Equine Coronavirus

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Introduction:

Equine Coronavirus (ECoV) is an emerging virus that has recently been isolated from adult horses. In the past, ECoV has been traditionally associated as a pathogen within foals.[9] Since 2010, there has been an increased frequency of sporadic clinical cases and outbreaks within adult horses that have been reported from Japan, the USA, and Europe.[7]

Coronaviruses are members of the *Coronaviridae* family. The virus is a single stranded, positive sensed, enveloped RNA virus. Coronaviruses are known to cause enteric, respiratory, hepatic or neurological disease within a variety of avian and mammalian species. ECoV is part of the subfamily *Coronavirinae*, in the *Betacoronavirus* genera. Other members of this group include bovine coronavirus, canine respiratory coronavirus, and human coronaviruses.[7]

Transmission of ECoV is by fecal to oral route. It is believed that both clinical and asymptomatic horses are responsible for direct or indirect transmission of the virus. The incubation period of the virus is two to three days. Clinical disease can manifest between 48 to 72 hours after natural or experimental exposure to ECoV. Clinical signs can last from a few days to a week. However, shedding of the virus can last from three days to three weeks.[6]

ECoV has been associated with febrile and enteric disease in adult horses.[9] The main clinical symptoms of a horse infected with ECoV include anorexia, fever, lethargy and soft to watery stool consistency.[5,9] There have been some reports of horses developing neurological signs that consisted of depression, ataxia, circling, head-pressing, seizures, and recumbency.[5,6] Clinical pathology is characterized by leukopenia due to neutropenia and lymphopenia. In addition, there have been reports of horses with severe hyperammonemia that have developed neurological signs that resemble hyperammonemic encephalopathy.[2] Outbreaks of ECoV have

been documented most commonly during the winter months and draft breed horses have been predisposed more than other breeds .[7,3]

Diagnosis for ECoV is through fecal PCR.[9] Treatment is through supportive care and prognosis is good. However, there have been reports of death associated with severe progression of clinical signs.[7] Preventative measures include strict biosecurity protocols. Further explanation of the pathophysiology, treatment, and preventative measures is described in this clinicopathophysiological report.

History/Presentation:

An approximately 9 year-old Warmblood mare named Darjeeling Cool presented to Mississippi State University, College of Veterinary Medicine (MSU-CVM) Equine Department on January 19, 2018 for a mass removal on her right lateral hindlimb, caudal to the stifle. The mass was initially seen by the owner in October of 2017 and was excised by the owner's primary veterinarian. Two months after removal of the mass, the owner noticed that it had reappeared in the same location. The primary veterinarian performed a biopsy of the mass and histopathology confirmed that the mass was a giant cell sarcoma of soft tissue parts. Based on the histopathology results, Darjeeling Cool was referred to the MSU-CVM for a surgical consult and mass removal.

Upon presentation, Darjeeling Cool was bright, alert, and responsive. She weighed 496.68 kg and had a body condition score of 7/9. Her vital parameters included the following: temperature of 101.4°F, pulse of 52 beats per minute, and respiratory rate of 20 breaths per minute. Her oral mucous membranes were pink and she had a capillary refill time of less than two seconds, indicating adequate hydration. Upon auscultation of thoracic cavity, no murmurs

of arrhythmias were appreciated and normal bronchovesicular sounds were heard. Normal borborygmic sounds were present in all four quadrants of the abdomen. A cutaneous mass was present on her right hindlimb, caudal to her stifle. The mass appeared to be approximately 4 cm x 3 cm x 1.5 cm with two sutures still present within the previous surgical incision site.

Pathophysiology:

ECoV primarily affects the villi of the small intestine. Horses that become infected, can develop a severe diffuse necrotizing enteritis that results from necrosis of epithelial cells in the tips of the villi.[6] With damage to the villi of the intestinal mucosa, there is a reduction in absorption of nutrients that can result in a malabsorptive diarrhea.[9] Loss of the protective epithelial barrier of the intestines can lead to secondary complications such as dehydration, electrolyte alterations, septicemia, toxemia and metabolic derangements.[2]

In clinical cases where horses develop neurological signs, they present with severe hyperammonemia. Horses showing neurological signs in the presence of hyperammonemia are classified as having hyperammonemic encephalopathy. Evidence for hyperammonemic encephalopathy is based on histopathological lesions within the brain. These lesions are characterized by the presence of Alzheimer type II astrocytosis in the cerebral cortex. Studies have not yet linked how the swelling of astrocytes occurs. There have been two hypothesized theories to explain this. One describes the overgrowth of urease-producing bacteria that produce an abundance of ammonia from the degradation of proteins. The other mechanism is that the disruption of normal intestinal mucosal barrier allows excessive ammonia absorption from the intestinal lumen into circulation.[2]

Diagnostic Approach:

Diagnosing ECoV can be challenging because it is difficult to differentiate clinical signs from other common enteric equine diseases prior to confirmatory diagnostic testing. Disease confirmation can be obtained by a fecal real time PCR test that can be sent out to a diagnostic laboratory. Real time PCR has an increased sensitivity and specificity compared to other diagnostic modalities. Electron microscopy, ELISA and viral isolation from feces have shown lack of sensitivity. Results for real time PCR have a turnaround time of approximately 24 hours.[5]

Treatment and Management:

Treatment of ECoV is primarily through supportive care as the disease is usually self-limiting. Horses that are showing mild clinical disease can be started on nonsteroidal anti-inflammatories (NSAIDs) to aid in reducing high fevers.[6] If NSAID therapy is warranted, it is advised to treat horses with gastric protectants, as horses are prone to stomach ulceration. Clinical cases that are more severely affected benefit from intravenous fluids to maintain hydration. In addition, if horses are developing signs of endotoxemia due to the disruption of the gastrointestinal barrier, antimicrobial therapy is warranted due to secondary clinical disease.[6] Since hyperammonemic encephalopathy has occurred in few clinical cases, it has been reported that treatment with oral lactulose or neomycin sulfate have had a positive impact with treatment.[6]

To aid in the prevention of the disease, researchers are looking to develop a vaccine from using a Bovine Coronavirus (BCoV) strain. BCoV is closely related to ECoV, both genetically and antigenically.[8] In a case study, horses were experimentally inoculated with a BCoV vaccine twice, with the first being 28 days prior to the second inoculation. From this study, horses that received the BCoV vaccine developed some antibodies against ECoV. However, further studies

need to be made to prove that the BCoV vaccine is sufficient to protect against ECoV.[8] At the present time, there is no current vaccine just for horses to aid in preventing the disease.

Management of ECoV can be done through proper biosecurity protocols and routine management practices to help reduce the risk potential of contracting the disease. Horses that develop or have persistent fever, anorexia, lethargy, or evidence of diarrhea should be isolated from healthy animals. Once isolated, diagnostics should be obtained to either rule in or out clinical disease. If an animal tests positive for ECoV, they should remain in isolation until clinical signs have been suppressed. Personnel working around infected animals should be aware of proper biosecurity practices. These practices include working with infected animals last after handling healthy animals, thorough washing of hands, adequate wearing of protective clothing, and proper disinfection of equipment.[6]

Before a positive tested animal gets reintroduced to herdmates, the animal should be tested again and obtain a negative result prior to reintroduction. Any new animals that have been purchased or animals that have returned from a show, should be placed into quarantine for three weeks prior to introduction with healthy animals. If coming back from a horse show, it is recommended that the horse trailer and vehicle used to tow the animal be properly cleaned and disinfected.[6]

Case Outcome:

The morning of January 23, 2018, Darjeeling Cool was prepared for surgery to remove her Giant Cell Sarcoma on her right hindlimb. A catheter was placed in her right jugular vein. Darjeeling received gentamicin 6.6 mg/kg and procaine penicillin 22,000 IU/kg intravenously for presurgical antimicrobial therapy. Prior to surgery she was sedated with detomidine and

butorphanol intravenously through the jugular catheter. Throughout surgery she was maintained on a detomidine CRI. An elliptical ring block was performed around the planned surgical site using carbocaine subcutaneously. A few minutes after the carbocaine was administered, a 25cm by 8cm wide fusiform incision was made around the mass using a #10 scalpel blade. This left a 2cm minimum skin margin around the mass. After the initial incision was made, blunt dissection of the subcutaneous tissue was performed using Brown Addison Thumb Forceps and curved Mayo scissors. The fascial layer was incised using a scalpel blade to expose the muscular layer underneath. Monopolar electrocautery was then used to transect the muscle, leaving approximately 0.5 cm of muscle attached to the fascial layer and the mass.

After the tumor was removed, the surgical site was lavaged with approximately 500 ml of sterile saline. Surgical instruments were changed for new sterile instruments for closure of the surgical site. At this time, all personnel changed their gloves as well. An attempt to close the muscle fascial layer was initiated with simple interrupted suture pattern using 2-0 Vicryl on a tapered needle. However, this was unsuccessful because there was too much tension. The skin approximately 4 cm cranial and caudal to the incision was undermined to relieve tension using Metzenbaum scissors. In addition to the undermining of skin, multiple 15mm tension releasing incisions were made on either side of the surgical incision site to aid in skin closure. The subcutaneous tissue was closed using a simple continuous suture pattern using 2-0 Vicryl. 2-0 PDS was then used in a near-far-far-near suture pattern to relieve tension and bring the skin edges together. A vertical mattress suture pattern was then used using 2-0 PDS to appose the skin edges.

Once the tumor was removed and the skin edges were apposed, chemotherapy was performed using intradermal infusion of carboplatin. Eight, 22-gauge 1.5-inch needles were

placed approximately 8mm apart from one another perpendicular to the incision site. Approximately 0.3mg to 0.5mg of the chemotherapy agent was infused at each of the sites. After the completion of chemotherapy, Darjeeling Cool then received thermofield therapy. A thermofield plate was placed over the incision site and wrapped with elasticon for support of making sure the plate did not move. The plate remained on her hindlimb for approximately 42 minutes to reach a target temperature of 42°C. Next, the incision site was covered with telfa pads and bandaged with elasticon to prevent exposure to environmental contaminants. Darjeeling Cool's surgery was uneventful and she recovered appropriately from sedation.

The mass was submitted for histopathology to determine if complete margins were obtained. For post-operative therapy, Darjeeling Cool was started on flunixin meglumine 1.1mg/kg every 12 hours intravenously to reduce inflammation and Uniprim 30mg/kg every 12 hours orally for antimicrobial therapy. In addition, strict stall rest was initiated for a few days post-surgery to prevent incision dehiscence due to the increased tension of the surgical site.

The day after surgery, Darjeeling Cool was bright, alert, and responsive. She was non-painful as she was placing full weight on her right hindlimb. At the incision site, there was some strike through of her bandage, but not enough to warrant intervention. Another thermofield therapy session was performed to help aid with the chemotherapy agent to spread and penetrate tissue. After the thermofield therapy was completed, her bandage was changed with some new telfa pads and elasticon. Silver sulfadiazine 1% topical ointment was started to be applied to her tension releasing incisions once daily when the bandage changes were done.

The following consecutive days post-surgery, Darjeeling Cool was bright, alert and responsive. Her physical examinations were all within normal limits. She was consuming water over her maintenance fluid intake of 25L/day, indicating adequate hydration. In addition, she

was consuming her feed and hay appropriately. Darjeeling was still confined to strict stall rest to reduce the chance of incision dehiscences due to the high tension of the surgical site. Daily bandage changes and treatment of the tension releasing incisions were performed. She was still receiving flunixin meglumine and Uniprim for post-operative therapy. In addition to the daily care and management of Darjeeling Cool, her owner wanted us to start applying emu oil along her incision site to aid in prevention of scaring, as she used this in her private practice. The start of this application daily began with the first treatment on January 26th.

However, the day after the first application of the emu oil, Darjeeling Cool's stay at MSU-CVM became more interesting. The morning of January 27th, Darjeeling Cool's 8am physical examination was abnormal as she was febrile with a 101.6°F temperature. Due to the elevated temperature, Darjeeling Cool was put on an every 4-hour check of her temperature and heart rate. At noon, she had a temperature of 102.9°F and had an elevated heart rate of 48 beats per minute. A house officer was notified and a full physical examination was performed. Darjeeling Cool had an adequate respiratory rate of 24 breaths per minute, normal borborygmic sounds in all four quadrants, normal lung and heart sounds, her mucous membranes were pink and moist, and had a capillary refill time of less than 2 seconds. In addition, she had normal digital pulses in all four limbs.

However, it was noted that she had urticaria around her incision site, along her hocks, and spread diffusely along her body. They ranged from 3 to 5mm by 3-5mm in size. She was pruritic along her face, front extremities and within her pectorals. Her incision site had mucoid discharge at the caudal, ventral portion. A repeated rectal temperature was performed around 1pm with it being 103.9°F. Blood was submitted for a CBC and chemistry panel. Her CBC results included a lymphopenia of 1008/ul. In addition to the bloodwork, a rebreathing exam and

ultrasonography of her abdomen and jugular catheter site were performed. The results of these diagnostic procedures were unremarkable. Based on her physical examination findings and diagnostic results, it was determined that possible differentials for her symptoms include a hypersensitivity reaction to the application of emu oil or a viral respiratory infection.

With the possibility of a hypersensitivity reaction to the emu oil, any residue of the emu oil was flushed with sterile saline and further treatments of applying emu oil to the incision site was discontinued. Continued brightness, rectal temperature, and heart rate checks were performed every 4 hours. At the 4pm check, her rectal temperature was 102.6°F and heart rate still remained the same at 48 beats per minute. In addition, her digital pulses were increased slightly in all four limbs and her urticaria had spread. After this, her heart rate and rectal temperature checks were then changed to every 2 hours.

At the 6pm check, she was febrile with a 103.0°F and was tachycardia with a heart rate of 60 beats per minute. A nasogastric tube was passed, but there was no net reflux. An additional ultrasonography was performed of the abdomen and the results were normal. With the nasogastric tube still in place, half a gallon of mineral oil and 6L of water were passed into the nasogastric tube, and then the tube was removed. 1.1mg/kg of flunixin meglumine was administered intravenously. Ice boots were placed on all four limbs to aid in the prevention of laminitis.

Throughout the night of January 27th, her heart rate and rectal temperature were monitored every two hours with full physicals every four hours. Rectal temperatures ranged from 101.1°F to 103.5°F. Heart rates ranged between 52 to 56 beats per minute. In addition, her digital pulses fluctuated throughout the night from being normal to slightly elevated. As a result,

ice boots were changed every two hours. As the night went on, her urticaria lesions slowly dissipated.

The morning of January 28th, Darjeeling Cool had been in the hospital for 10 days and was 5 days post-op from her mass removal surgery. She was bright, even though she was still febrile and had an elevated heart rate. Her appetite decreased, but she was still drinking her maintenance amount of water. There was still discharge present at the ventral aspect of her incision sight. At this time, she was still receiving flunixin meglumine and Uniprim powder every 12 hours.

After morning rounds, a repeated CBC and Chemistry blood panel were submitted. While waiting for the blood work results to come back, Darjeeling Cool spiked another fever of 104.4°F and was tachycardic at 64 beats per minute at her noon physical examination check. The results of her CBC included a leukopenia, neutrophilia and lymphopenia. Her chemistry blood panel results indicated mild hypocalcemia, mild hypophosphatemia, elevated CK, and hypomagnesemia. Due to the results of the diagnostic blood work, it was determined that she was suffering from endotoxemia secondary to an infectious cause. Intervention included placing a jugular catheter and started intravenous fluid at a rate of 1.0L per hour. In addition, polymyxin b was started at a dose of 6,000IU/kg intravenously every 8 hours as a bolus. To help aid in gastric ulcer protection, misoprostol 3mcg/kg was initiated orally every 8 hours.

In addition, 10mg/ml of acepromazine intramuscularly in her pectorals every 8 hours. Acepromazine was started to help increase vasodilation and prevent thromboembolism. Also at this time, the area around her incision site was swollen and warm to the touch. There was increased mucoid to purulent discharge coming from the ventral portion of her incision site. Due

to the increased amount of discharge, swelling, and heat felt on palpation. Uniprim antibiotic was discontinued and chloramphenicol 50mg/kg orally every 8 hours was started.

Four hours later at her 4pm physical examination check, she was walked for 5 minutes. When she came back to her stall, she began to circle and laid down in sternal position. While she was in this sternal position, she was stretching out her neck as if she was painful. She then laid down in lateral recumbency and began to have increased respiratory effort. At this time, it was assumed she was having mild colic signs. She was then walked to the stocks, sedated and a full diagnostic workup was performed. A nasogastric tube was passed, and once again no net reflux was retrieved. The tube was left in place. Rectal palpation examination was then performed and no abnormalities were palpated. Her feces were well formed, with no indication of being soft or fluid in consistency. An ultrasonography was performed of her abdomen and incision site. Her left quadrants were within normal limits, but her right quadrant showed her cecum and right dorsal colon had segmental mild edema present within the mucosal walls, indicating the possibility of colitis. At her incision site, there was no evidence of pockets of fluid, indicating that her incision was healing appropriately.

After the completion of her ultrasonography, one pound of biosponge and 6L of water were passed through the nasogastric tube. The nasogastric tube was left in place, oral supplementation of 6L of water was administered every other hour until midnight and which time the nasogastric tube was pulled. Throughout the remainder of the evening, her temperature ranged from 99.4 to 101.1°F with her heart rate being on average of 40 beats per minute.

On January 29th, Darjeeling Cool was 6 days post-op and 11 days being hospitalized. Her fecal output had decreased due to her inappetence. However, she was urinating appropriately. She appeared to be alert, but dull in her demeanor. A repeated CBC and

Chemistry was performed. On her CBC blood work results, her white blood cell count was increasing to a more normal value from comparison the day before. This indicated that our therapeutic treatment plan was working appropriately. In addition, she was hypocalcemic and hypomagnesmic. At this time, KCl, calcium gluconate 23% and magnesium sulfate were added to her intravenous fluid therapeutic plan. In addition to repeating bloodwork panels, a fecal sample was obtained and submitted for an equine diarrheal panel to UC Davis.

At her 4pm walk after her physical examination on January 29th, Darjeeling Cool appeared to be wobbly and acted like she was sedated. Due to this new clinical observation, her polymyxin dose was reduced to 5 vials and her treatment of acepromazine was decreased to a frequency of every 12 hours. After changing her treatment regimens, she was slightly ataxic at her 9pm walk.

The morning of January 30th, Darjeeling Cool was alert, but agitated. She began to start having a bowel movement, however the consistency was soft, normal. Her appetite was slightly better as she would only eat hay that was offered and would not touch any of her grain or mash. She was not walked as she was ataxic. While in her stall, it was observed as she would walk around, she almost had to think about where she needed to place her feet every time she took a step. She was circled in the stall by an intern, with attempts of her wanting to fall down. At this time, it was assumed that her ataxia could be a result of the high polymyxin b dosage and administration of acepromazine. To determine if these two drugs were the result of the ataxia, they were both discontinued and she was to be monitored for the next 24 hours to see if any additional neurological signs were observed.

Diagnostic blood work was repeated and her fluid rate was decreased to 0.5L per hour due to that her calcium and magnesium levels becoming more normal. With her stools becoming

soft formed and having abnormalities of her CBC (neutropenia and lymphopenia), it was advised if she became febrile she would have to be placed in isolation. At this time, Darjeeling Cool's equine diarrheal panel results were not in yet. No change to her therapeutic plan was implemented and continued daily care was performed.

Jan 31st, Darjeeling was 8 days post-op and had been hospitalized for 13 days. She was brighter and alert. She was not showing any signs of ataxia. Darjeeling started to eat grain and continued to eat her hay appropriately. Her stools started to become firmer and she was urinating more than normal due to the intravenous fluid overload and drinking water. A CBC was repeated and based off those results, her intravenous fluids was discontinued. However, her diarrheal panel results were still pending at this time. In the afternoon, Darjeeling Cool was reassessed for her ataxia by walking her. While on her walk, she was unaware of where her limbs were in relation to her body.

February 1st, Darjeeling Cool appeared to be alert and bright. Her appetite had decreased again. She ate very little if any her grain, but consumed all of the hay that was placed in front of her. Her fecal and urine outputs were within normal limits. She still was ataxic with increased ataxia in her hindlimbs as she was walked to the scale to get weighed.

February 2nd, Darjeeling was 10 days post op and had been hospitalized for 14 days. During morning rounds, her equine diarrheal panel results came back positive for ECoV. Since Darjeeling had not travelled, and none of the other horses on the owner's property had not travelled recently, the source of Darjeeling's infection to ECoV was suspected to be nosocomial as she probably contracted the virus from another ECoV positive horse that was in the clinic. To protect the health of other patients in the hospital, Darjeeling Cool was transferred to isolation. While in isolation, she had brightness checks every hour and was assessed using video

surveillance. Medical therapy of chloramphenicol, flunixin meglumine and misoprostol was continued. In addition, strict monitoring of how much feed she was consuming commenced due to her inappetence with wanting to eat grain.

While in isolation, we continued monitoring for any new neurological signs. For observation of ataxia, she was walked twice a day to an isolated paddock area. Two days after being in isolation, her gait returned to normal. Along with monitoring for neurological signs, continued monitoring of rectal temperature and heart rate were taken so that if any sign of infection occurred, early intervention of therapeutic treatment could be done. However, she was never tachycardic or febrile while she was in isolation.

The first couple days after being transferred down into isolation, she had partial inappetence where she would only want to consume all of her hay and partial amount of grain. However, when hand walks were added to her daily regimen, her appetite went back to normal of consuming both hay and grain. Her oral antibiotic, gastric protectant, and anti-inflammatory were discontinued on February 5th as she was no longer showing any clinical signs of enteric disease.

Throughout her continued stay at MSU-CVM, her incision site was thoroughly monitored as the owner was concerned with the incision site dehiscence and risk or scarring. The initiation of wound management was initiated when her incision site dehisced. Every morning, her incision site was flushed with sterile chlorhexidine followed by sterile saline. Silver sulfadiazine ointment was applied to the tension releasing incision sites. In addition, scarlet oil was sprayed onto the incision site to help formulate granulation tissue.

Darjeeling Cool remained in isolation until February 17th where she was discharged after being in the hospital for 30 days. Out of those days, she was hospitalized in isolation for 16 days. She was discharged with strict biosecurity instructions for two weeks. Darjeeling Cool was to be placed in isolation in a stall and pasture that was away from healthy horses to prevent other horses contracting Coronavirus. It was advised that Darjeeling Cool had separate feeding buckets, muck buckets, and tools to clean out her stall as Coronavirus's route of infection is cause by fecal-oral contamination.

One month after Darjeeling Cool had been discharged from MSU-CVM, her owner was called to see how she has been doing since returning home. Darjeeling's owner reported that she had no further signs of Coronavirus and that her surgical site had healed enough to resume light exercise.

In conclusion, ECoV should be included as a differential diagnosis for enteric disease since ECoV is a newly emerging disease in adult horses. ECoV is transmitted mainly through fecal to oral contamination. The main clinical symptoms of a horse infected with ECoV include anorexia, fever, lethargy and soft to watery stool consistency. In addition, neurological signs can also be seen. Diagnosis for ECoV is through fecal PCR. Treatment is through supportive care and prognosis is good. However, there have been reports of death associated with severe progression of clinical signs. Preventative measures include strict biosecurity protocols.

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