Neonatal Encephalopathy in Foals

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Abstract: Neonatal encephalopathy is a common central nervous system disorder of neonatal foals and human infants, resulting in clinical signs such as lethargy, inappropriate behavior, seizures, and other neurologic deficits. Although neonatal encephalopathy is frequently seen in equine practice, a paucity of veterinary clinical and basic science research data is available. Therefore, the pathophysiologic mechanisms of this disorder in equids, such as energy deprivation, excess excitatory amino acids, and free radical injury, have been extrapolated from human medicine. Equine veterinarians have used various diagnostic and therapeutic regimens from human medicine with reasonable success in equine patients. Understanding the potential pathophysiologic mechanisms involved in neonatal encephalopathy can facilitate management of affected foals.

Neonatal encephalopathy in foals has been associated with various terms, including neonatal maladjustment syndrome and hypoxic-ischemic encephalopathy. Descriptive terms such as barker foal, wanderer, or dummy foal have also been used. Regardless of the nomenclature, neonatal encephalopathy is a common disorder of infants and foals under the broad category of perinatal asphyxia syndrome. Asphyxia is caused by impaired oxygen delivery to cells, resulting from hypoxemia or anemia (decreased oxygen content in blood), while ischemia pertains to decreased blood perfusion. Despite the emphasis on a hypoxic-ischemic event in “hypoxic-ischemic encephalopathy,” hypoxia-ischemia or asphyxia has not been documented in all infants with neonatal encephalopathy; this is also true for affected neonatal foals. In some of these instances, increased proinflammatory cytokines associated with placental infection and fetal inflammation may have played a role in the development of the associated neurologic disturbances; therefore, neonatal encephalopathy may be a more appropriate term.

Biochemical events associated with hypoxia-ischemia include energy failure, membrane depolarization, brain edema, excess concentration of neurotransmitters, production of reactive oxygen and nitrogen species, and lipid peroxidation, all of which potentially contribute to brain dysfunction and neuronal death. Most information regarding the pathophysiology of neonatal encephalopathy is directed at infants. This information has been extrapolated to equine medicine because equine-specific information on neonatal encephalopathy in foals is exceedingly sparse. A basic knowledge of potential pathophysiologic mechanisms in nonequine species may provide essential information and therapeutics for diagnosing and treating neonatal encephalopathy in foals.

Pathophysiologic Mechanisms

A combination of biochemical and physiologic events, rather than a distinct singular event, may contribute to the pathophysiologic mechanisms associated with neonatal encephalopathy. It has been proposed that after a reversible hypoxic-ischemic brain insult, neuronal death occurs in two phases (FIGURE 1). The first phase—primary neuronal cell death—is associated with related events: cellular hypoxia, energy failure, and cellular membrane depolarization. An initial prevailing theme is energy failure as a result of oxygen and glucose deprivation to the brain secondary to hypoxia-ischemia. Oxygen is essential for normal aerobic energy production via oxidative phosphorylation, with the brain consuming approximately 20% of total body oxygen. The brain also consumes approximately 25% of total body glucose and depends on a constant supply of glucose to maintain homeostasis. Depletion of ATP, even during mild episodes of hypoxia-ischemia, may initiate a cascade of events ultimately resulting in neuronal death. More specifically, cell-membrane ion pumps rely on sufficient ATP to function; with decreased availability of ATP, decreased
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Activity of the sodium ion–potassium ion (Na⁺–K⁺) pump results in sodium influx into neurons, membrane depolarization, and concomitant water entry with subsequent cell swelling. In addition, the excitatory neurotransmitter glutamate accumulates in the extracellular space as a result of (1) failure of energy-dependent glutamate uptake into neurons and (2) increased glutamate release from neurons. Glutamate then activates receptors within the central nervous system (CNS), resulting in sodium entry through ionotropic receptors, passive influx of chloride and water, cell swelling, and potential cell lysis.

Conceptually, neuronal cell death from acute energy failure as a result of a hypoxic-ischemic event is plausible and certainly contributes to the pathophysiologic mechanisms of neonatal encephalopathy. However, studies suggest that this explanation is too simplistic and that a significant amount of neuronal cell death occurs after termination of the initial hypoxic-ischemic insult. Furthermore, experimental studies suggest that many, if not most, deleterious effects of previous ischemia are manifested during the reperfusion phase. The second phase of neuronal death—delayed neuronal cell death—is associated with reperfusion injury (oxidative stress), excitotoxicity, accumulation of intracellular calcium, activation of numerous enzymes and pathways, cytotoxic actions of activated microglia, inflammation, and apoptosis (FIGURE 1).

Many of the pathophysiologic mechanisms of delayed neuronal cell death are initiated during the acute hypoxic-ischemic insult, but the detrimental effects manifest hours to days after the initial insult. In addition to allowing influx of sodium into the neuron through specific receptors, excess extracellular glutamate results in considerable influx of calcium into neurons through specific glutamate receptors. Increased intracellular calcium is also a result of energy-dependent calcium pump failure and opening of voltage-dependent calcium channels. Increased intracellular calcium is very detrimental to neurons and other cells, has been implicated as a major contributor to neonatal encephalopathy.

![Figure 1. Proposed phases of neuronal injury and death in foals with hypoxic-ischemic encephalopathy. (A) Hypoxic-ischemic encephalopathy is associated with primary (acute) neuronal injury and death related to cellular hypoxia, energy failure, and cellular depolarization. This results in decreased ATP, failure of membrane pumps (Na⁺–K⁺, Ca⁺⁺), and influx of Na⁺ and Ca⁺⁺ into neurons and other cells. Increased intracellular Na⁺ results in cell swelling, while membrane depolarization contributes to glutamate release. (B) Secondary neuronal death is associated with excess extracellular glutamate, free radical production, and inflammation. (C) Presynaptic nerve ending and glutamate receptors within the neuronal cell membrane. Activation of these receptors results in the influx of Na⁺ (NMDA, AMPA, kainate) and Ca⁺⁺ (NMDA) into the cell. Increased intracellular Ca⁺⁺ causes activation of numerous pathways that can result in cell injury or death. (NMDA: N-methyl-D-aspartate; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid).](image-url)
and ischemia-reperfusion injury, and is associated with calcium-dependent activation of various pathways, cell or neuron swelling, injury, and/or death. In healthy animals, cells regulate calcium at very low and nonfluctuating intracellular concentrations because calcium serves as a secondary messenger necessary for numerous intracellular reactions. Very small increases in intracellular calcium can result in activation of phospholipases, proteases, nucleases, endonucleases, and nitric oxide synthase (NOS); increases in neurotransmitter release (glutamate); uncoupling of oxidative phosphorylation; and generation of free radicals, all of which potentially contribute to neuronal cell death via necrosis or apoptosis.

Specific Mechanisms of Cell Injury

The Role of Excitatory Amino Acids and Neurotransmitters

Glutamate is a primary excitatory amino acid neurotransmitter of the CNS, initiating downstream events through its interaction with various specific receptors, including receptors of N-methyl-D-aspartate (NMDA), kainate, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). These receptors are linked to ion channels and are therefore called ionotropic receptors. The NMDA receptor is linked to calcium channels, while the AMPA and kainate receptors are linked to sodium channels (FIGURE 1). In healthy animals, interaction between glutamate and these receptors occurs with vision, learning, and memory; however, when this interaction is associated with hypoxic-ischemic insults, it can result in neurodegeneration. In healthy animals, glutamate is released from presynaptic nerve terminals when neuronal depolarization occurs. Subsequently, glutamate is quickly removed from the synaptic cleft by glutamate transporters in local astroglia and converted to glutamine before being transported back into nerve terminals for reuse. Hypoxia or ischemia impairs function of astroglial glutamate transporters in the synaptic cleft. Impaired glucose delivery to the brain, associated with ischemia, further inhibits glutamate transporters that are normally fueled by glucose metabolism. Thus, hypoxic-ischemic insults can significantly disrupt excitatory synapse function, resulting in accumulation of extracellular glutamate and associated opening of ion channels operated by glutamate receptors. This excitotoxicity—in which excessive activation of glutamatergic neurotransmission results in neuronal flooding with intracellular calcium—can subsequently result in neuronal damage and cell death. Modification of the NMDA receptor to allow increased calcium influx further contributes to excessive intracellular calcium when a developing brain is subject to hypoxia.

Cumulatively, a hypoxic-ischemic insult results in accumulation of extracellular glutamate, activation of calcium channels (primarily NMDA channels), and, ultimately, increased intracellular influx of calcium into neurons. Consequently, increased intracellular calcium activates enzymatic pathways involved in the production of reactive oxygen species (ROS), including the conversion of xanthine dehydrogenase to xanthine oxidase, activation of NOS, and activation of phospholipase A. Furthermore, increased intracellular calcium activates aforementioned cellular pathways (lipases, proteases, nucleases) and the expression of apoptotic and antiapoptotic genes, all contributing to cell injury and/or death.

The Role of Free Radicals

The brain is very susceptible to oxidative damage because it contains low concentrations of endogenous antioxidants and high concentrations of polyunsaturated fatty acids that are vulnerable to lipid peroxidation. In addition, free radicals can activate specific “death genes,” resulting in apoptotic cell death of neurons. Reperfusion injury is an important factor responsible for brain injury in asphyxiated infants via increased production of ROS and nitric oxide (NO). Sources of free radical production include the mitochondrial electron transport system, xanthine oxidase, infiltrating neutrophils and microglia, the action of cyclooxygenase and lipooxygenase on arachidonic acid, and metabolites of NO; many of these pathways are initiated by calcium-activated processes. Various studies have clearly documented an increased presence of ROS during experimental models of human neonatal encephalopathy. In comparative studies in infants, higher concentrations of malondialdehyde were measured in plasma and cerebrospinal fluid from infants with neonatal encephalopathy, indicating increased lipid peroxidation. In addition, higher plasma concentrations of nitrate and/or nitrite (markers of NO) were detected. Furthermore, increased blood-brain barrier permeability was associated with increased severity of neonatal encephalopathy, suggesting more severe disruption of the blood-brain barrier in severe neonatal encephalopathy.

Particular attention should be directed at the important role of NO in neonatal encephalopathy and ischemia-reperfusion injury. Of the three forms of NOS (i.e., constitutive neuronal form [nNOS], constitutive endothelial form [eNOS], and inducible form [iNOS]), the constitutive forms are activated by calcium. Specifically, in neurons, nNOS is localized with NMDA receptors and activated by calcium influx through the NMDA receptor. Increased expression of nNOS occurs during the hypoxic-ischemic insult via activation of NMDA receptors and subsequent influx of calcium. During reperfusion and reoxygenation, nitric oxide radicals can be generated; subsequently, the highly toxic peroxynitrite can form and contribute to cellular injury. Collectively, reactive oxygen and nitrogen species significantly contribute to neuronal damage by inducing lipid peroxidation of cell membrane phospholipids that consequently break down cell membrane integrity.

The Role of Inflammation and Cytokines

The inflammatory response and proinflammatory cytokines are also involved in the pathogenesis of neonatal encephalopathy. Microglial cells, the resident macrophages within the CNS, can be activated by hypoxic-ischemic insults (specifically by excitatory amino acids and leukocyte migration) and subsequently produce proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and IL-18 as well as tumor necrosis factor α (TNF-α). The ensuing inflammatory response increases regional cerebral blood flow and alters neuronal and microglial function, resulting in brain
injury and cytotoxic edema. The inflammatory response also involves the upregulation of cellular adhesion molecules through endothelial cells by IL-1 in the brain's blood vessels, resulting in the infiltration and accumulation of neutrophils initially, followed by mononuclear cells. These inflammatory cells subsequently produce ROS and additional inflammatory cytokines, further contributing to cellular injury. Inflammatory cytokines also activate iNOS, which is associated with astrocytes and microglia, in a calcium-independent manner, resulting in further NO production. Concurrently, TNF-α activates microglial cells and may have direct cytotoxic effects on the CNS. Cytokines may injure white matter by inhibiting differentiation of developing oligodendrocytes, inducing oligodendroglial apoptosis, and causing myelin degeneration, thus exacerbating neuronal injury. Conversely, beneficial roles of inflammatory cytokines include activation of cells, such as neutrophils and microglia, that subsequently eliminate cellular debris and contribute to functional recovery. Thus, the inflammatory response subsequent to hypoxic-ischemic insults is necessary to remove cellular debris but may concomitantly result in cellular injury.

Some cases of “hypoxic-ischemic encephalopathy” show no evidence of a hypoxic-ischemic event. A theory regarding this type of neonatal encephalopathy points to possible involvement of the fetal systemic inflammatory response, in which proinflammatory cytokines (IL-1, IL-6, TNF-α) are produced by the fetal immune system in association with intrauterine infections (i.e., placentitis, chorioamnionitis). Studies have correlated increased proinflammatory cytokines with CNS lesions in neonatal infants. In one study involving neonatal infants for whom the maternal history included chorioamnionitis, there was a direct relationship between abnormal results of a neurologic examination and IL-6 concentrations. Furthermore, infants with the most extreme neurologic examination results had the highest concentrations of IL-6 and IL-8, suggesting that cytokines may play a role in the cascade of events leading to periparturient brain injury. Proposed mechanisms by which increased proinflammatory cytokines may damage the CNS include direct cytotoxic effects; increased blood-brain barrier permeability; increased production of NOS, cyclooxygenase, and free radicals; increased release of excitatory amino acids; and induction of systemic inflammatory response syndrome, resulting in the deleterious effects associated with inflammation as described above. Placentitis in pregnant mares is not uncommon and is a risk factor for the development of acute neurologic deficits in neonatal foals; therefore, it is plausible, but not yet confirmed, that a fetal inflammatory response may play some part in the pathophysiologic development of neonatal encephalopathy in foals.

**Causes and Clinical Signs**

Multiple peripartum conditions have been associated with neonatal encephalopathy in people. These conditions include severe uterine asphyxia as a result of reduced uterine or umbilical circulation, postnatal respiratory insufficiency, and severe cardiac malformations. Clinical signs of neonatal encephalopathy in infants vary with the severity of the insult. Signs associated with an acute hypoxic-ischemic insult include depressed consciousness, abnormal respiratory patterns, bradycardia, and severe seizures. Infants who survive to 72 hours of age usually improve over the next several days to weeks; however, certain neurologic deficits (e.g., mild to moderate stupor; abnormalities of sucking, swallowing, and tongue movements) may persist.

Many parallels in causes and clinical signs of neonatal encephalopathy exist between infants and foals. Conditions associated with peripartum asphyxia in foals include dystocia, induced parturition, cesarean section, placenta separation, meconium aspiration, twin foals, fetal infection, severe maternal illness, maternal surgery, and postterm pregnancies; alternatively, neonatal encephalopathy in foals can be associated with normal parturition (BOX 1). In a retrospective study of 78 neonatal foals with a primary diagnosis of neonatal encephalopathy, historical information revealed the presence of placental abnormalities (55% of foals), gestational problems (21%), premature placental separation (34%), and dystocia (30%). Foals with neonatal encephalopathy may appear healthy at birth but exhibit CNS abnormalities within hours of birth to 1 to 2 days of age.
Neonatal foals are immunocompetent at birth but immunologically naïve, having minimal immunoglobulins and no memory responses associated with adaptive immunity. Therefore, neonatal foals require consumption of antibody-rich colostrum to acquire immediate protection against various pathogens within the environment. In certain instances, neonatal consumption of adequate colostrum does not occur, resulting in failure of passive transfer (FPT) of maternal antibodies. These instances include maternal factors (e.g., rejection of the foal, agalactia, inadequate colostrum quality or quantity, premature lactation, maternal death during parturition) or neonatal factors (e.g., prematurity, sepsis, musculoskeletal disorders, neurologic disorders). The incidence of sepsis and related complications increases dramatically in foals with FPT. FPT can be diagnosed using various tests that quantitatively or semiquantitatively measure the concentration of IgG in whole blood, plasma, or serum. One of the more practical semiquantitative diagnostic tests for FPT is the ELISA (SNAP Foal IgG Test Kit, IDEXX Laboratories). In this test, the foal’s blood, plasma, or serum is mixed with reagents within the test device, resulting in color development of the test sample area. The intensity of color change is proportional to the IgG concentration in the foal’s sample. The color change of the foal’s sample is compared with calibrated IgG concentrations of 400 and 800 mg/dL. A color change representing an IgG concentration >800 mg/dL indicates adequate passive transfer, 400 to 800 mg/dL indicates partial FPT, and <400 mg/dL indicates complete FPT. Neonatal foals should be administered antibodies if complete FPT is identified. If a foal is younger than 12 hours, good-quality colostrum or equine plasma can be administered orally. At least 2 L of good-quality equine colostrum, divided into 300- to 500-mL increments, should be administered orally within the first 12 hours after birth. The ability of the small intestine to absorb colostrum decreases if antibodies have not been ingested within 6 hours after birth. If the foal is older than 12 hours, the ability of the small intestine to absorb antibodies through pinocytosis is greatly reduced or absent. Thus, plasma must be administered intravenously through tubing equipped with an inline filter. Observation for signs of a transfusion reaction, such as fever, tachycardia, tachypnea, or urticaria, is warranted. A starting dose of plasma to treat FPT is 1 to 2 L in a 50-kg foal, but the IgG concentration should be rechecked after plasma or colostrum administration to ensure that adequate antibodies have been administered to the foal. Similar recommendations are made in ill foals with IgG concentrations of 400 to 800 mg/dL. Foals with an IgG concentration of 400 to 800 mg/dL that are in a clean, well-managed facility and are clinically healthy may not require treatment, and their IgG levels are usually not rechecked later. Evaluation of passive transfer should be considered in all neonatal foals because of the prevalence of FPT and the severe complications associated with it.

**Box 2. In the Field: Failure of Passive Transfer**

Neonatal foals are immunocompetent at birth but immunologically naïve, having minimal immunoglobulins and no memory responses associated with adaptive immunity. Therefore, neonatal foals require consumption of antibody-rich colostrum to acquire immediate protection against various pathogens within the environment. In certain instances, neonatal consumption of adequate colostrum does not occur, resulting in failure of passive transfer (FPT) of maternal antibodies. These instances include maternal factors (e.g., rejection of the foal, agalactia, inadequate colostrum quality or quantity, premature lactation, maternal death during parturition) or neonatal factors (e.g., prematurity, sepsis, musculoskeletal disorders, neurologic disorders). The incidence of sepsis and related complications increases dramatically in foals with FPT. FPT can be diagnosed using various tests that quantitatively or semiquantitatively measure the concentration of IgG in whole blood, plasma, or serum. One of the more practical semiquantitative diagnostic tests for FPT is the ELISA (SNAP Foal IgG Test Kit, IDEXX Laboratories). In this test, the foal’s blood, plasma, or serum is mixed with reagents within the test device, resulting in color development of the test sample area. The intensity of color change is proportional to the IgG concentration in the foal’s sample. The color change of the foal’s sample is compared with calibrated IgG concentrations of 400 and 800 mg/dL. A color change representing an IgG concentration >800 mg/dL indicates adequate passive transfer, 400 to 800 mg/dL indicates partial FPT, and <400 mg/dL indicates complete FPT. Neonatal foals should be administered antibodies if complete FPT is identified. If a foal is younger than 12 hours, good-quality colostrum or equine plasma can be administered orally. At least 2 L of good-quality equine colostrum, divided into 300- to 500-mL increments, should be administered orally within the first 12 hours after birth. The ability of the small intestine to absorb colostrum decreases if antibodies have not been ingested within 6 hours after birth. If the foal is older than 12 hours, the ability of the small intestine to absorb antibodies through pinocytosis is greatly reduced or absent. Thus, plasma must be administered intravenously through tubing equipped with an inline filter. Observation for signs of a transfusion reaction, such as fever, tachycardia, tachypnea, or urticaria, is warranted. A starting dose of plasma to treat FPT is 1 to 2 L in a 50-kg foal, but the IgG concentration should be rechecked after plasma or colostrum administration to ensure that adequate antibodies have been administered to the foal. Similar recommendations are made in ill foals with IgG concentrations of 400 to 800 mg/dL. Foals with an IgG concentration of 400 to 800 mg/dL that are in a clean, well-managed facility and are clinically healthy may not require treatment, and their IgG levels are usually not rechecked later. Evaluation of passive transfer should be considered in all neonatal foals because of the prevalence of FPT and the severe complications associated with it.

**Diagnosis**

Diagnosis of neonatal encephalopathy in infants is based on historical information, neurologic examination, and supplementary diagnostics, including electroencephalography and brain imaging studies (computed tomography, magnetic resonance imaging).

In foals, many of the noted clinical signs can occur with other conditions, including neonatal sepsis, hypoglycemia, and prematurity. Therefore, neonatal encephalopathy in foals may occur as a primary problem or can complicate other clinical conditions. Diagnostics such as a complete blood count, serum biochemistry, arterial blood gas analysis, blood culture, urinalysis, and assessment of passive transfer of maternal antibodies (BOX 2) may be considered to identify other neonatal disorders and evaluate other body systems involved. Diagnosis of neonatal encephalopathy in foals relies on an accurate history, identification of neurologic deficits, and exclusion of other causes of CNS deficits, such as infectious, congenital, metabolic, or developmental conditions. Although no specific clinicopathologic findings have been highly suggestive of neonatal encephalopathy in foals, in the aforementioned study of foals with neonatal encephalopathy, 32% had an increased serum creatinine concentration, while 61% had an increased serum creatine kinase concentration. In addition, increases in the serum creatinine concentration (>3.5 mg/dL) and/or a low presuckle blood glucose concentration (<35 to 40 mg/dL) have been associated with placental insufficiency and an increase in neonatal encephalopathy.

Hypoxemia, hypercarbia, acidemia, and hypocalcemia may also be observed in foals with perinatal asphyxia, although these clinicopathologic abnormalities can arise from other neonatal disorders.

A recent equine study evaluated the usefulness of two biomarkers of brain injury, ubiquitin C-terminal hydrolase 1 (UCHL1) and phosphorylated axonal forms of neurofilament H (pNF-H), as potential antemortem diagnostic biomarkers of neonatal encephalopathy. In this retrospective study, UCHL1 and pNF-H from the plasma of 31 foals with a clinical diagnosis of neonatal encephalopathy were compared with those of 17 healthy foals. The authors reported that UCHL1 was significantly better than pNF-H for diagnosing neonatal encephalopathy. Specifically, the median concentration of UCHL1 (6.57 ng/mL; range: 2.35 to 11.90 ng/mL) was significantly higher in foals with neonatal encephalopathy compared with the median concentration in healthy foals (2.53 ng/mL; range: 1.4 to 4.01 ng/mL). The reported sensitivity and specificity of UCHL1 for diagnosing neonatal encephalopathy were 70% and 94%, respectively.

Measurement of UCHL1 is not readily available at this time, and further study is necessary to determine the usefulness of this biomarker.
### Table 1. Potential Therapeutics for Foals With Perinatal Asphyxia Syndrome

<table>
<thead>
<tr>
<th>Body System</th>
<th>Dose</th>
<th>Comment or Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central nervous system:</strong></td>
<td></td>
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<tr>
<td>Perform regular neurologic examinations</td>
<td></td>
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<tr>
<td>Control of seizures</td>
<td></td>
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</tr>
<tr>
<td>Diazepam</td>
<td>0.1–0.4 mg/kg IV, as needed</td>
<td>Monitor serum concentrations</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>2–10 mg/kg IV q12h for persistent seizures</td>
<td></td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>2–10 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.04–0.1 mg/kg IV, as needed</td>
<td>50 mg added to 90 mL of 0.9% NaCl produces a 0.5-mg/mL solution</td>
</tr>
<tr>
<td></td>
<td>0.02–0.06 mg/kg/h CRI for persistent seizures</td>
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<tr>
<td>NMDA antagonists</td>
<td></td>
<td></td>
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<tr>
<td>Magnesium sulfate</td>
<td>0.05 mg/kg/h IV CRI, loading dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.025 mg/kg/h IV CRI, maintenance dose</td>
<td></td>
</tr>
<tr>
<td>Reduction of CNS edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.25–1.0 g/kg IV as a 20% solution over 20 min, q12–24h</td>
<td>Contraindicated if cerebral hemorrhage is present</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>0.5 g/kg IV as a 10% solution over 30–60 min, q12–24h</td>
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<tr>
<td>Free radical scavengers/antioxidants</td>
<td></td>
<td></td>
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<tr>
<td>Vitamin E</td>
<td>5000 IU PO q24h</td>
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<tr>
<td>Vitamin C</td>
<td>100 mg/kg/d IV</td>
<td></td>
</tr>
<tr>
<td>Thiamine</td>
<td>10 mg/kg IV</td>
<td></td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>0.5 g/kg IV as a 10% solution</td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>44 mg/kg PO within first 4 hr</td>
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<tr>
<td>Respiratory system:</td>
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</tr>
<tr>
<td>Monitor arterial blood gas (Pao₂, Paco₂, pH, HCO₃⁻)</td>
<td></td>
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<tr>
<td>Hypoxemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intranasal O₂</td>
<td>3–5 L/min humidified oxygen</td>
<td>Maintain patient in sternal recumbency</td>
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<tr>
<td>Hypercapnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxapram</td>
<td>0.02–0.05 mg/kg/h CRI</td>
<td>May be more effective than caffeine</td>
</tr>
<tr>
<td>Caffeine</td>
<td>10 mg/kg PO or per rectum, loading dose;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 mg/kg PO or per rectum, as needed</td>
<td></td>
</tr>
<tr>
<td>Persistent/severe hypoxemia and hypercapnia</td>
<td></td>
<td></td>
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<tr>
<td>Surfactant replacement</td>
<td>Consider if surfactant dysfunction or deficiency is suspect</td>
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<tr>
<td>Antinflammatory medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>10 mg/kg PO q12h</td>
<td>Specific pharmacologic information not available for foals</td>
</tr>
<tr>
<td>Renal system:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitor urinalysis, urine output, body weight, and fractional excretion of electrolytes in urine; medications may not be very helpful; it is important to give IV fluids judiciously</td>
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</tr>
<tr>
<td>Fenoldopam</td>
<td>0.04 µg/kg/min CRI</td>
<td>Dopamine-1 receptor agonist</td>
</tr>
<tr>
<td>Furosemide</td>
<td>0.5–1.0 mg/kg IV q8–12h</td>
<td>Monitor serum electrolytes</td>
</tr>
<tr>
<td></td>
<td>0.12 mg/kg IV, loading dose; 0.12 mg/kg/h CRI</td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>0.5–1.0 g/kg IV as a 20% solution over 20 min</td>
<td>Osmotic diuretic</td>
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</tbody>
</table>
Neonatal Encephalopathy in Foals

**Table 1. Potential Therapeutics for Foals With Perinatal Asphyxia Syndrome (cont.)**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Dose</th>
<th>Comment or Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular system:</strong></td>
<td>monitor indirect or direct blood pressure, blood lactate level, and fluid therapy (body weight, central venous pressure)</td>
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</tr>
<tr>
<td>Dopamine</td>
<td>2–5 µg/kg/min CRI (as an inotrope)</td>
<td>Monitor heart rate and rhythm and blood pressure</td>
</tr>
<tr>
<td></td>
<td>5–10 µg/kg/min CRI (as a vasopressor)</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>1–3 µg/kg/min CRI</td>
<td>Monitor heart rate and rhythm and blood pressure</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.1–1.5 µg/kg/min CRI</td>
<td>Monitor heart rate and rhythm and blood pressure Corley44</td>
</tr>
<tr>
<td>Fluid therapy</td>
<td>2–5 mL/kg/h IV, maintenance rate</td>
<td>Evaluate fluid therapy frequently Palmer43</td>
</tr>
</tbody>
</table>

**Gastrointestinal system:** place nasogastric tube to evaluate for gastric reflux; if gastric reflux is significant, delay feeding and provide parenteral nutrition

- Antiulcer medication/gastrointestinal protectants
  - Sucralfate 20–40 mg/kg PO q6h
  - Omeprazole 4 mg/kg PO q24h Not labeled for foals younger than 4 weeks of age, but frequently used in neonates
  - Bismuth subsalicylate 0.5–4.0 mL/kg PO q6–24h

- Prokinetic medication
  - Erythromycin 0.1–1.0 mg/kg/h CRI
  - Lidocaine 1.3 mg/kg slow IV, loading dose; 0.06 mg/kg/min CRI
  - Metoclopramide 0.1–0.3 mg/kg IV over 30 min q6h 0.04 mg/kg/h CRI 0.1–0.25 mg/kg PO q6h Koenig J, Cole N. Equine gastrointestinal motility—ileus and pharmacological modification. Can Vet J 2006;47(6):551-559.

**Nutritional Support:** avoid enteral feedings if gastric reflux is significant

- Enteral feeding Mare’s milk: feed 10% to 25% of foal’s body weight per day; divide into every-other-hour feedings
- Parenteral nutrition 10 g/kg/d of dextrose; 2 g/kg/d amino acids; 1 g/d of lipids Starting formula provides 53 kcal/kg

**Hypoglycemia**


**Correction of metabolic derangements and prevention of secondary infection**

- Metabolic acidosis Provide NaHCO₃ supplementation only after foal has been properly hydrated with balanced IV crystalloid solution May cause hypernatremia or hypokalemia

- Electrolyte derangements Correct electrolyte derangements with oral or IV supplementation


- Ensure adequate passive transfer of maternal antibodies

- Administer plasma and colostrum If there is failure of passive transfer
Treatment

Treatment of neonatal encephalopathy in foals and infants is principally supportive and should address the multiple organ systems that may be involved in perinatal asphyxia. TABLE 1 outlines therapeutics used to treat foals with neonatal encephalopathy. This section discusses therapeutics and medications that target specific pathophysiologic mechanisms in infants with neonatal encephalopathy. Because energy depletion plays a role in the development of neonatal encephalopathy in infants, and because neonates have minimal energy reserves, it is imperative to maintain the blood glucose concentration within the reference range. Maintenance of adequate blood pressure and perfusion is also vital for supporting cerebral perfusion and avoiding further ischemic injury. This can be accomplished by identifying cause(s) of hypotension and cautiously administering intravenous fluid therapy and vasopressors and/or inotropes, if necessary. Systemic hypotension should be avoided because it may result in rupture of cerebral capillaries and hemorrhagic complications. In addition, strategies to decrease the cerebral metabolic rate to preserve energy have been investigated in infants. The most promising therapy is mild hypothermia; high doses of barbiturates or mild hypercapnia have also been suggested to decrease energy use. Hypothermia may also inhibit glutamate release from synaptic nerve endings, improve uptake of glutamate by astrocytes, reduce free radical production and NO synthesis, and decrease cortical cytotoxic edema. Mannitol has been used to reduce cerebral edema, but improved outcome has not been demonstrated in infants administered mannitol, perhaps because the edema may be intracellular. While seizure activity may arise from pathophysiologic processes involved in neonatal encephalopathy, seizure activity can greatly increase cerebral oxygen consumption and contribute to ongoing injury. Therefore, anticonvulsants (phenobarbital, diazepam, midazolam) are implemented if seizures are observed in infants.

Accumulation of glutamate appears to contribute to the pathogenesis of neonatal encephalopathy; thus, inhibition of glutamate release has been targeted. Because calcium influx is necessary for glutamate release at presynaptic nerve endings, calcium-channel blockers (flunarizine, nimodipine) have been administered to circumvent glutamate release in infants. Magnesium has also been administered to block the release of glutamate. Specific NMDA-receptor antagonists (e.g., dizocilpine, magnesium, ketamine, dextrorphan) have also been investigated. In efforts to abate cerebral inflammation associated with neonatal encephalopathy, medications that inhibit the inflammatory process (e.g., IL-1 antagonists, anticytokine antibodies, platelet activation factor antagonists, pentoxifylline) have also been investigated. Inhibiting free radical production with medications (e.g., allopurinol, iron chelators, superoxide reductase, 21-aminosteroids, dimethyl sulfoxide [DMSO]) or antioxidants (e.g., vitamins E and C) has also been considered in infants. Older studies using animal models have suggested that endogenous opiates may negatively influence ventilation of neonates with perinatal asphyxia. Based on this theory, naloxone, an opiate antagonist, may improve outcomes for newborn infants with perinatal asphyxia. However, reviews of this treatment have not provided adequate evidence that naloxone improves outcomes.

Alternatively, recent research has suggested neuroprotective effects of hyperbaric oxygen in rat models of neonatal encephalopathy by, among other mechanisms, reducing apoptosis, promoting proliferation of neuronal stem cells, enhancing oxygen radical scavengers, and increasing oxygen delivery to the brain. Furthermore, the use of hyperbaric oxygen in infants has demonstrated increased activity of superoxide dismutase; decreased levels of malondialdehyde, NO, and NOS; and improved neurologic assessments. While several of the aforementioned therapeutics have not been used in the veterinary clinical setting or are cost-prohibitive in equine medicine, several are readily available and have been used in foals (TABLE 1). In foals, single seizures can be controlled with diazepam; however, phenobarbital or, less commonly, midazolam may be considered for controlling repeated seizure activity. A normal blood glucose concentration can be maintained in foals by constant-rate infusion of dextrose, but hyperglycemia or hypoglycemia should be avoided. Preservation of adequate blood pressure through judicious administration of intravenous fluid therapy and vasopressors and/or inotropes is also readily achievable for neonatal foals. Investigation of the pharmacokinetics of pentoxifylline in adult horses has revealed that administration of this medication may inhibit TNF-α production in foals with neonatal encephalopathy. Additionally, a CRI of magnesium sulfate has been administered to foals in an effort to block calcium influx and, subsequently, release of glutamate. Antioxidants such as vitamins E and C can be administered along with thiamine to support cellular metabolism, including mitochondrial metabolism and Na⁺–K⁺ ATPases. DMSO is an inexpensive free radical scavenger that has been used in foals with neonatal encephalopathy, but the efficacy of this treatment is debatable. Allopurinol, a xanthine oxidase inhibitor, can be administered to decrease free radical formation. Allopurinol is one of the few medications that has demonstrated improved neurologic outcome in prospective clinical studies in infants. Mannitol has been used in foals with severe neonatal encephalopathy in an attempt to reduce edema of the CNS, but this medication may not be beneficial for treating intracellular (cytotoxic) edema, which occurs with this disease. Naloxone has been suggested as a therapeutic agent, but its use is very limited in equine neonatal encephalopathy, as is evidence for its efficacy. The use and availability of hyperbaric oxygen therapy in equine medicine are limited, but this therapy has been used to treat neonatal encephalopathy in foals.

Because there is no specific information regarding the outcomes of the above therapies for treating neonatal encephalopathy in foals, use of these therapies remains entirely speculative. Therapeutic objectives in foals with neonatal encephalopathy should include good supportive/nursing care, correction of clinico-pathologic alterations, and medications that support or target alterations in specific organ systems, when applicable (TABLE 1).
As noted in BOX 1, specific risk factors for the development of neonatal encephalopathy in foals have been identified, raising the question of potential prevention or amelioration in high-risk fetuses/foals with one or more predisposing factors. The clinician can first attempt to appropriately treat maternal disease (i.e., placentitis), if it is identified, before parturition. In addition, observation and intervention (if necessary) during parturition in mares with risk factors are important in attempting to prevent neonatal encephalopathy. Furthermore, recognizing distress in neonatal foals is vital for initiating appropriate therapy, such as cardiopulmonary cerebral resuscitation or respiratory support. Deliberate and mandatory obstetric training of midwives, obstetric medical staff, and house officers in one hospital decreased the incidence of neonatal encephalopathy from 27.3% to 13.6%, highlighting the significance of adequate training and prompt recognition and intervention of fetal or neonatal compromise in infants.60

Several detailed veterinary reviews are available regarding recognition of fetal compromise and equine neonatal resuscitation.61,62 No clinical trials have specifically investigated prevention of neonatal encephalopathy in foals, but proposed measures to prevent neonatal encephalopathy in other species include administering myriad medications and inducing hypothermia immediately after birth. However, a fine and perhaps ambiguous line separates prevention and treatment of neonatal encephalopathy. Of these reviews of various trials, only a few modalities have had encouraging results. Therapeutic hypothermia in animal studies and infants has been associated with significant and clinically important reductions in mortality and neurodevelopmental disability.63 However, this modality has not been explored in equine medicine. In another study, a significant decrease in neonatal seizures was documented in infants with neonatal encephalopathy who were administered phenobarbital (20 mg/kg IV) within 6 hours of birth; however, mortality and neurologic outcome were not altered.64 Reviews of randomized, controlled studies using glutamine, naloxone, dopamine, and other medications have not provided sufficient evidence to advocate the use of these medications for preventing neonatal encephalopathy or improving patient outcome.47,65,66

A potential preventive therapy that is under investigation involves modifying the steroidoidal environment of the fetal and neonatal brain. Recent studies have demonstrated that the brain is able to form steroids de novo (neurosteroids) that have a protective role and may prevent neonatal encephalopathy.67,68 More specifically, the allopregnanolone concentration is notably high in a healthy fetal brain and dramatically declines at birth.67,68 The high allopregnanolone level has a suppressive effect on the CNS (producing sleep-like behavior) during fetal life.67 However, the decrease in the allopregnanolone level after birth may increase the susceptibility of newborns to brain injury.67 The neuroprotective effects of neurosteroids are thought to result from γ-aminobutyric acid (GABA_A) receptor–mediated hyperpolarization, leading to a general reduction in CNS excitation.67 Acute hypoxia results in increased allopregnanolone synthesis in the brain, which may reduce neuronal cell death following acute asphyxia.67 Conversely, inhibition of neurosteroid synthesis in the fetal brain increases cell death.67 Thus, this information suggests that stimulation of neurosteroid production may protect the fetal brain from asphyxia-induced CNS injury, possibly serving as a preventive therapy, but further studies are necessary to explore this relatively new theory.

**Prognosis**

In general, foals with a primary diagnosis of neonatal encephalopathy without complicating factors have a good prognosis, with survival rates of 70% to 75% in some reports.2,5,37,69 Most foals that survive appear to recover completely.2,5 Subjectively, we have observed that most foals that survive the initial 5 days of life and demonstrate neurologic improvement over this period appear to have a good prognosis and no long-term neurologic deficits. This supposition is supported by a retrospective review of 78 foals with a primary clinical diagnosis of neonatal encephalopathy, in which neurologic signs lasted for 1 day in 29 foals, 2 days in 17 foals, 3 days in eight foals, 4 days in four foals, and 5 days in one foal; 19 foals did not survive.2 Many foals that survive go on to perform successfully.2,37,70 Foals with a guarded to poor prognosis include those that have complicating factors (e.g., sepsis), remain comatose or difficult to arouse, show no improvement in neurologic function during the first 5 days of life, or demonstrate severe, recurrent seizures.5,35 Rare, long-term neurologic deficits may include inability to suckle from the mare’s udder, prolonged visual impairment, residual spasticity, recurrent seizures, and unusual docility as adults.5,38

**Conclusion**

While neonatal encephalopathy is a relatively common CNS disorder in neonatal foals, information regarding the associated pathophysiological mechanisms in foals is based on information from human and laboratory animal models. The scientific literature provides abundant information on neonatal encephalopathy in infants; equine practitioners must base therapeutic plans on this information until equine-specific information is available. Addressing the multiple body systems that may be affected by neonatal encephalopathy in foals is essential for successful therapy. With diligent supportive and nursing care, foals with neonatal encephalopathy have a reasonable prognosis for survival.

**Disclosure Statement**

Dr. Bain discloses that he is coowner and vice president of Equine Oxygen Therapy.

**References**


