Antibiotic Induced *Clostridium* Colitis In the Horse

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Abstract: Antibiotic induced *Clostridium* colitis is a common problem of horses admitted into hospitals. *Clostridial* diarrhea has been associated with many factors that may alter the balance of intestinal flora, such as administration of antibiotics or withholding feed prior to surgery, but has also occurred in absence of any identifiable risk factors. This report describes a case of antibiotic induced *Clostridium* colitis post myelogram, including the sequela of the colitis and the treatment of the disease process. Differentials for post operative colitis are discussed as are diagnostics used to rule out these differentials.

Introduction:

Antibiotic induced *Clostridium* colitis is not an uncommon problem in tertiary care equine hospitals. This disease process will result in hyperemic mucus membranes, decreased capillary fill times, dehydration, protein losing enteropathy, endotoxemia and laminitis. The pathogenesis has not yet been completely mapped out, but the underlying disruption of the hindgut's microflora seems to be a common trigger of this disease. Risk factors, including antibiotics and hospitalization, have been identified as triggers for antibiotic induced *Clostridium* colitis, but their exact role has yet to have been elucidated.[1] Treatment goals aim to mitigate the effects of endotoxemia, provide gastroprotection and prevent the development of laminitis.

Treatment can span for weeks and cost thousands of dollars, and mortality secondary to *Clostridium* colitis is 26%.[2]

Case Details:

Presentation:

A 7 year old QH appendix gelding from Maryland presented to the Cornell University Equine Hospital for an evaluation of muscle atrophy and stumbling, increased tail twitching and occasionally posturing to urinate starting around June of 2010. He was used as an English pleasure horse. All prior testing for Equine Protozoal Myelitis by the rDVM had been negative (IFA, Sag 2,3,4). Prior cervical and pelvic radiographs were unremarkable. His owner reported that he "buckled under" in his pelvic limbs while under saddle, and had tripped and fallen to his carpi on several occasions. His rDVM requested a myelogram and further diagnostics.

On physical exam, the horse was bright, alert and in good spirits. His cranial nerve exam was within normal limits, although mild multifocal muscle fasciculations on his muzzle were noted. These were of questionable significance and resolved over time. He was noted to have a series of dermoid cysts along his midline dorsum that his owner stated he had had for years without issue. He was noted to have mild atrophy over his epaxial muscles and moderate atrophy over his rump on both sides, although slightly more pronounced on his left side.

During his neurologic evaluation he did not fall, and would readily catch himself when his tail was pulled to either side. He was slightly lame in his left thoracic limb, consistently dragged his right front toe and was base narrow gait in the rear. He was able to navigate curbs and inclined slopes with minimal trouble but would occasionally catch his right front toe. He circled more easily to the left than to the right, and stepped on himself and circumducted (would swing wide) with his hind limbs while circling to the right; he walked well with his head

elevated. The differential diagnoses included Equine Protozoal Myeloencephalitis, Polysaccharide Storage Myopathy, Equine Motor Neuron Disease, Equine Degenerative Myelopathy, Immune Mediated Myositis, Cervical Vertebral Malformation (Wobbler's Disease), and Primary Myocellular Membrane Dysfunction.

He was held off feed, and placed on trimethaprim-sulfa and metronidazole to combat the risk of aspiration pneumonia in preparation for general anesthesia the following morning.

Case Progression:

Day 2: The following morning, he was induced under general anesthesia for a myelogram, an electromyogram and muscle biopsies. The myelogram (with both natural and flexed views), was unremarkable and the electromyogram (along his left topline and right shoulder area), did not indicate neuromuscular dysfunction. Fine needle aspirates were also taken of the cyst like structures along his topline which later cytology revealed to be insignificant dermoid cysts. Muscle biopsies were taken from the superficial gluteal, sacrocaudalis dorsalis, and semitendinosis muscles. Each biopsy site was closed with continuous pattern absorbable suture. He was given 500mg of flunixin meglumine intravenously to reduce any pain and inflammation associated with the myelogram and biopsies.

The horse was noted to have a very prolonged recovery from anesthesia, laying laterally for over an hour. He was ataxic exiting the recovery stall. About 45 minutes later, he had a slight left head tilt and was blind in the left eye. His PLR was normal. He became difficult to handle and belligerent; this was a marked change from his usual easy going personality. He was moved to a padded stall; aggressive anti-inflammatory treatment was administered to reduce cerebral swelling and consisted of mannitol (0.5g/kg IV), dexamethasone (0.1mg/kg IV) and 5g

of thiamine (10mg/kg IV) as a neuroprotectant. His appetite was good and his other vitals were within normal limits.

Day 3: The horse's blindness and head tilt had resolved. Although he was still quiet in his stall, his vitals were within normal limits, and his gastrointestinal tract motility was considered within normal limitis. For the next 24 hours, the horse's vital condition was unremarkable. Although he had a normal physical two hours prior, when he was ready to be discharged to the care of his owners, he showed signs of mild colic (laying down and flank watching). His physical examination at that time identified mild abdominal distention and a slightly increased temperature (101.2F). A rectal exam revealed a pelvic flexure impaction and soft manure within the rectum. A half gallon of mineral oil (lubrication for impaction) and three pounds of biosponge in warm water were pumped through his nasogastric tube; biosponge binds *Clostridium* toxins which may be present if he were to be developing an antibiotic associated diarrhea/colitis and simultaneously firms the stool. He was given 80mg of xylazine and a half dose (250mg) of flunixin meglumine for pain. Within a period of several hours, the horse developed mild endotoxemia. This was evidenced by his elevated heart rate, dark red tacky mucus membranes, muscle tremors, depression, dark brown urine, elevated renal values and elevated hematocrit. An IV catheter was placed and IV fluids were administered overnight.

Our differentials at this point included infectious colitis (secondary to *Salmonella, Cl. difficile, or Cl. perfringens*), right dorsal colitis (secondary to NSAID administration), or peritonitis (secondary to intestinal rupture). The diagnosis was narrowed by the following means: A fecal culture was submitted for *Salmonella* isolation, which was negative on initially admission, but resubmitted given the horse's clinical signs. (This later came back negative). A fecal ELISA for *Clostridial difficile* toxins A and B was done which initially came back

negative, but upon resubmission several days later came back positive for *Clostridium difficile.* An ELISA against *Cl. Perfringens enterotoxin* was also negative, and abdominal ultrasound ruled out right dorsal colitis and peritonitis.

Day 4: The horse had become extremely endotoxemic overnight as evident by the red/purple mucus membranes with toxic lines, cold extremities, weak peripheral pulse pressure, profuse pipe-stream diarrhea, muscle tremors, and inappetance. Clinical pathlogy data revealed a leukopenia (5.1 thousand/uL, normal 5.2-10.1 thousand/uL), and a neutropenia with bands and toxic changes (0.8 thousand/uL, normal 2.7-6.6 thousand/uL). It also revealed the presence of azotemia creatinine was 2.8 mg/dL (normal 0.9-1.8 mg/dL) and a decrease in the hematocrit (32% normal 34-46%). Aggressive therapy was instituted to treat the endotoxemia and hemodynamic collapse consisting of hypertonic saline to expand the intravascular volume, intravenous plasma for its anti-endotoxic and colloidal enhancing properties, intravenous hetastarch to increase oncotic pressure, isotonic fluids, and a lidocaine continuous rate intravenous infusion for pain relief. Oral biosponge as a *Clostridium* toxin binder was also administered. Flunixin meglamine was given as an anti-inflammatory and analgesic, as was pentoxifylline as an anti-inflammatory and to increase distal limb blood flow. His hooves were iced every four hours in an effort to prevent the development of laminitis. Misoprostol was given to increase colon healing and gastric blood flow, as was omeprazole as a gastroprotectant. Broad spectrum antibiotics (enrofloxacin, metronidazole, and penicillin) were given to reduce bacterial translocation from the compromised intestinal mucosa.

Days 5-7: Over a period of the next couple days, his renal values (Creatinine 1.3 mg/dl), appetite, mucus membranes and heart rate gradually normalized. He remained mildly neutropenic with bands (2.7 thousand/uL and 0.5 thousand/uL respectively).

Days 8-11: Pipestream diarrhea continued throughout this period, and his total protein levels began dropping significantly (3.3g/dl, normal 5.2-7.8 g/dl). Multiple doses of hetastarch were administered to combat his falling oncotic pressure, which had resulted in ventral and preputial edema. Treatments of low dose flunixin meglamine, pentoxifylline, misoprostol, omeprazole, broad spectrum antibiotics and distal limb icing were continued. He was also maintained on maintenance fluids with 20 mEq/L of potassium.

Day 12: The horse's bloodwork showed no toxic changes in his neutrophils, indicating that his endoxemia was resolving and his laminitis risk was minimal at this point. Because of this, ice boots, pentoxifylline, penicillin, enrofloxacin and fluids were discontinued. Metronidazole and gastroprotectant treatments were continued.

Days 13-15: During this time, the horse's metronidazole dose was decreased. A hemogram and chemistry panel were repeated, which revealed a neutrophilia of 9.7 thou/uL (normal 2.7-6.6 thou/uL), which was expected following a neutropenia from his colitis. The chemistry panel revealed that his hyponatremia had improved to 132 g/dL (normal 134-141mEq/L), his bicarbonate was increased (33 mEq/L, normal 24-31mEq/L) and anion gap was low at 6 (normal 8-19); these abnormalities were attributed to his diarrhea. His packed cell volume and total protein were 35% and 3.0 g/dL respectively. The horse continued to have a good appetite and his blood work and physical state remained stable for the next couple days.

Day 16: The horse's appetite seemed mildly decreased and his manure again became very soft; however his gut sounds were within normal limits and his temperature was normal (99.7F). A dose of biosponge was administered to bind any *Cl. difficile* toxins in his gastrointestinal tract and a fecal sample was submitted for *Cl. difficile* toxin A/B testing, which was negative. His PCV/TP were repeated and found to be 38% and 3.0g/dL, indicating that his protein levels were

stable, and his colloid oncotic pressure was measured and found to be 7.9 mmHg. His plaque of non-painful pitting ventral edema had begun to decrease overnight. He continued to have soft manure during the day; however he remained bright and his temperature was always within normal limits. The metronidazole was increased in frequency back to every 6 hours, his misoprostol was decreased to 500ug PO BID, and he was restarted on omeprazole. The described medication changes were due to the return of soft manure. This return of diarrhea may be part of a normal disease process often associated with colitis in horses, as they often present with cyclic diarrhea as the hind gut flora slowly returns to normal.

Day 17: The horse's manure was again formed and his appetite had returned to normal. His PCV and total protein remained stable at 38% and 3.2g/dL respectively. He was continued on metronidazole (7g PO QID), misoprostol (500ug PO BID) and omeprazole (1 tube PO SID) and was discharged to the care of his owners.

Discussion:

While treating this horse's life threatening *Clostridium* colitis, it was easy to overlook why this horse initially came to Cornell. He was admitted to the Cornell Equine Hospital for an evaluation of his muscle wasting and intermittent ataxia under saddle.

Our differentials again included:

1. EPM (Equine Protozoal Myeloencephalitis): At least two protozoal parasites cause EPM, these are *Sarcocystis neurona* and less commonly, *Neospora hughesi.*

2. Polysaccharide Storage Myopathy (PSSM): This is a disease of an abnormality of sugar metabolism and storage within muscle cells of quarter horses, draft horses, and a variety of other breeds of horses. Muscle atrophy and an abnormal gait are characteristic of this disease, which

can be treated with a high fat diet and routine, regular exercise. A semitendinosis muscle biopsy will usually confirm the diagnosis of this disease process.

3. Equine Motor Neuron Disease (EMND): This is a neurologic disorder of adult horses which results from oxidative damage and degeneration of nerve cells traveling between the spinal cord and muscles. The disease is thought to be due to chronic lack of vitamin E in the diet and results in severe muscle wasting and weakness.

4. Equine Degenerative Myelopathy (EDM): This is a symmetric, non-compressive spinal cord disease of younger animals that is associated with degeneration of nerves within the spinal cord that causes ataxia. EDM is associated with vitamin E deficiency.

5. Immune Mediated Myositis: This is a disorder primarily of quarter horses in which rapid muscle atrophy of epaxial and gluteal muscle groups occurs secondary to an infection with Streptococcal bacteria. This disease usually causes painful/stiff muscles with elevated muscle enzymes.

6. Cervical Vertebral Malformation (Wobbler's Disease): This is an orthopedic disease caused by instability of the vertebrae of the neck leading to a stenosis (narrowing) of the vertebral canal and pinching the spinal cord.

7. Primary Myocellular Membrane Dysfunction: This occurs when the outer membranes of the muscle cells themselves are not functioning correctly.

The horse's muscle biopsies ruled out both Equine Motor Neuron Disease and Immune Mediated Myositis. His normal serum vitamin E ruled out Equine Degenerative Myelopathy and confirmed the rule out of Equine Motor Neuron Disease. Primary Myocellular Membrane Dysfunction was ruled out by the normal electromyogram.

Our horse's final diagnosis came back as mild Polysaccharide Storage Myopathy. Treatment for this includes an elimination of sweet feeds and feeding a high fat diet, feeding large amounts of a high quality grass hay, and giving the horse a routine, moderate and regular exercise regime.

Conclusion:

The pathophysiology of our horse's antibiotic induced *Clostridium* colitis likely started with an unknown stressor causing an alteration in intestinal flora which allowed for an opportunistic growth of *Cl. difficile*. Overgrowth of *Cl. difficile* leads to disintegration of tight junctions between endothelial cells in the gut by toxin A.[3] This is the primary cause of the protein losing enteropathy and bacterial translocation into the bloodstream. Toxin B, another enterotoxin produced by *Cl. difficile,* causes local damage leading to cellular necrosis. These combined processes lead to the increased mucosal permeability which causes protein loss, and decreased water absorption, and enables bacteria and their associated enterotoxins to translocate.

In adult horses, *Clostridial* diarrhea has been associated with factors that may alter the balance of the intestinal flora such as the administration of antibiotics or withholding of feed, but can occur in the absence of any identifiable risk factors.[2] A antibiotic treatment preceded *Clostridium difficile* associated diarrhea in only 26% of the cases treated.[2] A study by UC-Davis of 130 horses with gastrointestinal disease included the screening for *Cl. difficile* isolates and identified 3 strains based upon molecular banding patterns. They found that *Clostridium difficile* strain B (not to be confused with enterotoxin B) isolates were resistant to metronidazole, had a more severe clinical picture and were associated with a higher mortality rate.[4]
The majority of most *Cl. difficile* isolates predictably are susceptible to metronidazole. This has been proven in human literature; resistance to metronidazole is rare in human hospitals.

However, resistance has been shown to be common in equine isolates. Strain A was 93% susceptible to metronidazole, but interestingly, none of the isolates within strain B were susceptible to metronidazole.[4] The existence of this resistant strain was something that we wanted to rule out, so we submitted an anaerobic culture to check for metronidazole resistance. We were unable to get a growth of our *Clostridium* species, and therefore were unable to check for metronidazole resistance.

The exact pathogenesis of *Clostridium* colitis is not yet fully understood, nor is what exactly triggers the hind gut *Clostridial* overgrowth. Common underlying factors typically include stressors such as shipping, surgery and its associated hospitalization. Regardless of the cause, *Clostridium* colitis carries a high mortality rate and supportive treatment can last for weeks and at cost of ten thousand dollars.

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