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Neonatal Diarrhea and Septicemia in an American Miniature Horse

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History

A 30-hour-old American Miniature Horse colt weighing 10.9 kg was presented for evaluation of a possible scrotal hernia and mild dehydration. The foal was born without apparent difficulty, stood within 30 minutes of birth, and nursed normally. The foal passed normal meconium, followed by normal foal feces. The umbilicus had been dipped in iodine several times. The 8-year-old dam was not current on vaccinations. The mare was dewormed 1 month before foaling with fenbendazole and was regularly dewormed at 2-month intervals. This was the dam's fourth foal. The mare passed fetal membranes shortly after parturition. This horse had never received a blood transfusion and had belonged to the present owner for 7 years. The dam developed signs of colic and anorexia 6 hours after foaling. The foal developed diarrhea at the same time. The referring veterinarian examined the mare and foal. The foal was diagnosed with a bilateral scrotal hernia. The foal received intramuscular injections of tetanus toxoid and vitamin E–selenium. The mare was treated with mineral oil and intravenous fluids with dextrose because her liver enzymes were elevated. There is a strong association between anorexia and hyperlipidemia or fatty liver syndrome in periparturient Miniature Horse mares. The foal was treated for diarrhea with kaolin and pectin as well as probiotic paste, and manual reduction of the scrotal contents into the abdomen was performed at 3-hour intervals. The owner described the appearance of the testes and scrotum as unchanged since birth. On the morning of presentation, the foal had a temperature of 38.3°C (101.0°F) and continued to have diarrhea. He was active and nursing well.

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Physical examination

The foal's temperature was 38.5°C (101.4°F), the heart rate was 112 beats per minute with strong synchronous pulses, and the respiration rate was 60 breathes per minute. The foal was bright, alert, and responsive. He was in good flesh, had a good appetite, and nursed strongly from his dam. The mare's udder and milk production seemed to be normal. Thoracic auscultation of the foal revealed no cardiac abnormalities or abnormal lung sounds. The gums were pink, moist, and slightly hyperemic, with a capillary refill time of 2 seconds. The conjunctiva and sclera were hyperemic. No other ocular abnormalities were detected. Dehydration was estimated to be 5% by skin tenting. The umbilicus was dry and normal and stained with iodine. Palpation of musculoskeletal structures was normal. The palate seemed to be complete based on digital examination. Gut sounds were normal, but defecation of small amounts of pasty yellow feces was frequent. A digital rectal examination revealed no abnormalities. Gentle palpation of the abdomen did not seem to cause discomfort, and ballottement of the abdomen did not produce a fluid wave. Urination was normal. The testes seemed to be large for the foal's body size but of normal shape and consistency. No gut was palpable in the scrotum or inguinal area. The skin, ears, and hair coat were normal for full-term gestation, age, and breed.

Case assessment

The primary problems identified in the foal were (1) diarrhea; (2) dehydration; and (3) hyperemic gums, conjunctiva, and sclera.

Diarrhea in foals is associated with bacterial, viral, and protozoal enteritis; septicemia; nutritional causes; obstruction of the gut; ingestion of irritants; antibiotic administration; parasitism; and foal heat in the mare. The role of *Escherichia coli* as a pathogen in foal diarrhea is controversial [1]. *E coli* is a well-documented pathogen in other species, however, and is the bacterium most commonly isolated from blood cultures of neonatal foals with diarrhea and septicemia [2]. The presence of *E coli* in blood cultures in foals with diarrhea may be attributable to bacteria crossing an already damaged intestinal barrier rather than primary invasion from the intestine. Proven causes of bacterial diarrhea in the neonatal foal include *Salmonella* and *Clostridium* species. *Salmonella* species cause disease by invading the mucosa, multiplying in macrophages, and then potentially spreading throughout the body. *Clostridium* species multiply in the bowel lumen and then produce toxins that damage the mucosa, resulting in diarrhea, toxemia, and possible septicemic spread of other bacteria. *Rhodococcus equi* can cause diarrhea in older foals by infecting the intestinal lymph nodes, but *Rhodococcus* septicemia has been seen in extremely young foals. Other bacterial causes of diarrhea considered were *Actinobacillus*, *Bacteroides fragilis*, *Klebsiella* and other coliforms, and *Streptococcus*. Viral diarrhea was considered less likely because of the early

onset. The most likely viral cause for neonatal foal diarrhea is rotavirus, which has been documented to occur as early as 2 days of age. Other viral causes (coronavirus, adenovirus, and parvovirus) are less strongly associated with foal diarrhea. Rotavirus causes diarrhea by invading the epithelium of the small intestine and causing villus atrophy, malabsorption, and maldigestion. This allows lactose and fatty acid fermentation in the large intestine, which then leads to osmotic diarrhea. Protozoa, notably *Cryptosporidium*, have been associated with diarrhea in neonatal foals. This was ruled out in the current case, because protozoal diarrhea has a 3- to 7-day prepatent period. Nutritional diarrhea can occur in the foal of a heavily milking mare. The foal's small intestine can be overwhelmed, allowing undigested milk to ferment in the large intestine, which causes osmotic diarrhea. This could not be ruled out. Partial blockage of the intestine was unlikely, because colic was absent. Irritant ingestion and antibiotic use were ruled out by the history. Parasitism attributable to transmammary infection with *Strongyloides westeri* was possible, but its role in clinical disease is questionable, especially at this foal's age. Other types of parasitism were ruled out by the foal's age, as was foal-heat diarrhea. Foal-heat diarrhea is probably related to diet rather than to changes in the dam's milk or udder contamination, because orphan foals frequently have diarrhea at the same age.

Dehydration occurs because of abnormal fluid losses (attributable to the environment or to internal pooling) or inadequate intake of fluids. Inadequate intake of fluid could be ruled out because of the foal's normal appetite and the mare's apparently normal milk production. Diarrhea seemed the most obvious route of fluid loss to the environment, but endotoxemia can cause pooling of fluid by damaging the cardiovascular system. Renal water loss was unlikely, because neonatal foals with renal disease are usually oliguric. Bladder rupture can result in apparent dehydration by anorexia and osmotic means, because the hypertonic urine in the abdomen can cause fluid to move from the tissues into the abdominal cavity. Bladder rupture was considered unlikely in this case, however, because urination behavior and ballottement of the abdomen were observed to be normal at physical examination. Had this foal's scrotum actually been enlarged, bladder rupture and scrotal hernia would have been included in the differential diagnosis.

Hyperemic gums, sclera, and conjunctiva are associated with septicemia. Septicemia can only be definitively diagnosed by blood culture; however, neutropenia, neutrophilia, increased numbers of bands (immature neutrophils), hyperfibrinogenemia, toxic cell changes, and hypoglycemia are all suggestive of sepsis.

Case management

A CITE test (Idexx, Portland, Maine), complete blood cell count (CBC), fibrinogen value, serum chemistries, and urinalysis were run on day 1

(Table 1). It should be noted that normal hematologic and serum chemistry values vary with the age of the foal [3,4]. Blood was drawn using aseptic technique and submitted for aerobic and anaerobic blood cultures. The CITE test showed an IgG value greater than 800 mg/dL. Leukopenia (4170 cells/ μ L) and toxic granulocytes were noted on the CBC. The hematocrit (Hct) was 39%, whereas total hemoglobin (Hgb) was 13.7 g/dL. Serum chemistry showed hypocalcemia (8.5 mg/dL) and a slight hypokalemia (3.4 mEq/L). The results of the urinalysis were unremarkable (Table 2). The characteristic changes in serum chemistry that occur because of a ruptured bladder, including azotemia, hypochloremia, hyponatremia, and hyperkalemia, were not present (Table 3). Serum bicarbonate was within normal limits, and respiratory disease was absent; therefore, measurement of blood gases was not indicated. The CITE test indicated normal passive transfer of maternal antibodies. In calves and kids, gamma-glutamyltransferase (GGT) elevations are a marker of colostrum ingestion [5]. If this were the case in foals, the low normal GGT in this foal might indicate failure of passive transfer. Significant serum GGT elevation from ingestion of colostrum does not seem to occur in foals, however [6,7].

Table 1
Hematology report

Date/hospital day (%)	Normal values	8/7/98 Day 1	8/8/98 Day 2	8/10/98 Day 4
PCV	28–46	39	36.8	30.0
RBC $\times 10^6/\mu$ L	8.2–11.0	7.22	6.88	6.67
MCV (fL)	30–50	54	53.4	52.8
MCH (pg)	10–19	18.9	18.8	20.3
MCHC (%)	31–38	35	35.3	38.4
Reticulocytes/ μ L	0	0	0	0
Hemoglobin (Hb) g/dL	11–16.6	13.7	13	11.5
RBC morphology		Normal	Normal	1 + anisocytosis
Nucleated RBCs/ μ L	0	0	0	0
White blood cells/ μ L	5010–12,600	4170	4120	4760
Metamyelocytes/ μ L				
Band neutrophils/ μ L	0–150	0	0	0
Semented neutrophils/ μ L	2000–10,200	2627	2431	2190
Lymphocytes/ μ L	600–5000	1543	1607	2047
Monocytes/ μ L	20–390		41	524
Eosinophils/ μ L	0–70		41	
Leukocyte morphology		Rare toxic granulocytes	Rare toxic granulocytes	Normal
Platelets/ μ L	100–500	292	273	139
Coomb's test (direct/indirect)		Direct +		
Fibrinogen mg/dL	100–400	300	500	

Abbreviations: MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PCV, packed cell volume; RBC, red blood cell.

Table 2
Urinalysis report

Date/hospital day	Normal values	8/7/98/Day 1
Source (eg, catheter/void/cystocentesis)		Free catch
Color		Pale yellow
Appearance		Clear
Specific gravity	1.001–1.027	1.012
pH	5.5–8.0	5.0
Protein	Negative to + 30	Trace
Glucose	Negative	Negative
Acetone	Negative	Negative
Bilirubin	Negative	
Blood	Negative	Negative

The low white blood cell (WBC) count and toxic granulocytes (see [Table 1](#)) suggested bacterial septicemia. An Hct/Hgb ratio that is less than 3 (Hct/Hgb = 2.85 in this case) suggests hemolysis or laboratory error. The most likely cause of hemolysis in this foal was neonatal isoerythrolysis (NI). Serum bilirubin, although normal, was higher than usually seen from our laboratory, supporting the suspicion of hemolysis. The increase in bilirubin could also have been physiologic or caused by endotoxemia or hepatic disease, however. Other causes of increased bilirubin in a neonate could be septicemia, congenital defects of the liver, fatty liver in the foal or the dam, or

Table 3
Chemistry report

Date/hospital day		Normal values	8/7/98 Day 1	8/8/98 Day 2	8/11/98 Day 5
BUN	(mg/dL)	0–29.4	8.2	9.0	
Creatinine	(mg/dL)	0.4–3.6	0.9	0.8	
Alk phos	(IU/L)	530–2700	2209	1824	
SGOT (AST)	(IU/L)	85–460	122	125	
SDH	(IU/L)	0.6–4.6	5.4	8.3	
CPK	(IU/L)	25–350	201	156	
GGT	(IU/L)	10–38	10	12	
Total bilirubin	(mg/dL)	0.5–4.3	4.0	2.5	1.9
Glucose	(mg/dL)	108–223	201	141	
Na	(mEq/L)	123–159	137	136	
K	(mEq/L)	3.6–5.6	3.4	4.5	
Cl	(mEq/L)	90–114	106	106	
Ca	(mg/dL)	9.7–13.7	8.5	9.6	
P	(mg/dL)	3.4–7.4	5.2	6.5	
Total protein	(m/dL)	4.4–7.6	4.8	4.6	
Albumin	(m/dL)	2.3–3.4	2.4	2.4	
Cholesterol	(mg/dL)	100–478	139	134	
HCO ₃	(mEq/L)	19–27.4	21.9	21.9	

Abbreviations: Alk phos, alkaline phosphatase; BUN, blood urea nitrogen; CPK, creatine kinase; GGT, gamma glutamyltransferase; SDH, sorbitol dehydrogenase; SGOT, serum glutamic-oxaloacetic transaminase.

equine herpesvirus type 1 (EHV-1) infection in utero. Toxic causes, such as iron supplementation and drug (eg, corticosteroids, gas anesthesia, antiseizure medications) administration, were ruled out by the history. Physiologic hyperbilirubinemia is probably caused by a proportionally larger volume of blood in the neonate, shorter red blood cell (RBC) life, low volume of feed leading to increased absorption of bilirubin from the gut, insufficient ability to conjugate bilirubin, and lessened ability to excrete bilirubin. In physiologic hyperbilirubinemia, most of the bilirubin is unconjugated. Hemolytic disease also results in elevated unconjugated bilirubin, although endotoxin may decrease the ability of the bile canaliculi to excrete bilirubin, leading to increased conjugated bilirubin. Our laboratory did not differentiate between conjugated and unconjugated bilirubin.

Despite the elevated bilirubin concentration, hepatic disease was considered unlikely, because liver enzymes were normal, except for an unremarkable increase in sorbitol dehydrogenase (SDH) (5.4 IU/L, normal range: 0.6–4.6 IU/L). Hypokalemia was unremarkable (3.4 mEq/L, normal range: 3.6–5.6 mEq/L). Hypocalcemia (8.5 mEq/L, normal range: 9.7–13.7 mEq/L) was probably caused by a decrease in the protein-bound calcium, with normal ionized calcium because of low normal serum albumin. Because hemolytic disease was suspected, a direct Coomb's test was run. The direct Coomb's test was positive, which means that the foal's RBCs were coated with immunoglobulin or complement. This was suggestive of NI.

When sepsis was scored [8], the foal received 2 points for having a neutrophil count between 2000 and 4000 cells/ μ L, 0 points for having less than 50 bands/ μ L, 2 points for having toxic granulocyte changes, 0 points for having a fibrinogen level less than 400 mg/dL, 0 points for having a blood glucose level greater than 80 mg/dL, 0 points for having an IgG value greater than 800 mg/dL, 3 points for marked scleral injection, 0 points for having a normal temperature, 0 points for having a normal mental state, 3 points for having diarrhea, and 3 points for having a sick dam (colic). The total sepsis score was 13. Scores greater than 11 on this scale indicate sepsis. Because of these findings, diagnoses of diarrhea, probable septicemia, and possible NI were made.

Treatment and outcome

Treatment on day 1 included aseptic intravenous catheter placement, intravenous fluid supplementation with 0.45% sodium chloride (NaCl)/2.5% dextrose (100 mL) with 20% calcium dextrose (1 mL) added every 2 hours, potassium penicillin (22,000 IU/kg) administered intravenously every 6 hours, and amikacin (6.6 mg/kg) administered every 8 hours. The fluids were administered as supportive care for diarrhea and septicemia at a rate of approximately 90 mL/kg/d. This is a maintenance fluid rate for a foal, because a foal has proportionally more water than an adult. A maintenance rate was chosen because the foal was nursing well; therefore, this fluid

rate and the foal's nursing would compensate for excess fecal fluid losses. Antimicrobials were chosen for broad-spectrum activity. Amikacin was chosen over gentamicin because it is less nephrotoxic. The dosing of amikacin was controversial. Dosing regimens ranging from 4 to 8 mg/kg every 8 to 12 hours to 20 to 25 mg/kg every 24 hours have been recommended. Monitoring of blood levels of aminoglycosides is recommended but was not possible in our clinic. Recently, once-daily dosing has been reported to be efficacious because of high blood levels and prolonged postantibiotic effect as well as safer because of lessened nephrotoxicity. In this case, at the time the foal was treated, dosing three times per day was deemed most legally defensible, and with the supplementation of fluid therapy so as to protect the foal's kidneys, safe and efficacious. The current recommendation for dosing of amikacin is 25 mg/kg administered once daily [9]. No corticosteroids were given for treatment of possible NI because of lack of symptoms and the contraindication of suspected septicemia. The foal's vital signs and membrane color were monitored closely.

On day 2 of treatment, the foal's temperature was 38.2°C (100.8°F), the heart rate was 100 beats per minute, and the respiration rate was 56 breathes per minute. The mucous membranes were normal, without signs of jaundice. The foal was bright, alert, difficult to catch, and nursing well. Defecation and urination were normal. A CBC and serum chemistry (see [Tables 1 and 3](#)) revealed that the Hct had decreased to 36.8%, Hgb to 13 g/dL, and Hct/Hgb ratio to 2.83 and that there was leukopenia (4120 cells/ μ L) with toxic granulocytes, increased fibrinogen (500 mg/dL), reduced total bilirubin, unremarkable serum calcium, and mild elevation in SDH. Laboratory findings were still suggestive of septicemia. Blood from the mare and foal was cross-matched to pursue the possibility of NI further. The mare's serum and the foal's RBCs were incompatible. This demonstrated that the previous finding of a positive Coomb's test was not spurious. NI was suspected. Treatment was unchanged, because the Hct was not so low as to warrant transfusion. On day 3, the foal's temperature was 38.6°C (101.5°F), the heart rate was 104 beats per minute, and the respiration rate was 36 breathes per minute. The Hct was further decreased to 33%, and plasma total solids were 4.9 g/dL. Blood culture confirmed septicemia with *E coli*, which was sensitive to aminoglycosides. Treatment was unchanged, because gram-positive or anaerobic pathogens were still possible. On day 4, the foal's temperature was 38.6°C (101.6°F), the heart rate was 116 beats per minute, and the respiration rate was 52 breathes per minute. A CBC was performed, and leukopenia was still present (4760 WBCs/ μ L), but to a lesser extent and without toxic changes. The Hct was 30%, Hgb was 11.5 g/dL, and Hct/Hgb ratio was 2.61; yet, no signs of jaundice were present, and urine was observed to be of normal straw color. Fluids were discontinued. On day 5, the foal put up a remarkable struggle during the examination, which probably accounted for the elevated temperature of 39°C (102.2°F), pulse rate of 132 beats per minute, and respiratory rate of 52

breathes per minute. A final serum total bilirubin measurement was normal. This, combined with normal-colored urine and lack of jaundice, suggested that marked hemolysis was not occurring. On day 6, the physical examination was unremarkable, with a temperature of 38.7°C (101.8°F), pulse rate of 132 beats per minute, and respiratory rate of 32 breathes per minute. The foal was discharged. Because the owner's work schedule would not allow dosing three times daily, the foal was switched to once-daily intramuscular dosing of amikacin, 20 mg/kg, and twice-daily dosing of procaine penicillin G, 20,000 IU. This antibiotic regimen was to be continued for 5 additional days. The owner was advised to watch the foal for signs of jaundice or weakness. Careful observation for signs of NI was recommended for the mare's next foal. Blood typing the foal, the mare, and any stallion to which the mare might be bred was recommended. The foal and dam were reported to be in excellent health 22 days after admission. No anaerobic or gram-positive bacteria were isolated from the blood.

Possible reasons for the foal's failure to develop clinical NI despite being having a positive result on a Coomb's test and his dam's serum (and presumably colostrum) containing antibodies to his erythrocytes include the following:

1. The mare had antibodies to Ca antigen on the foal's erythrocytes without sensitization. This does not result in hemolysis. Anti-Ca alloantibodies may, in fact, be protective against NI caused by alloantibodies to other blood groups [10].
2. The mare was previously sensitized to a less antigenic blood antigen than the Qa or Aa antigens most commonly associated with clinical NI. Several other antigens have also been implicated in NI [11,12].
3. The mare had previous exposure to Qa, Aa, or other blood group antigens on the foal's cells but produced a weak antibody response.
4. The CITE test was in error, and the foal had partial failure of passive transfer and only a weak response to erythrocyte antigens. The CITE ELISA test has been found to have poor sensitivity and high specificity [13]. The poor sensitivity makes it more likely that the foal would have an unidentified false-negative test result for failure of passive transfer. It should be duly noted that the company has discontinued this test, replacing it with the SNAP ELISA (Idexx) test, which has higher sensitivity, although lower specificity.

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