INTRODUCTION
Our knowledge of the pathophysiology of neonatal encephalopathy (NE) has changed over the years. This session will provide an overview of our current understanding of the disease, and review how treatment of these cases has evolved.

DEFINITION
Neonatal encephalopathy is a common neurologic disorder of neonatal foals. Also referred to as hypoxic ischemic encephalopathy (HIE), perinatal asphyxia (PAS), neonatal maladjustment syndrome (NMS) and dummy foal syndrome, the use of the term neonatal encephalopathy is becoming more widely used as it encompasses many of the proposed mechanisms of the disease.

CLINICAL SIGNS
Clinical signs of NE can be mild or severely debilitating and can be present immediately after birth, or develop over several days. Below is a list of some of the associated clinical signs
- Lack of affinity for the mare
- Absent suckle reflex
- Aimless wandering
- Altered mentation from hyperreactivity and seizures to dullness and somnolence
- Dysphagia
- Abnormal vocalization
- Respiratory distress (centrally mediated or due to pharyngeal or laryngeal dysfunction)
- Tongue protrusion
- Floppy or asymmetric ear movements

PATHOPHYSIOLOGY
Historically, neonatal encephalopathy was thought to result exclusively from a hypoxic incident, hence the name HIE. True hypoxic ischemic encephalopathy can occur during events such as prolonged umbilical cord compression, birth asphyxia from prolonged stage 2 labor and cardiopulmonary failure. Foals with true hypoxic disease typically have histologic lesions in their brain consistent with the insult. However, there is little evidence that most foals with neonatal encephalopathy sustain a hypoxic ischemic insult. There is now increasing recognition for the role of inflammation in NE. The most common cause of NE in our population of foals is placentitis, however any inflammatory foci has the potential to cause NE, such as laminitis or cellulitis.
Inflammation in the mare can lead to maternal systemic inflammatory response syndrome (SIRS) and subsequently fetal systemic inflammatory response syndrome (FIRS). Once pro-inflammatory cytokines are stimulated, they can cross the fetal blood-brain-barrier, leading to
neuroinflammation. Neuroinflammation causes a cascade of events leading to CNS dysfunction. The role of neurosteroids in neuroinflammation has been receiving increasing attention. Normally, neurosteroids are protective of the fetal brain and have been shown to be responsible for somnolence of the fetus in utero. The placenta is responsible for supplying substrates for the formation of neurosteroids in the fetal brain. Under normal circumstances, once the placental stimulus is removed at birth, there is a decline in neurosteroid level, allowing the foal to awaken. In foals with neonatal encephalopathy however, neurosteroid levels do not decline. Progestagens (progesterone, epitestosterone and androstenedione) are neurosteroids that have the ability to cross the blood brain barrier and have neuromodulatory effects and could be involved in the etiology of neonatal encephalopathy.

TREATMENT

The Past

There are many approaches to treating foals with NE. A number of medications that were derived from traditional beliefs, experimental models and human trials have largely gone out of fashion because they lack real evidence of effectiveness. In some cases, studies have been controversial and a number of therapies have been shown to have adverse effects in humans.

A. DIMETHYL SULFOXIDE (DMSO): DMSO is used by many practitioners as a potential anti-inflammatory, diuretic, and free radical scavenger. Evidence of its effectiveness in foals is lacking.

B. MANNITOL: mannitol was traditionally given to reduce cerebral edema and as a free radical scavenger, however we have recognized that cerebral edema is not typically a feature of foals with NE. As a result, its use is not strongly supported.

C. THIAMINE: is thought to have a neuroprotective role by maintaining cellular fluid balance and metabolic functions, however it has unproven efficacy in foals with NE.

D. Magnesium Sulfate (MgSO₄): there is some evidence in human medicine that MgSO₄ acts as a fetal neuroprotective agent when administered to pregnant women at risk of preterm birth. By blocking Ca channels via NMDA receptor antagonism, MgSO₄ is thought to prevent neuronal damage secondary to a hypoxic ischemic insult. A review of literature suggested that for every 63 women treated, MgSO₄ may benefit 1 child. However, more recently, several prospective human studies showed adverse toxic effects, including decreased cerebral perfusion and a 10 times increased risk of neonatal death. Its use in foals (or late term mares) is therefore not recommended.

E. VITAMIN E: vitamin E can be used to prevent oxidative damage. It must however be administered PRIOR to any insult, therefore its effectiveness as a treatment in foals with NE is not well supported.

F. NALOXONE: the use of naloxone in the treatment of hypoxic ischemic insults in humans and foals has been controversial. One study showed that post asphyxia blood-brain barrier disruption was related to poor neurological outcome in a lamb model, and that naloxone prevented neurological dysfunction. However, other studies have demonstrated that naloxone exacerbates hypoxic-ischemic brain injury in neonatal hypoxic rats.
The Present
The mainstay of treatment in foals with NE is supportive care, however specific treatments for foals with seizure activity will also be discussed.

1. **CONTROL OF SEIZURES**
Seizure activity should be minimized because seizures are known to increase oxygen and metabolic demands of the foal, and potentially worsen NE.

Phenobarbital: is a standard treatment for seizures in foals. Small doses (2-3mg/kg) can be given over 20 minutes, and repeated, until seizures are controlled. Phenobarbital's peak effect is at 45 minutes, so waiting for at least 45 minutes before re-dosing is recommended. It is important to recognize that it also has a long half-life in some foals (>200 hours), and once an effective level has been achieved, foals will generally become sedate or somnolent. I always warn owners that this will occur so they don’t expect the foal to be alert for several days. Phenobarbital also has a number of side effects including hypothermia, hypotension and pharyngeal collapse (leading to upper airway obstruction). These effects should be closely monitored for and can be readily addressed with early intervention.

Diazepam: I tend not to reach for phenobarbital immediately when a foal starts to display seizure activity. Some foals may have an isolated or single seizure and phenobarbital may not be warranted. I tend to give my foals several chances on diazepam, before I reach for the phenobarbital. Once seizures become persistent, or the response to diazepam is short lived, then I will move toward using phenobarbital. Diazepam is very fast acting (unlike phenobarbital) so its other use can be to control a seizure while phenobarbital is reaching its peak effect. The dose for diazepam is 0.05 - 0.4 mg/kg IV. I tend to begin at the low end of the dose range, and monitor its effect. A 50kg foal is generally responsive to a 2.5 - 5mg (0.05 - 0.1mg/kg) IV bolus.

Other: Midazolam has received some attention as a treatment for seizures in children and foals, however with the potential to decrease cerebral perfusion and cerebral oxygen delivery, its use is controversial. Generally foals will respond to diazepam and phenobarbital, therefore I rarely find a need to reach for other alternates. Occasionally foals will have persistent and prolonged seizures, despite treatment. In these cases, the prognosis may be grave due to the presence of severe CNS lesions.

2. **SUPPORT PERFUSION**

**Intravenous fluid therapy:** intravenous fluid therapy in neonatal foals is a large topic that I could devote hours of lecture to, and provide pages of information on. For the purpose of this review, I will touch on a few main principles and practical approaches.

It can be very easy to fluid overload a sick neonatal foal, and the practice may have detrimental effects on the patient. We are tending to steer away from using repeated fluid boluses during initial resuscitation. Foals are born in a fluid overloaded state, and adding to this can cause harm by placing pressure on the cardiovascular and renal system, leading to organ edema, organ dysfunction and increased morbidity and mortality. Renal disease can also complicate intravenous fluid therapy in these foals (discussed later). The aim is to provide ‘not too little, and not too much’ fluid in order to meet metabolic needs and support perfusion. I have a lot of success using the Holliday-Segar dry maintenance approach to fluid therapy. This is one of the
most commonly used techniques in calculating maintenance fluid therapy in children. It is based on caloric expenditure and water requirement, and accounts for urinary and insensible losses. The Holliday-Segar formula is as follows:

- First 10kg (1-10kg) = 100ml/kg/day
- Second 10 kg (11-20kg) = 50ml/kg/day
- For weight in excess of 20kg = 25ml/kg/day

Example: 50kg foal
- First 10kg body weight = 1000ml/day
- Second 10kg body weight = 500ml/day
- Remaining 30kg bodyweight = 750ml/day
- Total 2250ml/day or 94ml/hr

Type of intravenous fluid: the use of colloids vs crystalloids depends on a number of factors such as presence of hypovolemia and hypoperfusion. Inopressor therapy will not be covered in this presentation, however can be a very important mainstay of treatment of foals with NE.

3. ENSURE OXYGEN DELIVERY
Pulmonary oxygen loading: we can be faced with a number of respiratory problems in foals with NE. Some foals fail to make, or have delayed transition from fetal to neonatal life. In addition, we are often faced with ventilation/perfusion abnormalities, atelectasis, hypoventilation (centrally mediated), respiratory fatigue, poor perfusion, anemia and a number of lower airway diseases (acute respiratory distress syndrome, aspiration pneumonia, infectious pneumonia and traumatic chest injuries such as fractured ribs). These can lead to blood gas abnormalities, metabolic derangements and fatal consequences. It is important to monitor for changes in respiratory function and address problems promptly.

4. PREVENT SEPSIS
Colostrum is not just about providing immunoglobulins. Colostrum has a role in promoting local gastrointestinal immunity and establishing a barrier between luminal bacteria and the foal. In addition, colostrum contains numerous biologically active substances including important pro- and anti-inflammatory cytokines, immune modulators and other proteins. Despite the benefits of, and importance of feeding colostrum, many foals should not be fed more than trophic amounts of colostrum due to concerns for neonatal gastroenteropathy (discussed below). In foals that cannot be given adequate colostrum, or in foals with evidence of sepsis, plasma administration is recommended. Appropriate antimicrobial coverage should also be given according to blood culture results, geographic location and common types of pathogens encountered in a particular region or hospital environment.

5. PROVIDE NUTRITION
Foals with NE require careful nutritional support. Initially, supplying an exogenous glucose support is necessary. After 24 hours of treatment, a decision has to be made as to whether the foal will tolerate enteral nutrition. The criteria I follow when deciding whether to feed a foal includes; passage of meconium, absence of abdominal distension, absence of colic signs,
normalized body temperature and passage of enema fluid at the completion of an enema. Foals with seizure activity or prolonged somnolence are foals that in my experience do not tolerate enteral feeding. Neonatal gastroenteropathy is a term used to encompass a number of disorders ranging from mild functional deficits (e.g. enema dependence and poor motility) to moderate diseases (e.g. colic signs, abdominal distension) and more severe conditions (e.g. pneumotosis intestinalis, mucosal necrosis and sloughing, intussusceptions). Feeding foals can promote some of the above conditions and as a result, parenteral nutrition is commonly used in sick foals. Trophic feeding (1-2 oz every 6 hours) however can be beneficial by promoting health of enterocytes and reducing the occurrence of bacterial translocation. Ideally, fresh colostrum is used as it contains many important substances that deliver nutrition to enterocytes. Alternatively, fresh mare’s milk or frozen colostrum or frozen mare’s milk can be used.

6. MONITOR AND SUPPORT RENAL FUNCTION
Neonatal nephropathy is another broad term used to describe a number of conditions that can often be seen either independent of, or in conjunction with foals with NE. It occurs when foals fail to make the transition to neonatal functions and can result in water and sodium retention, tubular dysfunction and necrosis. The conditions are usually transient, but require particular attention when devising fluid therapy plans, electrolyte supplementation and choosing medications (avoiding nephrotoxic agents). Monitoring urine production closely is warranted because early therapy can prevent chronic renal disease from developing.

7. OTHER
What about ‘squeezing’ foals?
Recently, further exploration of the role of neurosteroids in foals with NE has led to the idea that stress experienced by the foal during normal parturition and the pressure induced by passing through the pelvic canal, signals the decrease in neurosteroids that lead to quiescence or a somnolent state in utero. Since foals with NE have been shown to have higher levels of neurosteroids, a new approach to mimicking the birth canal ‘squeeze’ to signal a decrease in neurosteroids has proven to have some success.

SUMMARY
Our understanding of the pathophysiology and therefore treatment of neonatal encephalopathy continues to evolve. There are many different approaches to dealing with these cases, however a number of basic principles should be followed. Dealing with foals with neonatal encephalopathy often requires constant nursing care and regular veterinary monitoring.

References can be provided on request.