitis is a major complication of Salmonellosis in horses. Accordingly, therapies directed at preventing laminitis are also integral to treatment. Administration of antimicrobials to adult horses with Salmonellosis is controversial, with some clinicians favoring broad-spectrum parenteral antimicrobials, particularly in horses with neutropenia.

Salmonellosis is a zoonotic disease that can be passed to humans through contaminated or undercooked food and after interaction with infected animals.[4] The combination of this zoonotic potential and the potential for transmission to other animals supports the need for proper isolation protocols that include gloves, gowns and booties, in association with frequent handwashing and disinfection.

History and Physical Examination

Bo is a sixteen year-old Quarter Horse gelding who presented to MSU-CVM Equine Department on 6/2/2019 for hindlimb swelling, which was worse in the right rear limb. The owner first noticed this problem when she got home the previous evening, after being gone all morning and afternoon. There was no history of recent injections in either limb. She had administered one scoop of Anti-Hist granules before heading to MSU-CVM. A few months prior, the owner mentioned there was

a hay spoilage incident. Two goats died after eating the hay and her father was hospitalized following contact with the hay. Bo had access, but at that time there had been no evidence of disease. Bo was housed in a pasture with two other horses. His diet consisted of 3 pounds of 12% sweet feed twice daily. He had not been vaccinated nor did he have a Coggins test within the previous year. Bo had been dewormed, had his teeth floated and sheath cleaned, and his feet trimmed in the six months prior to presentation.

Upon presentation, Bo was depressed, but responsive. He weighed 886 pounds with a body condition score of 3/9. His rectal temperature (101.0 ^{o}F) and respiratory rate (16/min) were normal, but he was tachycardic (64 beats/min). He had pink and moist mucous membranes with a normal capillary refill time of less than two seconds. On auscultation, no arrhythmias, murmurs, crackles, or wheezes were appreciated. Normal gastrointestinal motility was heard in the lower quadrants, and decreased motility was noted in the upper quadrants. Digital pulses were normal in all four limbs. The submandibular lymph nodes were palpable, but within normal limits. The right hindlimb was noted to be severely edematous from the stifle to fetlock. The left hindlimb was mildly edematous, primarily in the fetlock region. Though Bo walked with a stiff gait in both rear limbs, neither heat nor pain were identified on palpation. Ventral edema was noted in the chest and prepuce. Alopecia was noted along the dorsum and both hocks, and lice were evident throughout his coat, with a large number evident in his mane.

Initial Problem List and Differential Diagnoses

The initial problem list included 1) bilateral rear limb swelling without heat or pain; 2) ventral edema; 3) tachycardia; and 4) dorsal dermatitis with pediculosis. Differential diagnosis considered for the rear limb swelling included infectious and non-infectious inflammatory cellulitis or myositis, etiologies of edema including decreased oncotic pressure and increased hydrostatic pressure, as well as trauma and neoplasia. Decreased oncotic pressure and increased hydrostatic pressure were also considered in the etiopathogenesis of the ventral edema. Decreased lymphatic drainage associated with

the observed rear limb swelling was considered to be, at the least, a contributing factor to the ventral edema. The primary etiologies considered initially for tachycardia included pain, extracellular fluid volume depletion, excitement, cardiac disease, septic shock, and electrolyte abnormalities. The initial diagnostic plan included CBC, serum biochemistry profile, thoracic and abdominal ultrasound.

Case Progression

Complete blood count demonstrated a leukocytosis characterized by a profound mature neutrophilia (30,495 neutrophils/ul, N: 2500-6000), lymphopenia (963/u, N: 1500-7700/u), monocytosis (642/ul, N<500/ul) and hyperfibrinogenemia (600 mg/dl, N: 100-400 mg/dl). Though a component of stress could not be ruled out, the profound neutrophilia coupled with hyperfibrinogenemia were considered evidence of a severe infectious nidus or, less likely, a non-infectious inflammatory nidus with some degree of chronicity. The serum biochemistry panel identified hyponatremia (119.5 mmol/L; N:132-146 mmol/L), hypochloremia (95.8 mmol/L; N:98-106 mmol/L), hypocalcemia (8.9 mg/dl; N: 11.2-13.6 mg/dl), hypomagnesemia (1.1 mg/dl; N:1.6-2.5 mg/dl), and hypoproteinemia (total protein: 5.1 g/dl) characterized by hypoalbuminemia (1.5 g/dl; N: 2.9-4.1 g/dl). Osmolality was decreased (233 mOsm/kg; N: 280-310 mOsm) due to hyponatremia. Evaluation of the thorax via ultrasound demonstrated a mild increase in fluid in both the ventral thoracic cavity and the pericardial sac. Increased fluid was also noted in the ventral abdomen via ultrasound. Gastrointestinal motility was within normal limits, and the colon wall was thickened.

Extending from the profound hypoalbuminemia that was identified, ventral and rear limb edema, along with increased thoracic, abdominal and pericardial fluid were attributed primarily to decreased oncotic pressure. Hypoalbuminemia results from decreased production, increased loss, and third space sequestration. While normal liver enzymes (GGT, AST) ruled out decreased ability of the liver to synthesize albumin, some degree of Bo's hypoalbuminemia could be attributed to decreased production associated with malnutrition. Significantly, Bo's CBC demonstrated a profound inflammatory response. In horses and many other species, albumin is a negative acute phase protein.[16]

Accordingly, this reported shift away from albumin synthesis during inflammation was clearly relevant for Bo. Albumin loss via the kidney and gastrointestinal tract are the most common etiologies for hypoalbuminema. Normal renal parameters (and a low cholesterol/absence of lipemia ruling out nephrotic syndrome) decreased the likelihood of such profound hypoalbuminemia having a renal origin. Unfortunately, urine protein was not evaluated. Considered with evidence of colon thickening on ultrasound and the presence of hyponatremia and hypochloremia, gastrointestinal albumin loss via heavy parasitism and/or colitis were considered likely. Accordingly, parasite ova were evaluated in the feces (eggs per gram of feces).

Hypomagnesemia and hypocalcemia were considered contributing factors in Bo's tachycardia. Hypoalbuminemia confounds interpretation of decreased serum calcium concentrations, but the magnitude of Bo's hypocalcemia was considered relevant to the observed tachycardia. Ionized calcium quantification would have been useful in clarifying the relationship between hypocalcemia and tachycardia but was not pursued for financial reasons. The aforementioned evidence of colonic disease coupled with profound inflammatory leukogram also supported sepsis as an etiology for Bo's tachycardia.

Following the initial work up, a coagulation profile was performed. When the profile was found to be within normal limits, two liters of hydroxyethyl starch were administered intravenously over a period of several hours to address evidence of clinically relevant decreased oncotic pressure. Flunixin meglumine (1.1 mg/kg q12 h) was also initiated for its anti-inflammatory effects. As the patient was afebrile and the nidus of inflammation remained unclear, antimicrobial considerations were to be re-evaluated in the morning.

The morning of 6/3/19, Bo's attitude ranged between bright and depressed. He had been eating and drinking well through the night. His ventral abdominal edema had increased, and two soft fecal piles were noted. Thoracic radiographs were within normal limits, ruling out pneumonia as the source of the inflammatory leukogram. His sheath was evaluated, and no masses were identified. 12 strongyle

type eggs per gram of feces were identified. Though this value is not considered actionable, this test does not rule out larval cyathostomiasis. A repeat CBC identified a decrease in the mature neutrophil count from that of admission (14274/ul) and no change in hyperfibrinogenemia (600 mg/dl), confirming that a portion of the neutrophilia, monocytosis and lymphopenia at admission were attributable to stress (and also decreasing the likelihood of Addison's disease as relevant to the hyponatremia, based upon the ability to mount a stress leukogram). Serum biochemistry panel indicated that chloride and magnesium were within normal limits while hyponatremia (128.8 mmol/L) and hypocalcemia (9.5 mg/dl) were improving. Slight decreases in serum creatinine (1.04 mg/dl), total CO_2 (23.8 mEq/L) and albumin (1.4 mg/dl) were also noted. Treatment consisted of 2 liters of hetastarch IV, flunixin meglumine (1.1 mg/kg IV q12 h), and hydrotherapy of the rear limbs followed by a nitrofurazone sweat wrap. A pyrethrin spray was applied to treat the pediculosis and antimicrobial therapy was initiated (chloramphenicol 50 mg/kg q6 hours).

From days 3 through 7 of hospitalization, Bo developed more severe diarrhea. On day 5, Bo's admission fecal culture for Salmonella was positive, and he was moved to isolation. At least half of his fecal outputs were projectile liquid with the remaining being cow pie in consistency. During this period, he was able to address his fluid needs via oral intake, without intravenous fluid supplementation. His appetite, which had decreased after initiating chloramphenicol, gradually improved and he began grazing. Treatments included chloramphenicol (50 mg/kg orally q6 hours), probiotics, and Biosponge (2-4 pounds per 24 hours on days 6 and 7). On day 7 his mucous membranes were noted to be more injected. CBC demonstrated a progression of the prior neutrophilic leukocytosis (16,965 neutrophils/ul) with monocytosis (780/ul) and hypofibrinogenemia (100 mg/dl) while plasma sodium, potassium, chloride and total CO_2 remained unchanged from their prior values, which were near normal. Flunixin meglumine was reinstituted (1.1 mg/kg q24 hours on days 7 and 8). In the early morning of day 8, progression was noted in the severity of diarrhea, tachycardia,

depression, and injected mucous membranes. Supplementation with intravenous fluids was deemed necessary (lactated ringers 2 L/hour). Throughout this time Bo continued to eat and drink.

Case Outcome

Due to financial constraints, the owner elected to euthanize Bo on day 8. Gross examination during necropsy revealed diarrhea staining in the perineal region and on the hindlimbs. Widespread serous atrophy of fat was identified, including in peri-renal, omental fat and fat overlying the abdominal muscles, colon, and base of the heart. There was increased opaque, yellow and watery fluid within the abdominal and thoracic cavities (about one half liter in each cavity).

The small and large intestines were diffusely distended by fluid with the wall of the right ventral colon thickened, edematous, and reddened. Histologic examination of the colon and cecum identified diffuse typhlocolitis, characterized by severe lymphoplasmacytic inflammation with ulceration and necrosis. Diffuse transmural edema with marked lymphatic vessel dilation, as well as marked leukocytic inflammation and congestion of the submucosal vessels were also evident. Frequent encysted cyathostome species were noted within the cecum and colon. In the small intestine, duodenal villi were atrophied with loss of crypts and moderate expansion of the lamina propria by edema, lymphocytes, plasma cells and occasional eosinophils. Hyperplasia of goblet cells was noted. In addition, the lamina propria of the esophagus was infiltrated by a large number of lymphocytes with fewer plasma cells and macrophages.

Histologic examination of the liver demonstrated severe chronic periportal megalocytosis of hepatocytes along with significant anisocytosis and anisokaryosis of hepatocytes within portal regions with occasional mitotic figures. Within the lung tissue, septae were mildly expanded by increased clear space. There were increased numbers of fibroblasts and collagen surrounding large airways and vessels and approximately 30% of alveoli were flooded with homogenous light pink fluid and large numbers of circulating neutrophils. All other organs were observed to be within normal limits.

Pathophysiology

Salmonella enterica subspecies *enterica*, a gram-negative, facultative anaerobic bacteria, is a common cause of diarrhea in adult horses[2]. There are more than 2000 serovars of *Salmonella enterica* subspecies *enterica*, and the most common serovars causing equine disease include Typhimurium, Newport, and Agona.[11] The organism is commonly spread through fecal-oral transmission from feed and water that has been contaminated by rodent and farm animal species that carry and shed the organism.[6] Shedding from horses can be increased by stressful events, intense physical activity, antimicrobial treatment, surgery and gastrointestinal tract disorders.[3] Though uncommon, the organism can also be transmitted through aerosol droplets.[2] *Salmonellae* tend to be stable and adapt to the environment, remaining viable in soil and water for protracted periods (300 days in soil and nine months in water).[2]

In the case of equine diarrhea, ingested *Salmonellae* reach the colon and deploy pathogenic factors that interact with the Microfold (M) cells and enterocytes to enable penetration of the epithelial cells of the intestinal lining.[1] During this attachment phase, remodeling of the cell membrane leads to lamellipodial extension and enveloping of the bacteria.[1] Once the bacteria invade the intestinal epithelium, endotoxins, exotoxins, cytotoxins and enterotoxins are produced by *Salmonella* and cause diarrhea.[7] For example, endotoxins damage blood vessels in the region, leading to disseminated intravascular coagulation.[7] More invasive strains may also invade into the lymphatic system following ingestion by macrophages, leading to an inflammatory response in the regional lymph nodes.[1] These collective events lead to intestinal malabsorption, progressing to diarrhea and septicemia.[7]

There are three forms of enteric Salmonellosis in horses: subclinical, mild clinical and acute.[8] The subclinical form is characterized by an absence of overt clinical signs.[8] Approximately 3% of horses can be diagnosed as subclinical carriers.[7] These individuals are considered to be carriers of the disease that can cycle through periods of active shedding with intervening periods in which they do not shed. Clinical signs associated with the mild acute form include lethargy, pyrexia, anorexia, and soft feces.[8] This stage is typically self-limiting, lasting about four to five days. Clinical signs of acute

salmonellosis include lethargy, anorexia, tachycardia, profound neutropenia, abdominal pain and foul-smelling diarrhea.[13] Diarrhea may be evident within 6 to 48 hours following the onset of the fever.[13] Dehydration occurs rapidly due to the profound transmural loss of fluids into the colon lumen. Transmural electrolyte and protein losses lead to hyponatremia, hypochloridemia, hypokalemia and protein losing enteropathy.[15] Sepsis, hypovolemic shock and electrolyte abnormalities rapidly progress as the disease continues. Mucous membranes similarly progress from injected to dark red to purple as an indicator of progressive sepsis. Colic may be evident due to severe ileus, gas distention and colonic inflammation.[13] Progression of disease results in multiple organ dysfunction syndrome including laminitis, hepatitis, disseminated intravascular coagulation and eventually culminating in death.[6] Recovered horses can shed *Salmonellae* for several months. To prevent spreading within the herd, it is recommended that affected horses be quarantined until shedding is no longer detected.[3]

The primary differential diagnoses for enteric Salmonellosis in adult horses include larval cyathostomiasis, Potomac horse fever, equine coronavirus, enteric Clostridiosis (*Clostridium perfringens* and *Clostridium difficile*), right dorsal colitis, inflammatory bowel disease, neoplasia, and peritonitis.[5] To rule out these differentials, PCR testing for representative toxin DNA or DNA from the respective organism, as well as ultrasound, xylose absorption, and abdominocentesis may be performed.[5] Historical findings may be particularly beneficial in discerning the relevance of particular differential diagnoses. Diagnosis of Salmonellosis is typically affiliated with clinical signs, history of a stressful event, and severe neutropenia.[5] The disease is most commonly diagnosed by isolating the organism via fecal culture.[2] A fecal sample should be collected once a day for five days, due to the tendency for intermittent shedding.[2] Isolates should be serotyped and tested for antibiotic susceptibility. Samples with greater liquid content have been shown to have a lower sensitivity due to a decrease in organism concentration in the sample.[8] Culturing the rectal mucosa through a biopsy may increase the chances of isolating the organism, but may increase the risk of septicemia in the horse.[2]

Real-time PCR on feces has been demonstrated to be more sensitive than the culture, and is typically used in conjunction with fecal culture to provide more rapid diagnosis.[2,8]

Necropsy of an infected horse can facilitate diagnosis, with the hallmark finding being typhlocolitis from which the organism is isolated.[6] Fibrinous or hemorrhagic inflammation of the cecum and colon with the mucosa showing superficial necrosis and grayish pseudomembranes are commonly noted. Ulceration can be observed in chronic cases. Other common findings include mesenteric lymphadenopathy with hemorrhage and edema, gastric hyperemia, and congestion of the small intestine with mucoid or hemorrhagic exudate. Culture can be acquired post mortem for definitive diagnosis via punch biopsy of the rectal mucosa, wall of the cecum, large colon, ileum, mesenteric lymph nodes or spleen.[2]

Horses diagnosed with salmonellosis should be isolated to prevent the spread of disease.[6] Aggressive treatment may be necessary to prevent or address fluid and electrolyte losses, metabolic acidosis, septicemia and laminitis.[9] Intravenous isotonic polyionic fluid administration is a mainstay of therapy to address fluid losses. Supplemental colloid therapy, including plasma and hetastarch, may be indicated to address hypoproteinemia.[14] Hydration, electrolytes, albumin, total protein, oncotic pressure and acid-base status should be regularly monitored as these parameters can rapidly change in diseased horses. As commercially prepared fluids are deficient in potassium, calcium and magnesium, supplementation with potassium chloride, calcium gluconate, and magnesium sulfate may be indicated.[14] Due diligence to avoid over or under supplementation is warranted.[2] Sodium bicarbonate therapy should be restricted to those rare individuals in which fluid supplementation and electrolyte normalization fail to address acidosis.

Antimicrobial administration to horses with suspected or confirmed *Salmonellae* diarrhea is controversial.[1] In most studies, antimicrobials such as chloramphenicol, trimethoprim-sulfadiazine, gentamicin and cephalosporin do not accelerate the resolution of colitis. Though antimicrobials may not aid in the acceleration of treatment of the enteric disease process, they may aid in the prevention of

bacteremia.[1] Antimicrobial resistant strains are becoming prominent, so a culture and sensitivity is advised prior to antimicrobial administration. Due to the increase in drug resistant strains, antimicrobial usage should primarily be reserved for foals and immunocompromised individuals in which translocation across the mucosa has been well documented.[1]

Other forms of treatment include gastrointestinal protectants and non-steroidal anti-inflammatory agents (NSAIDs).[9] While gastrointestinal protectants such as omeprazole and H_2 antagonists do not improve colon healing, they do aid in the prevention of gastric ulcers that can arise as a consequence of anorexia in horses.[9] BioSponge, or di-tri-octahedral smectite, is an orally administered medication that has been demonstrated to bind to a variety of bacterial toxins, effectively preventing their absorption, while not interfering with the activity of commonly administered oral antimicrobials.[12] Polymyxin B, by contrast, is an intravenously administered antimicrobial agent that irreversibly binds to lipopolysaccharide (LPS), preventing its interaction with host immune cells which triggers inflammatory cascades.[9] Hyperimmune serum presents another method of neutralizing the endotoxins that can be released by Salmonella, effectively modulating leukocyte activation.[9] This product is derived from horses that have been immunized with gram negative bacteria that have been genetically modified to confer a degree of cross-protection across multiple gram-negative enteric species.[9]

NSAIDs, like flunixin meglumine and ketoprofen, aid in counteracting the inflammation associated with GI derived toxins, including LPS, by inhibiting the cyclooxygenase enzymes.[9] As a consequence of this activity, NSAIDs also provide analgesia and aid in the prevention of inflammatory cascades of relevance to laminitis.[9] NSAIDs have well recognized side effects in horses, including gastrointestinal ulceration, renal papillary necrosis, and right dorsal colitis (which are of greatest concern in dehydrated animals). However, it is important to recognize that flunixin meglumine (and other NSAIDs that inhibit both COX1 and COX2) have been demonstrated to inhibit enterocyte healing. Accordingly, NSAIDs of this class should be employed judiciously in horses with colitis.[9]

It is critical to recognize the potential risk of laminitis in horses with enteric Salmonellosis, prior to the onset of signs. Currently, the only effective preventive therapy for equine laminitis is cryotherapy, i.e. emersion of the distal limb in ice (from the carpus or hock to the foot).[13] This therapy has been demonstrated to not only prevent the onset of laminitis, but to prevent the progression of clinically recognizable laminitis. Employing this therapeutic modality early in the course of therapy, particularly in horses demonstrating evidence of systemic inflammatory response, is vital since many horses who could be saved from enteric Salmonellosis are euthanized because of the poor prognosis that accompanies severe laminitis.

People contract Salmonellosis by eating contaminated, undercooked meat or not washing their hands after interacting with contaminated animals and their surroundings.[4] People who are most at risk include infants, immune compromised individuals, and adults over 65 years of age.[4] Given the significant zoonotic potential of horses that have enteric *Salmonellosis*[4], individuals interacting with affected horses should be vigilant with regards to handwashing and disinfection, in order to prevent transmission. As previously indicated, personal protective equipment including gowns and gloves can also be employed, particularly by individuals who will be moving between affected and non-affected horses on the same premise. Food and water should not be ingested by people near contaminated areas.[4]

Conclusion

Salmonella is one of the common causes of equine adult diarrhea. Clinical signs include lethargy, anorexia, tachycardia, profound neutropenia, abdominal pain and foul-smelling diarrhea. Not all horses who are infected will show overt clinical signs. The horse in this case report presented with relatively mild clinical signs, despite clinical pathology findings that supported more severe, chronic and compensated enteric disease. Necropsy confirmed significant typhlocolitis from which *Salmonella enterica* subspc *enterica* serovar Newport was identified. Horses diagnosed with enteric Salmonellosis via fecal culture should be isolated from the herd to limit spread of the disease. Treatment is primarily

supportive and directed at controlling pain, dehydration, and toxemia, while maintaining colloid oncotic pressure and optimizing mucosal healing. Laminitis is a major complication of enteric Salmonellosis in horses, making therapies directed at preventing laminitis integral to treatment. While antibiotic therapy is currently controversial for treating the enteric insult, antimicrobials should be administered where the risk of sepsis is considered to be high. Prognosis is proportional to the response to therapy, and therapeutic management of acute severe cases can quickly become cost intensive.

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