Common Problems of the Equine Neonate

Pamela A. Wilkins, DVM, PhD, DACVIM-LA, DACVECC

Equine Medicine and Surgery

University of Illinois College of Veterinary Medicine

Failure of Passive Transfer

Failure of passive transfer (FPT) occurs when there is insufficient absorption of immunoglobulins from colostrum resulting in serum IgG concentrations < 400 mg/dL after 24 hours of age. Foals with adequate immunoglobulin transfer have an IgG concentration > 800mg/dL. Foals with FPT are more likely to develop sepsis. FPT can be due to ingestion of poor quality colostrum, premature lactation, failure to ingest or absorb colostrum or increased immunoglobulin consumption.

The diffuse epitheliochorial nature of the equine placenta does not permit in utero transfer of immunoglobulins to the fetus, thus foals are essentially agammaglobulinemic at birth. Although foals are immunocompetent at birth they rely on immunoglobulins and immune factors provided by colostrum for protection in the first 4 to 8 weeks of life. Colostrum is usually produced in the last 2 to 3 weeks of pregnancy. It contains primarily IgG although other factors and immunoglobulins are present which are also important in the foal's immune protection. Immunoglobulins are absorbed via pinocytosis by specialized enterocytes. Maximal absorption occurs within 8 hours of birth, there is minimal absorption after 24 hours.

The minimum amount of IgG necessary to provide adequate immunity is generally recognized to be > 800 mg/L. However foals with IgG concentrations < 800 gm/dL can remain healthy, thus other factors such as exposure to and virulence of environmental pathogens, management factors, and colostral antibody titers to specific pathogens all play a role in the susceptibility of the foal to infection. FPT does not directly cause any clinical signs of disease and sepsis can cause an increase consumption of immunoglobulins.

There are several tests available for measuring IgG levels. Levels are usually measured at 18 to 24 hours when serum IgG levels have reached their peak. The single radial immunodiffusion (RID) is the most quantitatively accurate test, however results are not available for 18 to 24 hrs. Glutaraldehyde coagulation and zinc turbidity test are quick inexpensive tests.

They are best used as screening tests as they detect the foal that is likely to have FPT however their specificity is low thus a positive test may not indicate FPT. Immunoassays are convenient and easier to use. Both tests have a similar sensitivity but higher, though not ideal, specificity.

Treatment depends on the systemic condition of the foal and environmental conditions. Healthy foals with an IgG concentration between 400-800 mg/dL on well managed farms with low disease prevalence may not require treatment. However foals with an IgG concentration < 800 mg/dL that are systemically ill or in poor environmental conditions should have immunoglobulin supplementation. Foals with an IgG concentration < 400 mg/dL should have immunoglobulin supplementation, regardless. Immunoglobulin supplementation is by oral or intravenous administration depending on gastrointestinal function and age of the foal. Foals 12 to 24 hours of age with a functional GIT can be given oral immunoglobulin supplementation. Efficacy of absorption is decreased after 12 hours of age. Foals > 18 hours of age or with gastrointestinal dysfunction require intravenous supplementation. Immunoglobulin levels should be re-evaluated after any supplementation to ensure concentrations are > 800 mg/dL.

Equine colostrum is the ideal supplement. Administration of 1-2 L of good quality colostrum divided into 200 to 400 ml increments is recommended if complete FPT is suspected. Breeders should store frozen good quality colostrum. After the newborn foal has nursed from one side, 200-250 ml of colostrum can be milked from the other side and stored. Bovine colostrum can be used but is not ideal as bovine immunoglobulins have a short half-life in foals and are not directed against equine pathogens. Concentrated equine serum and lyophilized immunoglobulin result in detectable IgG levels however levels are < 800 mg/dL with recommended doses.

Many commercially available USDA licensed plasma products are available. Generally 1 liter of plasma containing 1200 mg/dL will increase a 45 kg foal's IgG by about 200 mg/dL. Septic foals may need larger amounts due to continued utilization of immunoglobulins. Plasma can also be used from a local donor who is negative for alloantibodies, infectious diseases and ideally Aa and Qa alloantigens.

The quality of the colostrum can be assessed and the foal supplemented at birth if required. Good quality colostrum should have an IgG > 3000 mg/dL. Colostral immunoglobulin levels can be measured using a Colostrometer or BRIX 0-50% sugar refractometer, the latter is

easier and more reliable to use. A specific gravity > 1.060 corresponds to an IgG > 3000 mg/dL and reading > 23% on the sugar scale corresponds to > 6000 mg/dL.

The IgG concentration of foals should be measured at 12 hours of age and, if needed, oral supplementation can be given.

Neonatal isoerythrolysis

Neonatal isoerythrolysis (NI) is an alloimmune hemolytic anemia of newborn foals caused by antibodies against the foal's erythrocytes in mare's colostrum. NI usually occurs in foals from multiparous mares and involves Aa and Qa factors.

Etiology

Aa and Qa factors (surface antigens) are the most immunogenic factors and account for approximately 90% of NI cases. The Ca blood group appears to influence the incidence of NI as Aa negative mares with anti-Ca antibodies do not produce antibodies against Aa factors. In mule foals a specific donkey factor has been identified.

The prevalence of NI in Thoroughbred and Standardbred populations is low. All mares bred to donkeys are at risk of producing foals that develop NI, however only about 10% of mule foals develop NI.

Pathophysiology

There are prerequisites required for the development of NI. The absorbed alloantibodies bind to the foal's RBC surface antigen resulting in hemolysis.

- If hemolysis is severe, decreased tissue oxygenation and cardiovascular collapse can occur resulting in seizures and multiorgan failure.
- Toxic hepatopathy from severe hemolysis or hepatic necrosis from hypoxia can occur.
- Severe hyperbilirubinemia can result in deposition of unconjugated bilirubin in the CNS resulting in kernicterus.

Clinical presentation

Typically, foals are clinically normal at birth and develop signs after ingestion of colostrum. Clinical signs vary depending on rate and severity of hemolysis and resulting anemia and can occur from 5 hours to 7 days after birth. Peracute cases occur at a younger age.

- Clinical signs in mild, slow onset NI include lethargy, tachypnea, tachycardia and pale icteric mucous membranes .

- In more severe acute onset cases the foals may be febrile, stop nursing and develop pigmenturia.
- Peracute cases may be found dead or present with signs of multiorgan failure and seizures and may not have developed icterus.
- Depression and neurological signs associated with kernicterus may be present.

Differential diagnosis

- Sepsis
- Meconium impaction
- Liver disease
- Hypoxic ischemic syndrome (HIS)
- EHV-1
- Internal or external hemorrhage

Diagnosis

Diagnosis is based on clinical signs and demonstration of maternal alloantibodies on the foal's RBC (Table 4). Typically the foal has anemia and hyperbilirubinemia. Severely affected foals may also have increased L-lactate concentrations, metabolic acidosis, pigmenturia and elevated liver enzyme activities. Alloantibody thrombocytopenia and neutropenia may be present.

- Hemolytic cross-match is the most reliable test. A positive test for NI is recognized by a strong hemolytic reaction in the minor crossmatch- mare serum against foal erythrocytes. The alloantibodies responsible for NI are stronger hemolysins than agglutinins thus tests for agglutination are not as reliable.
- The Jaundiced Foal Agglutination (JFA) assay can be performed in the field and in experienced hands correlates well with the hemolytic test.
  - In this test, the foal's RBCs are mixed with the mare's blood and evidence of agglutinating (or clumping) confirms anti-RBC antibody is present.

Management/Treatment

Treatment of NI depends on the severity of clinical signs.

- If clinical signs are present before 24 hours of age, the mare's colostrum should be withheld.
- If only mild hemolysis occurs, specific treatment may not be necessary.
- In more severe cases a blood transfusion and supportive therapy may be necessary.

If the foal has not been nursing and is hypovolemic, fluid therapy is instituted to improve tissue perfusion and oxygenation. Intranasal oxygen insufflation can be utilized to improve oxygen saturation. The decision for a blood transfusion depends on the clinical signs (weakness, tachypnea and tachycardia) and laboratory findings. Indicators of impaired tissue perfusion are used as PCV is unreliable.

- A combination of indicators of impaired tissue perfusion, PCV < 12 % and hemoglobin < 5 g/dL are used by the author.

Washed dam's RBC are the ideal choice for transfusion. A Qa Aa negative blood donor or Standardbred, Morgan or Quarter horse gelding with no prior history of blood transfusion are also suitable. The optimal volume required can be calculated, or 2-3 liters can be given empirically.

Deferoxamine mesylate may prove helpful for iron elimination in these cases.Prognosis is favorable for uncomplicated cases.

- Foals have a poorer prognosis if there is continued hemolysis after blood transfusions and are at risk of developing kernicterus and severe degenerative hepatopathy, both which carry a grave prognosis.

NI is a preventable disease. At risk brood mares, Aa and Qa negative mares and mares which have produced NI foals, can be identified. These mares can be bred to Aa Qa negative stallions, however due to the high prevalence of these antigens in the population this is impractical. Thus the "at risk mare" should be screened for anti-RBC antibodies which are produced in the last month of pregnancy. If anti-RBC antibodies are present a hemolytic or JFA test should be done on the foal prior to nursing. If positive, foals should be supplemented colostrum from another source and should not nurse from the mare for 48 hours or as determined by the JFA test. The mare should be milked frequently and milk/colostrum discarded.

Rib fractures

Ribs fractures in newborn foals are most commonly associated with trauma during parturition. Rib fractures in older foals are usually due to external trauma such as a kick or paddock accident. The resulting costochondral dislocation or rib fracture can be sub-clinical or cause a variety of clinical signs including sudden death.

Etiology

Rib fractures are more common in foals from primiparous mares and dystocias. Contributing factors have included shape of the thoracic cage, retention of an elbow during parturition, manipulation during delivery, and abnormally narrow pelvic canal. The foal's weight or thoracic circumference are not believed to be a factor and there does not appear to be a sex predilection.

Pathophysiology

The fracture or osteochondral dislocation appears to be caused by pressure on the thorax during passage through the pelvic canal. The most common site of injury is the cranioventral half of the thorax at the costochondral junction or adjacent proximal area. The majority of fractures are subclinical however the periosteal damage and surrounding muscle damage and blood vessel disruption can result in hematomas and pain. If the fracture extremities displace axially, parietal pleura can be perforated and underlying structures damaged resulting in bruising or laceration of the heart, lung, diaphragm and major vessels. Fatal myocardial lacerations can occur with fractures on either the right or left side and there is a higher risk of death with a higher number of fractured ribs.

Clinical presentation

Clinical signs are variable and depend upon the number and location of ribs affected and severity of the damage to the adjacent structures. Less severe clinical signs include crepitation on rib palpation, "clicking" sound on auscultation, edema localized over or ventral to the fractured ribs. Signs of pain include increased heart and respiratory rates, grunting or groaning when manipulated or lying on the affected side Auscultation of the thorax may reveal ventral dullness and lack of breath sounds if a hemothorax is present or lack of breath sounds dorsally if a pneumothorax is present. Respiratory distress can be seen in foals with multiple rib fractures and a flail chest, pneumothorax, hemothorax, or diaphragmatic hernia. Subcutaneous emphysema over the sides of thorax or axilla region may be present. Pale mucous membranes can be indicative of internal hemorrhage into the pleural or abdominal cavities. Tachycardia may reflect primary cardiac disease like myocardial bruising, laceration or hemopericardium. Sudden death is not uncommon and occurs when a major vessel, coronary vessel or myocardium are lacerated.

Differential diagnosis

- Diaphragmatic hernia
- Pneumonia
- Neonatal isoerythrolysis

- Umbilical remnant hemorrhage

Diagnosis

Palpation of crepitus over the fracture site is not a consistent finding and rib fractures are often not detected on physical examination. The ribs should be palpated by sliding the hand up cranially under the elbow and using gentle pressure with flat fingers. Radiographs are not reliable for detection of fractured ribs in neonates. Ultrasonographic examination is more reliable and allows visualization of the fracture site and displaced extremities, and evaluation of the adjacent structures. Analysis of the pleural fluid should be performed if a concurrent infectious component is suspected.

 Management/Treatment

Conservative treatment with box rest for 3-4 weeks is successful in the majority of uncomplicated rib fractures. Analgesics may be used judiciously; however providing pain relief may increase the foal's level of activity and chance of a fatal movement of a fractured end. Sedation may be needed to encourage decreased activity. Although different positioning is recommended for improved ventilation, foals are more settled if allowed to find their own side of comfort. Prophylactic broad-spectrum antimicrobial coverage is recommended if the foal is compromised or a hemothorax is present. Surgical repair has been advocated in cases with multiple rib fractures or those with potential for severe internal injury.

Initial treatment of complicated fractures with damage to underlying structures is aimed at stabilization of the foal by ensuring adequate ventilation and treatment of hypovolemic shock. Intranasal oxygen insufflation should be administered if hypoxemia is present and specific treatment of the pneumothorax and hemothorax should be instigated if the foal exhibits respiratory distress.

Meconium Impaction

Meconium impaction is one of the most common causes of colic in the neonatal foal. The foal normally begins passing meconium within the first few hours after birth and it is usually passed within 48 hours. If retained, the impaction and subsequent gas accumulation can cause tenesmus and mild to severe signs of abdominal pain.

Meconium is formed throughout fetal development and is a mixture of swallowed amniotic fluid and intestinal secretions including bile. Meconium has a characteristic olive brown color and can be thick and tarry or in pellets.

Meconium impactions can result from impaired gastrointestinal motility, failure to ingest colostrum, dehydration and prolonged recumbency. There is an increased incidence of meconium impactions in colts. The impaction can lead to complete intestinal obstruction and gaseous abdominal distension.

Signs of colic can begin within a few hours to 36 hours after birth, though most commonly occur 12-24 hours after birth. Early signs are restlessness, standing under the mare not nursing, aimless wandering, tail swishing and posturing to defecate. The signs of discomfort are often after nursing and the foal is usually bright in between colic episodes. More advanced cases have gaseous abdominal distension and more severe clinical signs of colic.

Differential diagnoses

- Intestinal atresia or agangliosis (lethal white syndrome)
- Ileus: Sepsis, HIS, Prematurity
- Enterocolitis
- Rectal irritation from enemas
- Strangulating intestinal lesions
- Uroperitoneum
- Intussusception

History, clinical signs and age will assist with diagnosis. Digital examination of the rectum with a well-lubricated finger may, but not always, detect meconium. Meconium can be palpated through the abdominal wall in relaxed recumbent foals. Abdominal ultrasonography is used to identify meconium and help rule out other causes of colic. Meconium is visualized as intraluminal masses. Fluid distension of proximal segments and an increase in anechoic peritoneal fluid may be present. Contrast radiography can be used to help identify the impaction.

Management/Treatment

Treatment is aimed at resolving the impaction, providing pain relief and systemic support. The majority of meconium impactions respond to medical treatment. In extreme cases surgical removal may be required; however this carries a poor prognosis.

Gentle digital manipulation may be able to remove retained meconium however usually an enema is required. Initially either a warm soapy water enema or commercial phosphate-based enema (Fleet®) can be used. The foal needs to be adequately restrained and tubes well lubricated to avoid rectal damage. Fleet® enemas are convenient and work well. Warm soapy water gravity

enemas (300-500 ml/50kg foal) can be used with a nonirritant soap such as Ivory®. Repeated enema administration can cause rectal irritation, edema and tenesmus. If initial enemas are not successful, an acetylcysteine retention enema should be given. It is important to have the foal relaxed and sedated so the enema fluid is not pushed out prematurely. The foal is placed in lateral recumbency, with hindquarters moderately elevated and a 30 Fr. Foley catheter with 30ml balloon is inserted 5-10 cm into the rectum and slowly inflated to avoid straining. The acetylcysteine solution is administered slowly and left in place for 30-45 minutes. The enema can be repeated after 12-24 hours. Intranasal oxygen insufflation (5 L/min) is provided to foals with abdominal distension or systemic compromise whilst the enema is being given. Oral laxative therapy (120-160 ml mineral oil) is used in proximal impactions if no reflux is present. The use of dioctyl sodium sulfosuccinate, glycerin, and castor oil use is not recommended. The use of metal instruments and repeated digital manipulation should be avoided. Percutaneous bowel trocharization should only be considered in extreme circumstances.

Butorphanol (0.01 – 0.04 mg/kg IM or IV; 2-4 mg/50 kg foal) is the preferred analgesic as it also provides sedation which assists with enema administration. Flunixin meglumine (1mg/kg) can be used however repetitive doses should be avoided due potential for toxicity. Xylazine needs to be used cautiously as it can cause respiratory depression and ileus in compromised foals.

Intravenous fluid therapy is given if needed to restore circulating volume. If the foal does not respond to the initial enema, restriction of milk intake may be required until the impaction resolves. During this time energy and maintenance fluid requirements are met by intravenous fluids with glucose or parenteral nutrition. It may be necessary to provide INO_2 insufflation to foals with severe abdominal distension.

Antimicrobial therapy may be necessary as disruption of the mucosal barrier can predispose to increased bacterial translocation and foals may have ingested insufficient quantities of colostrum whilst painful. Patent urachus, bleeding umbilical remnant, bladder rupture and scrotal hernia are secondary complications which may occur from straining.

Patent Urachus

Patent urachus is a relatively common problem identified in foals during the neonatal period. The urachus is the extension of the urinary bladder of the fetus to the allantoic cavity,

contained retroperitoneally within the umbilical cord between the 2 umbilical arteries, and is involved in the removal of nitrogenous wastes from the fetus. In humans the urachus is generally closed by 12 weeks of gestation and becomes the median ligament of the bladder, although it may very rarely be patent. The median ligament of the bladder serves to support the ventrally oriented and upright position of the bladder.

Species with epitheliochorial placentation and retention of both the allantoic cavity and contained fluids throughout gestation, such as the horse, will have an open and functional urachus until the time the umbilical cord separates at parturition, leaving both internal and external umbilical remnants. Although functional closure of the urachus occurs at this time, anatomic closure does not. The urinary bladder and associated internal umbilical remnant gradually retract from the body wall over the first several weeks of life, leaving the umbilical arteries to become the round ligaments of the bladder, the umbilical vein to become the Falciform ligament of the liver and the urachus involutes. The supporting fold of the urachus present in prenatal life primarily involutes with the urachus following birth, but a small fold remains to become the median ligament of the bladder, attaching the ventral surface of bladder to the pelvic floor and the linea alba.

Following birth the umbilical cord will naturally separate at a site located approximately 2-3 cm from the hairline, corresponding to narrowing of the umbilical arteries and vein. The external umbilical stump may display some variable patency for up to 24 hours as it dries out and involutes over a three to seven day period. The umbilical stump should be completely healed by three to four weeks of age.

Routine care of the umbilical stump has been well described. Dipping of the umbilical stump of newborn foals into a variety of disinfectant solutions 2 to 3 times daily following birth is common practice. Solutions used include 0.5% chlorhexidine and 1% povidone iodine. Use of dilute chlorhexadine solutions have been shown to significantly decrease the incidence of umbilical stalk infection and death in human infants and is now most commonly recommended for foals. Care should also be used with application of silver nitrate, historically and still commonly used to promote urachal closure, as a necrotic focus can develop. Excessive drying caused by application of concentrated iodine solutions or silver nitrate causes bacterial trapping and tissue devitalization, providing a favorable environment for bacterial growth and promoting patency of the urachus.[3,7]

Patent urachus is readily recognized when a foal is either observed to have a stream of urine originating from the umbilicus or it is noticed that the hair around the umbilicus is consistently wet. Regional urine scalding of the skin may be apparent if urine has been emanating from the urachus for a period of time and there may be local maceration of skin at the umbilicus or in regions of the ventral abdomen and medial hind limbs. Identification of urachal patency can be somewhat challenging in male foals that urinate into their prepuce, more common if the penile frenulum is still intact. In these cases, placing a flat hand perpendicular to midline and oriented vertically on the ventrum between the umbilicus and the prepuce will deflect the urine stream originating from the prepuce and allow direct visualization of any urine stream from the umbilicus.

Evaluation of Patent Urachus

History is an important component of evaluation for patent urachus. Patent urachus can develop shortly after birth or later in the first 7-14 days of life. Foals with patent urachus may present as otherwise healthy, showing early signs of infectious disease, or with prolonged recumbency due to another primary disease process. It is seldom a complaint of foals older than 2 weeks of age and the author has not recognized a case of patent urachus in a foal of weaning age. There are no studies directed fully at the evaluation of patent urachus as a single entity or following the fate of the urachus -and the internal umbilical remnant- sequentially over the first weeks and months of life in normal foals. If available, knowledge of the circumstances of parturition may be beneficial as may information related to periparturient problems such as dystocia or placental abnormalities.

The umbilical cord itself may contribute to patent urachus and other umbilical problems. An excessively long umbilical cord can be associated umbilical cord torsion, predisposing to urachal compromise by causing obstruction of blood flow and obstruction to urine flow from the fetal urinary bladder to the allantoic cavity. Decreased cord length (less than 30 cm) predisposes to increased traction on the umbilical cord that can compromise the integrity of the urachus.

In addition to addressing questions of history and placental abnormalities, a thorough physical examination should be undertaken with particular attention paid to the umbilical remnant. Patent urachus is associated in many reports with infection with other umbilical structures and also with uroperitoneum secondary to failure of urachal integrity. Routine clinical

pathology testing including CBC, plasma or serum chemistry and assessment of adequacy of passive transfer of maternal immunity should be performed.

Ultrasonographic examination is an important diagnostic and monitoring tool in cases of patent urachus and examination of the umbilical remnant has been reviewed and extensively presented elsewhere.

The presence of patent urachus in a neonatal foal indicates that the umbilical remnant is abnormal. It does not, however, indicate any specific abnormality.

Simple patent urachus: In these cases patency may be present immediately after birth or become apparent in the first few days of life in an otherwise healthy and vigorous foal. This form of patent urachus generally resolves spontaneously as the foal become more active and micturates more frequently, applying tension to the internal umbilical remnant and encouraging closure of the urachus. Historically, the umbilical cord may have broken close to foal or been cut or tied off close to the foal. These cases may also be observed in male foals urinating into their prepuce, resulting in a constantly wet macerated umbilical stump. In some cases the umbilical stump may have been treated often and vigorously, again resulting in a constantly wet umbilical stump. Paradoxically, use of silver nitrate or higher concentrations of iodine solutions can result in patent urachus secondary to excessive drying and subsequent necrosis of the umbilical stump.[3]

Mechanical patent urachus:

Patency of the functionally but not yet anatomically closed urachus may occur secondary to abdominal straining, such as seen with meconium retention/impaction or stranguria secondary to urachitis. Urachitis is commonly associated with urachal diverticulum, where the urachal portion closest to the bladder remains open, resulting in some urine pooling in the urachus. This condition is only recognized with an ultrasonographic examination of the internal umbilical remnant and can result in minor discomfort and straining following urination but generally requires no specific treatment and usually resolves within 1-3 days.

Infectious patent urachus:

The urachus becomes patent associated with infection of structures of the internal umbilical remnant and generally manifests when a foal is several days to 1-2 weeks of age. Infection may remain clinically silent for a period of time but localized clinical signs of umbilical stump swelling, purulent discharge, heat and pain on palpation are compatible with umbilical infection. The umbilical stump should be evaluated daily for evidence of local infection although infection

may not manifest externally. Inflammation, infection and necrosis can become locally extensive. In these cases where infection has become locally extensive, or becomes systemic, clinical signs may include fever, depression and poor suckling. It has been postulated that infection might ascend along the urachus to the urinary tract and facilitate bacteremia. Local urachal infection may also result in uroperitoneum due to formation of internal urachal defects associated with areas of necrosis; foals with urachal infection or trauma should be ultrasonographically evaluated frequently, even daily, for this complication. Development of uroperitoneum generally requires surgical intervention and correction by removal of the umbilical remnant once the foal is medically stable. Detailed discussion of uroperitoneum, including identification and treatment, is beyond the scope of this manuscript.

Urachal patency associated with critical illness:

Foals with critical illness or with problems such as congenital severe flexural deformities may experience prolonged recumbency with development of patent urachus an expected problem in these cases by experienced clinicians. Its genesis is generally similar to simple patent urachus, with components of mechanical patent urachus, as the ventrum of these foals are frequently damp, causing maceration of the umbilical stump, and they are not assuming a normal body position to urinate. Trauma secondary to recumbency may also result in early loss of the umbilical stump. These foals may not recognize a full bladder and the need to urinate, resulting in increased pressure on the urachus from the full bladder. This is a particular problem with critically ill male foals due to the resistance to passive urination presented by their long urethra. In the majority of these cases umbilical or urachal infection is not the primary cause.

Perinatal Asphyxia Syndrome(PAS)/NE/HIE

Hypoxic ischemic encephalopathy (HIE), currently referred to as neonatal encephalopathy (NE) in the human literature, is one systemic manifestation of a broader syndrome of perinatal asphyxia syndrome (PAS) and management of foals presenting with signs consistent with a diagnosis of HIE requires the clinician to fully examine other body systems and provide therapy directed at treating other involved systems. While PAS primarily manifests as HIE, the gastrointestinal tract and kidneys are frequently affected by peripartum hypoxia/ischemia/asphyxia and complications associated with these systems should be expected.

The cardiovascular and respiratory systems may also be affected and endocrine disorders are also encountered in these patients.

HIE has been recognized as one of the most common diseases of the equine neonate for generations. It has been known in the past as dummy foal syndrome and as neonatal maladjustment syndrome. The designation HIE, while not perfect, attempts to describe the syndrome in terms of the suspected underlying pathophysiology.

A wide spectrum of clinical signs are associated with HIE and can range from mild depression with loss of the suck reflex to *grand mal* seizure activity. Typically, affected foals are normal at birth but show signs of central nervous system (CNS) abnormalities within a few hours following birth. Some foals are obviously abnormal at birth and some will not show signs until 24 hours of age. HIE is commonly associated with adverse peripartum events, including dystocia and premature placental separation, but a fair number of foals have no known peripartum period of hypoxia, suggesting that these foals result from unrecognized *in utero* hypoxia. Severe maternal illness may also result in foals born with PAS. In humans, ascending placental infection is now suspected to be a major contributor to NE in infants and the incidence of NE is increased with the presence of maternal fever, suggesting a role for maternal inflammatory mediators.[120]

The underlying pathophysiologic details of HIE in the foal are unknown and, to date, accurate experimental models of HIE and PAS in the foal have not been described. However, a great deal of attention has been paid to peripartum hypoxia/asphyxia by our human counterparts, as the effects of adverse peripartum events in the human neonate have far ranging implications for the affected human neonate and for society. Therefore, equine neonatologists have long looked to human studies and models of the human disease for understanding of the syndrome in the equine neonate.

Therapy for the various manifestations of hypoxia-ischemia involves control of seizures:

Cerebral support, correction of metabolic abnormalities, maintenance of normal arterial blood gas values, maintenance of tissue perfusion, maintenance of renal function, treatment of gastrointestinal dysfunction, prevention/recognition/early treatment of secondary infections and general supportive care. It is important that seizures be controlled as cerebral oxygen consumption increases five-fold during seizures. Diazepam can be used for emergency control of seizures. If seizures are not readily stopped with diazepam, or more than two seizures are

recognized, then diazepam should be replaced with phenobarbital given to effect. The half-life of phenobarbital can be quite long in the foal (more than 100 hours) and this should be kept in mind when monitoring neurologic function in these cases after phenobarbital administration. If phenobarbital fails to control seizures, midazolam or phenytoin therapy may be attempted. It is important to protect the foal from injury during a seizure and also to ensure the patency of their airway to prevent the onset of negative pressure pulmonary edema or aspiration pneumonia. Control of acute onset seizures in neonatal foals has conventionally relied on short-term (immediate) control using IV/IM bolus administration of diazepam. Recurrent seizures in foals have been treated with either repeated diazepam administration and/or infusion of phenobarbital or phenytoin.[1] Single seizure episode control with diazepam is frequently effective, relatively inexpensive and simple; however, recurrent seizures become more difficult to manage, and, control with phenobarbital becomes problematic in either a practice or referral institution setting due respiratory depression, which may be more severe in neonates because of reduced hepatic clearance, associated with its use. The onset of activity may be15 minutes or longer following IV administration, with peak effect not present until 60 minutes. Other potential deleterious effects of phenobarbital use include bradycardia, hypotension and hypothermia, particularly at larger doses. Because of this, slow titration using small IV boluses (2-3 mg/kg IV over 15-20 minutes) of the drug and close observation are required to find the lowest effective dose. Ideally, phenobarbital use in foals should be implemented in conjunction with monitoring of plasma drug concentration. Therapeutic concentrations are reported as 5-30 µg/ml.   The clearance of phenobarbital is slow in the neonate and the effects are prolonged once administered. Complete evaluation of CNS function may be delayed for several days following cessation of phenobarbital due its prolonged effects.

The potential for drugs such as phenobarbital to complicate the clinical management of neonatal seizures led to the search for alternative means for seizure control. Midazolam is a potent short-acting benzodiazepine that is a safe and highly effective agent for controlling status epilepticus and has been investigated in the treatment of refractory (i.e. phenobarbital and/or phenytoin resistant) neonatal seizures in human infants.[2-5] It is reported to be more potent than diazepam in a seizure model in dogs on a mg basis. The use of midazolam as a first line treatment in seizure management has gained popularity with some equine neonatologists.

Probably the most important therapeutic interventions are aimed at maintaining cerebral perfusion. This is achieved by careful titration of intravenous fluid support, neither too much nor too little and judicious administration of inotropes and pressors in order to maintain adequate perfusion pressures. Cerebral interstitial edema is only truly present in the most severe cases; in most cases the lesion is intracellular edema and most of the classic agents used to treat cerebral interstitial edema, mannitol and the like, are minimally effective treating cellular edema. We occasionally use thiamine supplementation in the intravenous fluids to support metabolic processes, specifically mitochondrial metabolism and membrane Na+/K+/ATPases, involved in maintaining cellular fluid balance. This therapy is rational and inexpensive but unproven in efficacy. In our clinic we rarely use DMSO, have only used it rarely for the last several years, and have recognized no change in outcome by discontinuing its use. When we use intravenous DMSO, it is reserved for use within the first hour after an acute asphyxial insult and then used primarily for its hydroxyl radical scavenging effects and its theoretical modulation of post-ischemic reperfusion injury.

Despite a lack of consensus regarding the use of magnesium in the treatment of infants with HIE, we have used magnesium sulfate infusion as part of our therapy for selected HIE foals for the past several years. Our rationale is based primarily in the evidence demonstrating protection in some studies and a failure of any one study to demonstrate significant detrimental effects. Our clinical impressions to date suggest that the therapy is safe and may decrease the incidence of seizure in our patients. We administer magnesium sulfate as a constant rate infusion after a loading dose is given over 1 hour. I have continued the infusion for up to 3 days without demonstrable negative effect beyond some possible trembling, but given the current evidence, a 24-hour course of treatment may be effective and all that is necessary. Post-asphyxial treatment may certainly be beneficial in foals with HIE and maternal magnesium therapy may beneficial in certain high-risk pregnancy patients.

Foals with PAS often have a variety of metabolic problems including hypo- or hyperglycemia, hypo- or hypercalcemia, hypo- or hyperkalemia, hypo- or hyperchloremia and varying degrees of metabolic acidosis. Foals suffering from PAS will also have frequent recurrent but of hypoxemia and occasional bouts of hypercapnia. INO_2 is generally needed in these cases both as a preventative therapy and as direct treatment, as the appearance of the abnormalities can be sporadic and unpredictable. Additional respiratory support, particularly in

those foals with centrally mediated hypoventilation and periods of apnea or abnormal breathing patterns, include caffeine (*per os* or *per rectum*) and positive pressure ventilation. Caffeine is a central respiratory stimulant and has minimal side effects at the dosages used (10 mg/kg loading dose; 2.5 mg/kg prn). Mechanical ventilation of these patients can be very rewarding and is generally required for less than 48 hours.   Maintaining tissue perfusion and oxygen delivery to tissues is a cornerstone of therapy for PAS in order to avoid additional injury. Oxygen carrying capacity of the blood should be maintained; some foal will require transfusions to maintain a PCV > 20%. Adequate vascular volume is important, but care should be taken to avoid fluid overloading the foal. Early evidence of fluid overload is subtle accumulation of ventral edema between the front legs and over the distal limbs

The kidney is a target for injury in these patients and it is not unusual for renal compromise to play a significant role in the demise of these foals. Clinical signs of renal disease are generally referable to disruption of normal control of renal blood flow and tubular edema leading to tubular necrosis and renal failure. These foals present with signs of fluid overload and generalized edema. It is important that urine output and fluid therapy be balanced in these cases to prevent additional organ dysfunction associated with edema. We do not aim for urine production rates of 300 ml/hour, as has been presented by other authors as a urine output goal for critically ill equine neonates. Rather, we look for urine output that is appropriate to fluid intake and we do not attempt to drive urine output to an arbitrary goal by excessive fluid administration or pressor utilization. Expecting critically ill foals to produce such large volumes of urine, particularly those on restricted diets or receiving total parenteral nutrition (TPN), is an exercise in futility and manipulating fluid, pressor and/or diuretic therapy in attempt to meet an artificial goal is, quite simply, poor medicine.

Foals with PAS suffer from a variety of problems associated with abnormalities within the gastrointestinal tract. Commonly they present with ileus, recurrent excessive gastric reflux and gas distention. These problems are exacerbated by constant feeding in the face of continued dysfunction and continued hypoxia. Frequently, enteral feeding cannot meet their nutritional requirements and partial or total parenteral nutrition is required (see section on TPN). Special attention is required to passive transfer of immunity and glucose homeostasis in these cases. Appearance of damage to the gastrointestinal tract can be subtle and lag behind other clinical abnormalities for days to weeks. Low grade colic, decreased gastrointestinal motility, decreased

fecal output and low weight gain are amongst the most common clinical signs of gastrointestinal dysfunction in these case, but more severe problems, including necrotizing enterocolitis and intussusception, have been associated with these cases. The return to enteral feeding must be slow in many of these cases.

Foals with PAS are also susceptible to secondary infection. If infection is recognized in these patients after hospitalization, attention should be given to the likelihood of nosocomial infection and antimicrobial therapy should be directed, until culture and sensitivity results become available, based on known nosocomial pathogens in the NICU and their susceptibility patterns. Repeat determination of IgG concentration should be made and additional intravenous plasma therapy may be required. Nosocomial infections are notoriously rapidly overwhelming and any acute deterioration in the condition of a foal with PAS should prompt a search for nosocomial infection.

The prognosis for foals with PAS is good to excellent when it is recognized early and aggressively treated in term foals. Up to 80% of these neonates survive and go on to lead productive and useful athletic lives. The prognosis decreases with delayed or insufficient treatment and concurrent problems such as prematurity and sepsis.

Sepsis:

The survival rate of foals being treated for sepsis has improved, despite the lack of a 'magic bullet'. Next to hypoxic ischemic asphyxial syndromes, sepsis is the number one reason for presentation and treatment at referral centers.

Concensus criteria conferences[1]in the early 1990's defined sepsis and septic shock for humans. Sepsis was defined as " the systemic response to infection manifested by two or more of the following conditions as a result of infection: a) temperature > 38°C or les<36°; b) heart rate>90 beats per minute; c) respiratory rate > 20 breaths per minute or $PaCO_2$<32 torr; and d) white blood cell count >12,000 cell/μl, < 4,000 cell/μl, or >10% immature (band) forms. Septic shock was defined as sepsis induced hypotension or the requirement for vasopressors/ionotropes to maintain blood pressure despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria or acute alteration in mental status. Septic shock has been rather cavalierly referred to as 'a rest stop on the road to death'. Unfortunately this is all too often true. These definitions are broadly acceptable and applicable to neonatal sepsis in foals and many of the treatment modalities in

human medicine have been applied in some manner to the equine neonatal patient. Additional definitions that have come into to vogue, and that are actually useful at times include: SIRS, the systemic inflammatory response system; MODS, multiple organ system dysfuction; and MOFS, multiple organ failure syndrome. SIRS is sick, MODS is sicker and MOFS is dying. CARS is the compensatory response syndrome, which ideally balances SIRS and keeps it from becoming detrimental. Managing the septic patient involves early recognition of all the potential alphabet combinations and either supporting the patient or intervening in the face of multiple clinical consequences, termed 'CHAOS' (Cardiovacular compromise; Homeostasis; Apoptosis; Organ Dysfunction; Suppression of the immune system). Inflammatory mediators are involved in all these processes and can be either beneficial or detrimental, depending on timing and opposing responses. Neutrophils, platelets, lymphocytes, macrophages and endothelial cells are all involved and the implicated inflammatory molecules grow daily in numbers.

Sepsis in the foal can initially be quite subtle and the onset of clinical signs is variable depending on the pathogen involved and the immune status of the foal. For the purposes here the discussion will be limited to bacterial sepsis, but the foal also is susceptible to viral and fungal sepsis, which can appear quite similar to bacterial sepsis. Failure of passive transfer (FPT) of immunity can contribute to the development of sepsis in a foal at risk. The current recommendation is that foals have IgG levels greater than or equal to 800 mg/dl for passive transfer to be considered adequate. Other risk factors for the development of sepsis include any adverse advents at the time of birth, maternal illness or any abnormalities in the foal. Although the umbilicus is frequently implicated as a major portal of entry for infectious organisms in the foal, the gastrointestinal tract may be the primary site of entry. Other portals of entry include the respiratory tract and any wounds that may be present.

Early signs of sepsis include depression, decreased suck reflex, increased recumbency, fever, hypothermia, weakness, dysphagia, failure to gain weight, increased respiratory rate, tachycardia, bradycardia, injected mucous membranes, decreased capillary refill time, shivering, lameness, aural petechia and coronitis, among others. If recognized early, patients with sepsis may have a good outcome, depending on the pathogen involved. Gram negative sepsis remains the most commonly diagnosed but, increasingly, gram negative septicemia is being recognized. It becomes important to attempt to isolate the organism involved early in the course of the disease. If possible, blood cultures should be obtained and, if localizing signs are present,

samples obtained as deemed appropriate. Until antimicrobial sensitivity patterns for the pathogen involved are obtained, broad-spectrum antimicrobial therapy should be initiated. Intravenous amikacin and penicillin are good first line choices but renal function should be monitored closely. Other first line antimicrobial choices might include high dose ceftiofur sodium or timentin. Failure of passive transfer should be treated if present. Intranasal oxygen insufflation at 5-10 liters per minute should be provided even if hypoxemia is not present to decrease the work of breathing and provide support for the increased oxygen demands associated with sepsis. Mechanical ventilation may be necessary in cases of severe respiratory involvement seen with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). If the foal is hypotensive, pressor agents or inotropes may be administered by constant rate infusion. Inotrope and pressor therapy is generally restricted to referral centers where these drugs can be given as constant rate infusions and blood pressure can be closely monitored. Non-steroidal antiinflammatory agents are used by some practitioners, as are corticosteroids in specific circumstances. Use of these drugs should be judicious as they may have several negative consequences for the foal including, but not limited to, renal failure and gastric/dunodenal ulceration.

Nursing care is one of the most important aspects of treating septic foals. Foals should be kept warm and dry. They should be turned at two-hour intervals if they are recumbent. Feeding septic foals can be a challenge if gastrointestinal function is abnormal and total parenteral nutrition may be needed. If at all possible foals should be weighed daily and blood glucose levels monitored frequently. Some foals become persistently hyperglycemic on small glucose infusion rates. These foals may benefit from constant rate low dose insulin infusions. Recumbent foals must be examined frequently for decubital sore development, the appearance of corneal ulcers and for heat and swelling associated with joints and physis.

The prognosis for foals in the early stages of sepsis is fair to good. Once the disease has progressed to septic shock the prognosis decreases although short term survival rates are as good as those seen in human critical units. Long-term survival and athletic outcomes are fair. Racing breed foals that make it to the track perform similarly to their age matched siblings.