Perinatal mortality in horses and camelids

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Abstract

The neonatal health of foals and crias is affected by the quality of the uterine and placental environment before birth, threats they face during birth, and vulnerabilities of the first week of life. When identifying the cause of neonatal death, careful examination of the dam, fetal membranes, and the fetus is critical. The most common threats for horses and camelids are failure of passive transfer, bacterial sepsis, diarrhea, and congenital defects. Identification of compatible lesions and confirmation with laboratory testing will allow better management of the herd.

Keywords: Perinatal mortality, neonatal mortality, horses, South American camelids

Introduction

The transition period between birth and early days of life (neonatal or perinatal life is usually defined as the first week of life) is likely the most challenging and high-risk period for any animal. Half of foal mortality occurs in first 30 days (5.8% of live births), mostly (3.3%) in the first 2 days.[1] In South American camelids, ~ 20 - 80% of crias do not survive the first year, whereas in North America, 5% loss is more typical.[2] Causes of neonatal death overlap considerably with those of abortion and stillbirth, (including infectious, traumatic, developmental, genetic, toxic, and nutritional causes). Only causes of neonatal death will be discussed in this review.

General approach to investigate perinatal mortality

Understanding the normal progression from intrauterine to terrestrial life and identifying deviations from that path are important. Critical points of concern are: placental sufficiency in late pregnancy, any disruptions during delivery leading to delay, dystocia or hypoxia, trauma at birth or early life, environmental stressors such as cold, dampness or heat, and ingestion of inadequate amounts of good quality colostrum. A thorough breeding and medical history of the dam is critical to identify whether the fetus is premature and whether the dam and fetus might be susceptible to potential infectious diseases. Unlike production animals, most horses and camelids are observed closely during parturition and the conditions and circumstance of the neonate's birth can be well documented. For instance, mares give birth during night and camelids during daylight hours; variations from these norms are possible, but should trigger greater scrutiny and may predict more insidious problems.[2] In addition, a complete postmortem examination of the neonate and a complete physical and reproductive examination of the mare or hembra is required.

It is important that fetal membranes are carefully examined. Placental abnormalities may be predictive of future problems despite apparent vitality of foal or cria. Evidence of placental insufficiency such as villous hypoplasia or infection such as chronic vasculitis (thickened tortuous vessels) or chorionic infarction (thinned translucent sharply demarcated regions of chorioallantois) may indicate that the fetus may develop weakness and poor postnatal development or sepsis within first few days. In large breeding facilities, barn managers can be trained to evaluate fetal membranes and save them for more detailed inspection by the veterinarian during regular business hours.

Observation of postnatal nursing and confirmation of passive transfer of antibodies via colostrum are also crucial to predicting neonatal survival. Failure of passive transfer (FPT) is the cause of at least 13% of neonatal equine deaths, and likely is associated with many more.[1] Complete FPT in foals is typically defined as a serum IgG concentrations of < 400 mg/dl on day 1, and partial FPT as serum IgG concentration of 400 - 800 mg/dl. In crias, an estimated 9% had FPT.[3] In crias, > 1,000 mg/dl of IgG is expected on days 1 or 2. Serum total protein can be used, but is a less accurate estimate and should be used as a last resort, with < 4.9 g/dl being compatible with FPT in 2-day old crias.[4] Some foals and crias survive and thrive despite FPT, but it can often lead to life-threatening sepsis, various infections, and hypoglycemia, and complicate other comorbidities.

Prematurity is considered when a foal is born earlier than ~ 320 - 335 days of pregnancy and when crias are born < 335 days; however, there is considerable variation in pregnancy lengths, seasonal variations, and some neonates will appear

premature even if born within the expected range (these are often called 'dysmature').[2] Low birth weight, lethargy, tendon laxity, and floppy ears may suggest dysmaturity or prematurity. In crias, ears may be bent backwards and unerupted incisors are often observed. In foals, domed or prominent forehead has been frequently reported. A poor suckle reflex can also lead to FPT. These animals are especially prone to hypothermia and metabolic derangements including hyper- or hypoglycemia. A lack of surfactant in these animals can lead to hypoventilation and hypoxia.

Causes of mortality in foals

Neonatal sepsis is the leading cause of death. At least 24% of bacteremic foals have been associated with maternal factors such as placentitis or dystocia.[5] General cleanliness, FPT, and husbandry factors are associated with sepsis. Postnatal umbilical, gastrointestinal, and respiratory portals of infection are also associated with the development of life-threatening bacteremia. Blood cultures are definitive and can help guide therapy if taken antemortem. Gross lesions include tacky and red mucous membranes, interstitial pneumonia, adrenal hemorrhage, hepatitis, splenitis, meningitis, uveitis, arthritis, osteomyelitis, enteritis, serosal hemorrhages, and often thrombosis of major arteries. Ileus can also be associated with sepsis leading to a whole new list of complications.[6] Gram-negative bacteria, (especially, *Escherichia coli* [*E. coli*]), are considered the most common cause; however, *E. coli* can often be an innocent bystander or opportunist, so identification of virulence factors by PCR is necessary. Other bacteria, including gram-positive bacteria, should not be discounted, as they can also be substantial causes of neonatal sepsis. Fungi, particularly *Candida albicans*, can also have a role, particularly in immunocompromised foals.[7]

Gastrointestinal conditions include diarrhea, enterocolitis, gastric and duodenal ulcers, meconium impaction, and congenital defects such as atresia ani. Bacterial infectious causes include primarily *Clostridium perfringens* (type A and C primarily in foals < 10 days old) and *Clostridium difficile*, and *Salmonella* sp. all leading to hemorrhagic and necrotizing enterocolitis. Rotavirus and to a much lesser extent, coronavirus, are viral causes of neonatal diarrhea. Microvilli are blunted, leading to a malabsorptive, voluminous, watery diarrhea.[8,9]

Gastric ulceration is another very common condition in foals, most often observed in neonates in the squamous mucosa adjacent to the margo plicatus.[9,10] Duodenal ulceration is more common in older foals. Both conditions can develop quickly and perforation may occur before clinical signs are evident. Causation is still hotly debated, but it is likely multifactorial and complicated, involving environmental and physiologic stress, nonsteroidal anti-inflammatory medications, diet, or other comorbidities.

Meconium impaction is the most common cause of colic in neonatal foals, but it should be differentiated from more serious and likely fatal intestinal or anal atresia and intestinal aganglionosis. Meconium is a yellow-green collection of sloughed cells and intestinal mucus mixed with amniotic fluid that represent the foal's first defecation. Impaction of this material is common, usually easily treated, and rarely is a cause of mortality. In contrast, intestinal atresia is uniformly fatal without surgical intervention. Cause of intestinal atresia has been speculated to be ischemia secondary to vascular supply disruption to a section of intestine, possibly associated with intestinal displacements. In calves, there was an association with transrectal palpation and atresia, but no similar association was reported in other species. A grading system has been proposed:[11]

Type I	membrane atresia (a diaphragm occludes the lumen)
Type II	cord atresia (a fibrous cord-like remnant of intestine)
Type IIIa	blind end atresia (a segment is missing with a mesenteric defect)
Type IIIb	blind end atresia (the distal segment is coiled)
Type IV	multiple sites of atresia

Prognosis for these cases is guarded, even with surgical intervention. Intestinal aganglionosis is a hereditary condition, associated with the lethal white syndrome, an autosomal recessive mutation. Submucosal and myenteric ganglia are absent from the distal small intestine to the colon leading to ileus. Due to the extent of the lesion, these horses are usually euthanized. Genetic testing (presence of endothelin B receptor genotypes) is now available for this disease for diagnosis and genetic management of possible carriers.[12]

'Dummy foal' or neonatal maladjustment syndrome (formerly known as hypoxic-ischemic encephalopathy) is a condition observed in foals that experience hypoxia for a variety of reasons during the perinatal period.[13-16] Placental disease and dystocia[17] are the most common causes, but any prolonged or repeated hypoxia can result in a foal with a variety of neurologic signs including stupor, abnormal posture, unwillingness or inability to nurse, abnormal facial movement, head-pressing, and seizures.

Neonatal isoerythrolysis, resulting in hemolytic anemia in foals, is a relatively uncommon but serious disease observed in ~ 1 - 2% of horses and up to 10% of mules.[18,19] This condition occurs when a mare produces alloantibodies against a red blood cell (RBC) antigen present on a foal's RBCs, and the foal ingests those alloantibodies in colostrum. Foals are initially normal, but develop icterus, pigmenturia, weakness, lethargy, and ultimately cardiovascular collapse. A hemolytic cross-match assay is the most reliable test. Kernicterus has been reported in affected foals with prolonged hemolysis that demonstrate neurologic disease and death. Histopathology demonstrates the deposition of unconjugated bilirubin and neuronal necrosis in the gray matter of the cerebellum, basal ganglia, subthalamic nuclei, and the hippocampus.[19]

As in any neonate, a variety of congenital conditions can also be observed that may or may not have a genetic basis, including those already mentioned and cardiac conditions like ventricular septal defect, heart valvular defects, cerebel-

lar hypoplasia (or abiotrophy), tendon laxities and contractions, microphthalmia, cleft palate, and umbilical defects.[20] Schistosoma reflexus, polydactyly, and other lesions are rarely observed.

Causes of mortality in South American crias

Bacterial sepsis, often associated with FPT, is a common cause of neonatal death. Gram-negative bacteria, especially *E. coli*, are most common, but others include beta-hemolytic *Streptococcus* and *Listeria monocytogenes*. Culture of lung, liver, and spleen can be useful, but lesions can be quite variable depending on the organs most affected. Histologically, the presence of megakaryocytes in the pulmonary vasculature is strong evidence of a systemic and exhaustive immune response. Multifocal to diffuse interstitial pneumonia, hepatitis, splenitis, nephritis, hypopion, and meningoencephalitis can be observed in varying degrees, and in peracute cases, there may be few if any lesions. Notably, septic joints are less common in crias than ruminant and equine neonates. Brain and vertebral abscesses are another possible sequela to sepsis.

Infection with *Mycoplasma haemolamae* is a condition observed commonly in North and South America, and is similar to hemotropic mycoplasmas observed in cattle, pigs, and cats.[2] They are small, 0.5 µm diameter round, ring, or linear organisms identified at the periphery of red blood cells on blood films. They are primarily transmitted by insect vectors or iatrogenically, but vertical transmission has been documented with crias infected at 1 day of age before colostrum ingestion. These organisms are associated with weight loss, anemia, weakness, and lethargy. These are often easily observed on blood films, but low-level infections may require PCR.

Similar to foals, neonatal diarrhea is a major threat to young crias. Differentials should include bacterial endotoxemia or enterotoxemia, coccidiosis, cryptosporidiosis, coronavirus, rotavirus, or bovine viral diarrhea virus and coinfections should also be considered. Bacterial culture should identify most bacterial causes; however, if *E. coli* is identified, PCR for virulence factors is recommended to differentiate commensal *E. coli* and pathogenic strains. Salmonellosis has very rarely been identified in septicemic crias, but has not been associated with diarrhea.[21] Iatrogenically induced *Clostridium difficile* and infections with *Clostridium perfringens* have been reported but are not common.

Multiple coccidians can be an issue, but particularly in young camelids, *Eimeria macusaniensis* is the most significant and can lead to lethargy, weight loss, anorexia, diarrhea, and unfortunately, sudden death.[22] With coccidiosis, necrosis and villous loss are the primary lesions noticed throughout the jejunum and ileum, though fibrosis may be prominent in longer standing cases. The duodenum and colon are typically spared. Organisms are often present in the deep crypts, but in heavy infections, the entire villus is affected. Even in massive infections, however, fecal examinations for *Eimeria macusaniensis* are often negative. Cryptosporidia, likely *C. parvum*, has been identified frequently in cases of neonatal cria diarrhea and has a similar pathogenesis to observed in cattle. Antemortem detection can be challenging and the use of acid-fast stains on fecal smears is likely the most effective test (simple, fast, and sensitive), whereas PCR can also be useful. Postmortem gross lesions are few, other than liquid feces, but the organisms can be identified microscopically on the villus tips as 5 - 10 µm basophilic spheres. Several studies have also identified *Giardia* sp. leading to villus atrophy and malabsorptive diarrhea.

Rotavirus is a common viral cause of diarrhea in young crias, particularly in South America, and is highly transmissible, but usually it must be accompanied by other pathogens or conditions to lead to death. Gross lesions are limited to liquid diarrhea. Rotaviral diarrhea has 3 mechanisms: destruction of enterocytes leading to malabsorption and villus atrophy, release of vasoactive agents leading to ischemia and enteric nervous stimulation, and production of a nonstructural protein that acts as a secretory enterotoxin.[8] Coronaviruses in camelids have also been well-documented and can be severe; however, the severity is likely related to the involvement of other pathogens and stress.[21] Bovine viral diarrhea virus (BVDV) is a known entity to bovine practitioners, but BVDV can also infect camelids leading to clinical disease. Crias, in particular, can be persistent carriers, transmitting infections to new herds. Reported clinical signs are similar to cattle: diarrhea, unthrifty condition, abortion, and birth defects depending on the time of infection of either the cria or dam. PCR is considered the test of choice, with spleen, thymus, ileum (with Peyer's patches), lung, or whole blood being best specimens. Serum can be used for paired serological testing, but currently, is not definitive in camelids. Persistent infections are best confirmed with positive PCR tests conducted 3 - 4 weeks apart.[23]

Respiratory disease in crias has some unique features due to their adaptations to high altitudes. Their oxyhemoglobin dissociation curves distinctly differ from other domestic mammals, with a shift to left allowing for an increased affinity for oxygen in the lungs.[24] Thus they are less susceptible to negative effects of hypoxia after pneumonia, heart defects, atelectasis, prolonged recumbency, or other pulmonary conditions. 'Dummy crias' that have had perinatal hypoxia can often survive without serious effects, if they are given supportive care, and cerebral necrosis or other lesions may be less severe than expected in crias that have died after severe hypoxic events.

In crias, particularly in North American populations, congenital defects are more common than other domestic species.[24] Common defects include choanal atresia, cleft palate, cerebellar hypoplasia, prognathism and brachygnathism, hydrocephalus, cerebellar hypoplasia, deafness, atresia ani, vulvar hypoplasia, cardiac defects, and skeletal abnormalities including angular limb deformities, arthrogryposis (sometimes associated with brain defects), polydactyly, kyphosis, and scoliosis. Not all these defects are hereditary, but many are and reporting of this information is important for breeders to make informed decisions on mating choices.

Conclusion

The most critical period in any mammal's life is the time of parturition and adjustment to life outside the uterus. Establishment of a strong immune response via passive transfer of immunoglobins in colostrum and development of an independent immunocompetence that will last the rest of animal's life is a common feature of normal camelid and equine

neonates. When death occurs during the neonatal period, evaluation of prepartum environment (dam's health and placental quality) and examination of the fetus is critical. Foals and crias share many of the same threats during this period, but these potential problems can be addressed by careful husbandry, including accurate diagnosis of neonatal deaths for better herd management.

Conflict of interest

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