Equine Neonatology
Neonatal Syndrome

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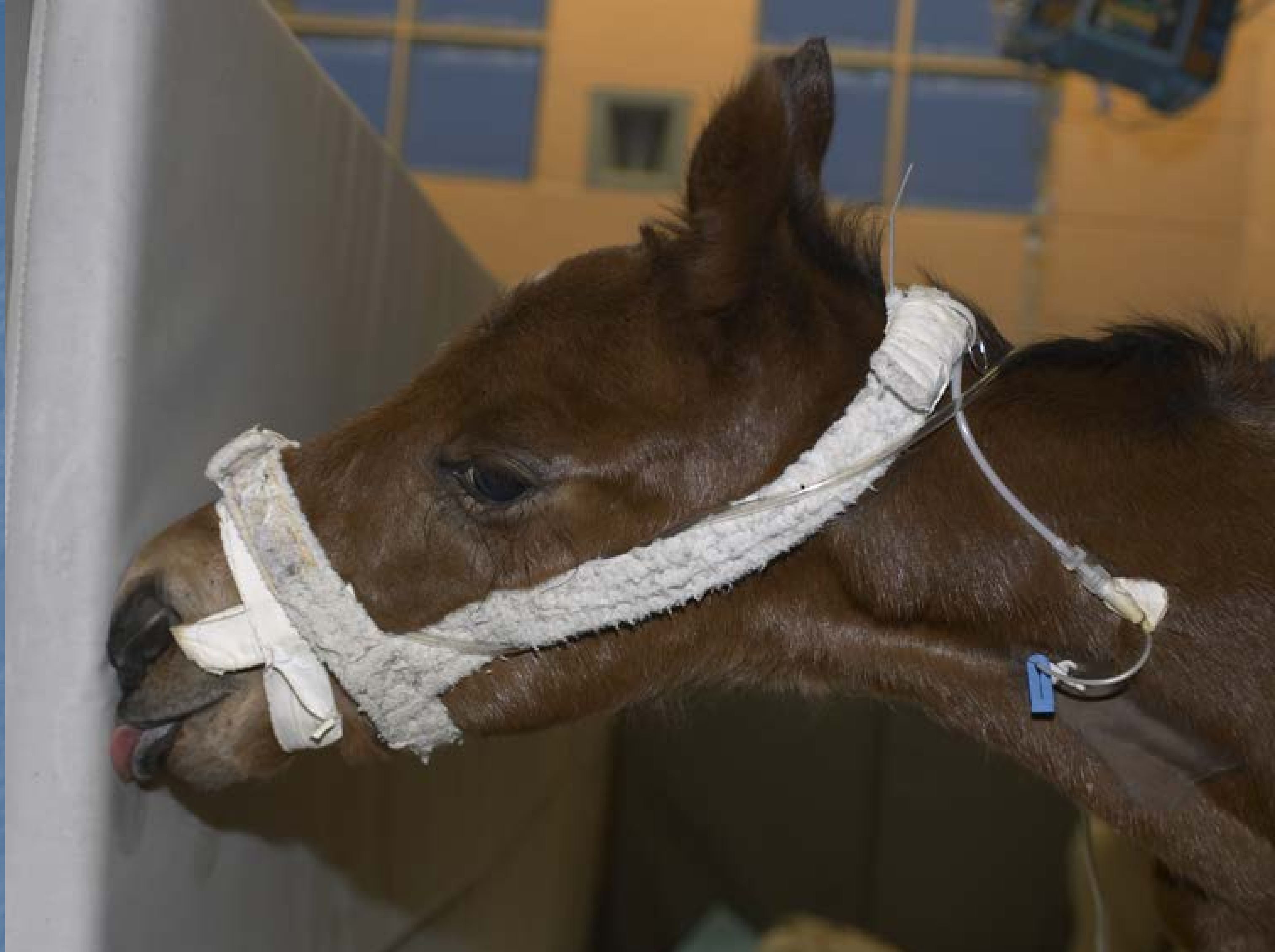


Neonatal Encephalopathy

Hypoxic Ischemic Encephalopathy (HIE)

Neonatal Maladjustment Syndrome

Changes in Behavior

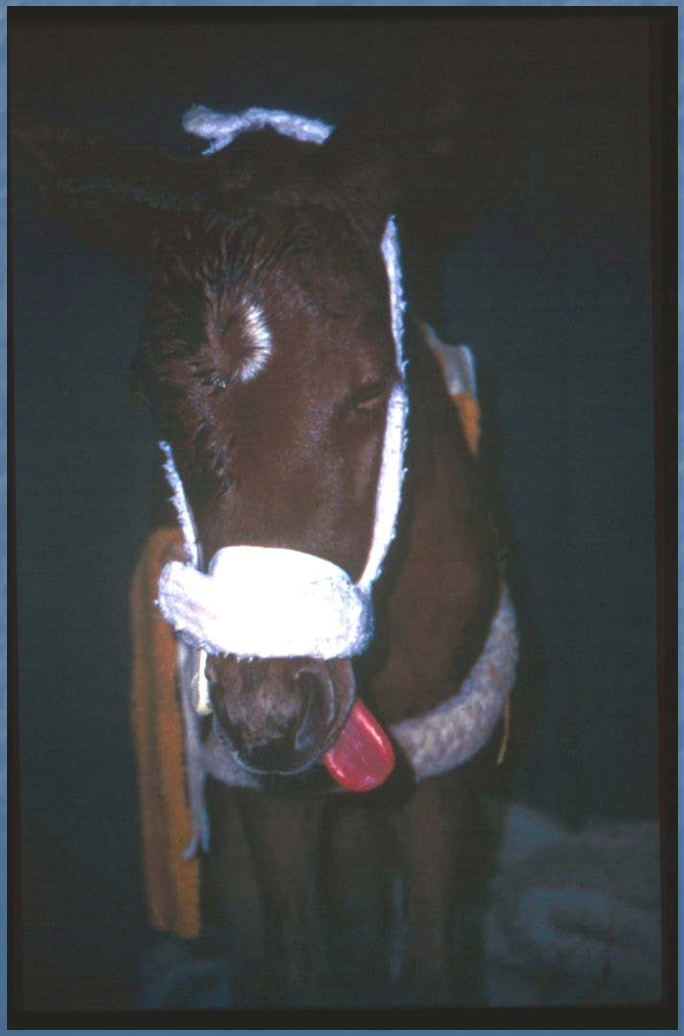
Neonatal Intensive Care

Hypoxic-Ischemic Syndrome

- Human Neonates - cerebral palsy
  - Prolonged Stage II
  - Lawsuits
  - Clinical studies on onset
    - Intranatal
    - Prenatal
    - Postnatal
- Experimental Studies
  - Hypoxic ischemic insults
  - Hypoxic ischemic encephalopathy (HIE)

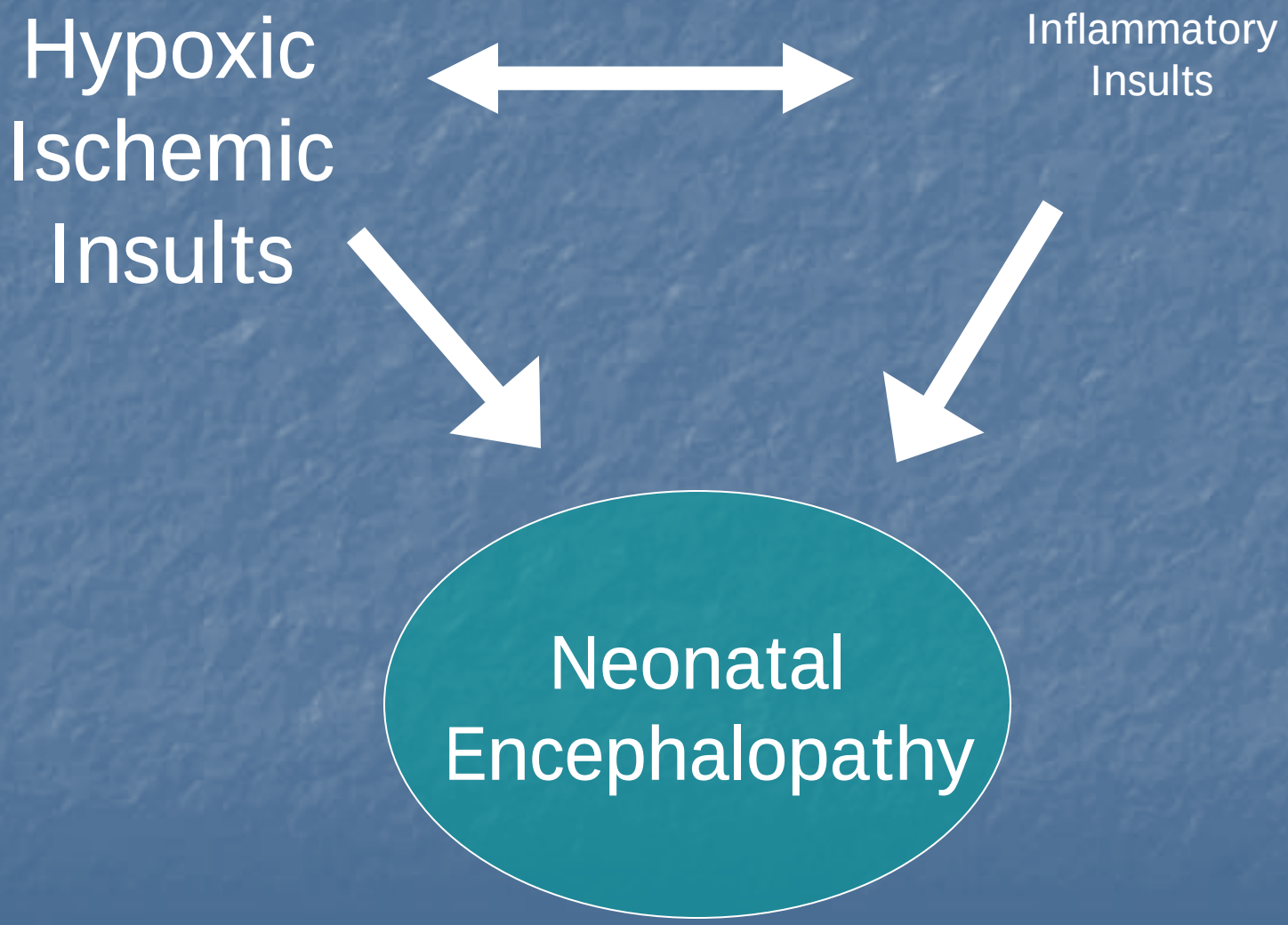
Neonatal Problems
Neonatal Syndrome

- Selective neuronal pathology
- Renal pathology
- Gastrointestinal pathology
- Metabolic failure
- Cardiovascular pathology
- Endocrine abnormalities
- Pulmonary pathology



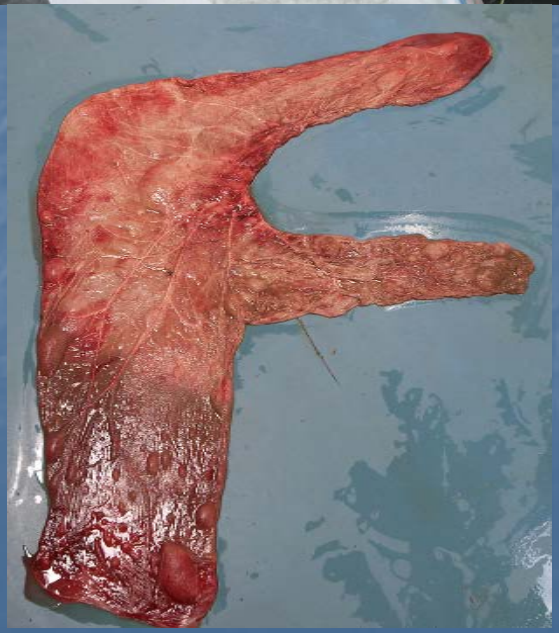
Neonatal Problems

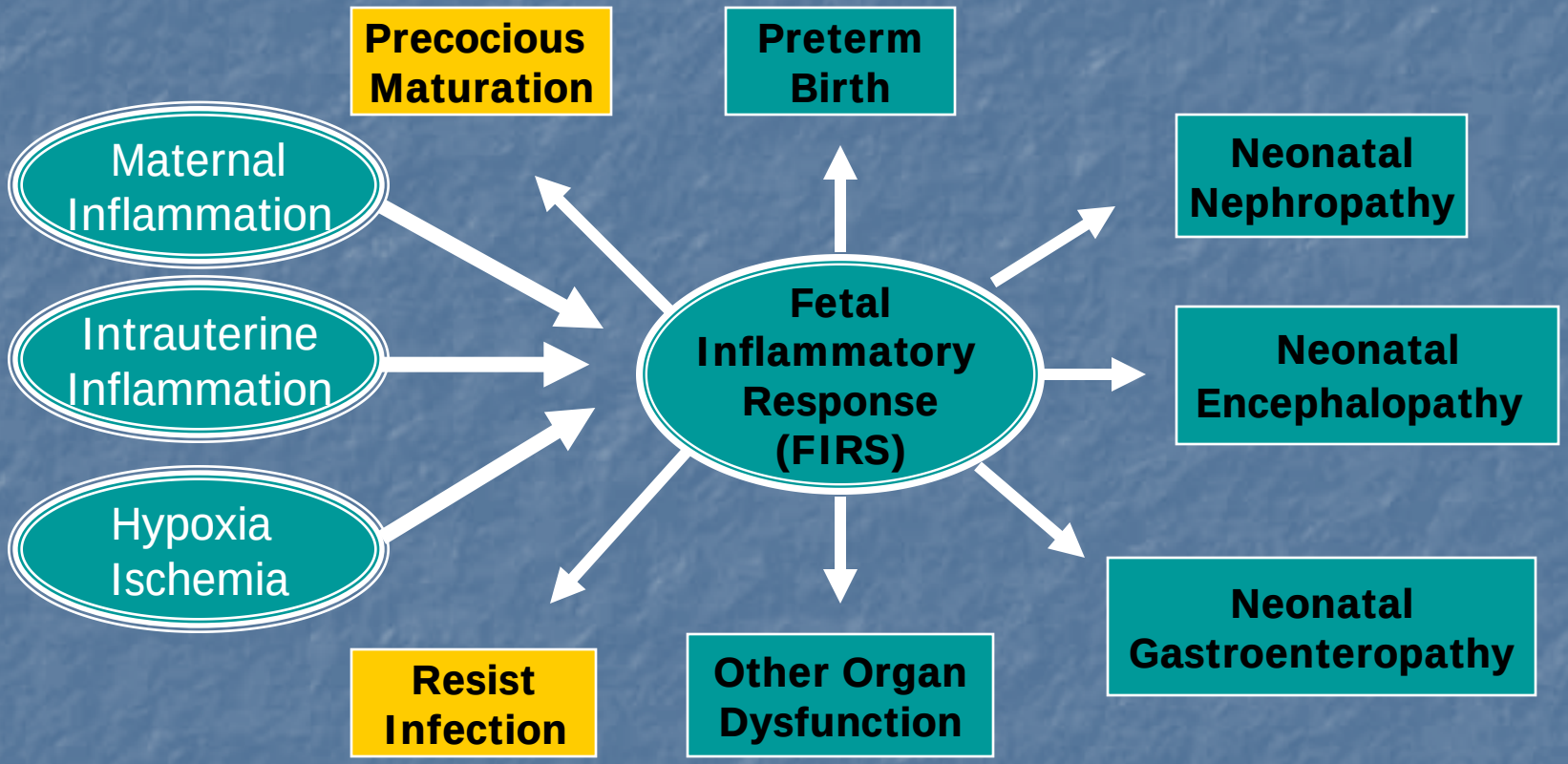
- Hypoxic ischemic asphyxial disease?
  - Often no evidence
- Inflammatory placental disease
  - Strong correlation
- Role of inflammatory mediators?
  - Cytokines, local vasoactive mediators
  - Primary effect?
  - Secondary hypoxic ischemic insult?


Hypoxic
Ischemic
Insults
Inflammatory
Insults
Neonatal
Encephalopathy

Role of Placentitis

- Many neonatal diseases
  - Multiple etiologies
  - Disruption of fetal life
    - Predispose to neonatal disease
    - Origin of the neonatal disease
- Placentitis - untreated
  - Neonatal diseases
    - CNS, Renal, GI
- Placentitis - treated
  - Protects against neonatal diseases

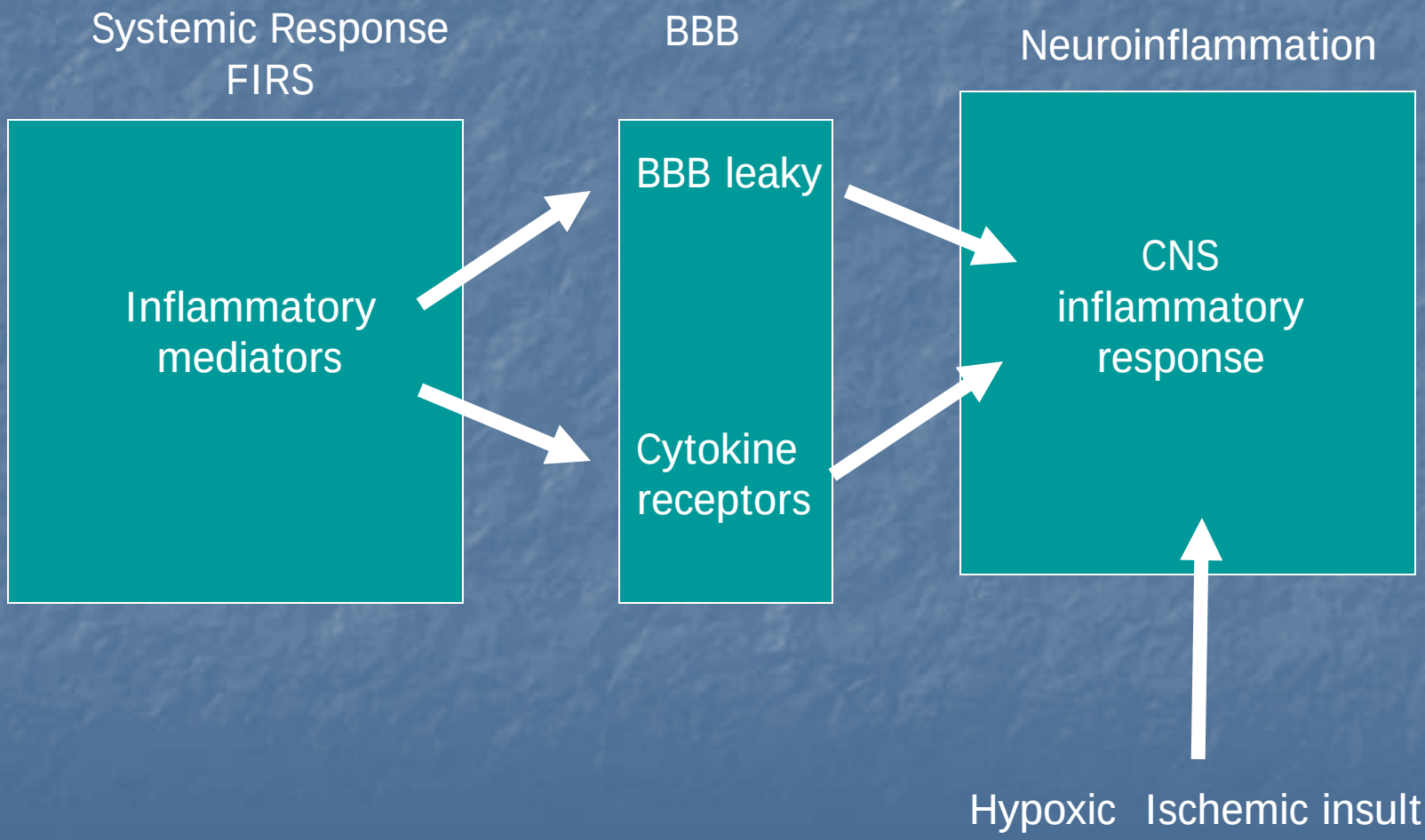



Precocious Maturation
Preterm Birth
Maternal Inflammation
Intrauterine Inflammation
Hypoxia Ischemia
Fetal Inflammatory Response (FIRS)
Neonatal Nephropathy
Neonatal Encephalopathy
Neonatal Gastroenteropathy
Resist Infection
Other Organ Dysfunction

Septic Encephalopathy

- Fetal
  - Neuroinflammation
  - FIRS (Fetal Inflammatory Response Syndrome)
    - Fetal placentitis
- Maternal
  - Maternal placentitis
  - SIRS
  - Focal maternal infections

Septic Encephalopathy



Preconditioning vs Sensitization

- Preconditioning
  - Exposure low levels of messengers
  - Protection
    - Repeat exposure to higher levels of mediators
    - Hypoxic ischemic insults
- Sensitization
  - Negative preconditioning
  - More susceptible
    - Repeat exposure of inflammatory messengers
    - Mild hypoxic ischemic insults

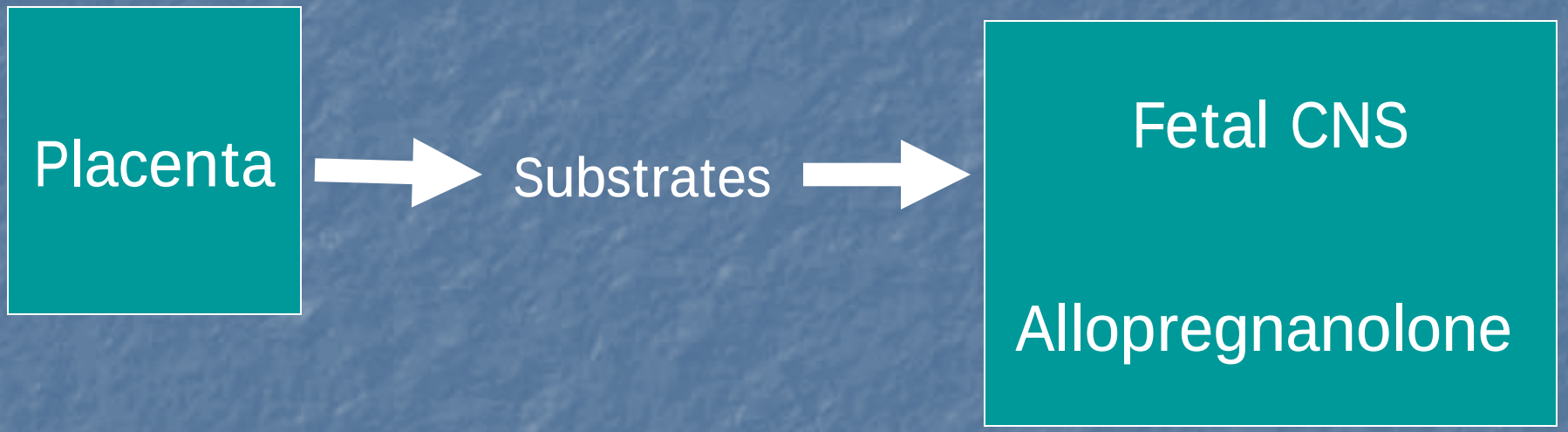
Neuroinflammation

- Important in the pathogenesis of
  - Septic encephalopathy
  - Hypoxic ischemic encephalopathy
- Microglia cells are key
  - Up-regulation of proinflammatory cytokines
  - Up-regulation of trophic factors
- Can result in
  - Morphological alterations
  - Biochemical alterations
  - Functional alterations

Neuroinflammation

- Response depends on mix
  - Proinflammatory
  - Anti-inflammatory
  - Specific mediators
- Mild disease – often no morphologic changes
  - Motor
  - Perceptual, visual
  - Behavioral
  - Cognition
  - Excitatory responses
- Excitotoxicity

Neurosteroids



- Protect the brain during fetal life
- Responsible for the somnolence
- At birth
  - Removal of the placental
  - Levels drop rapidly
  - Fetus to “awake up”

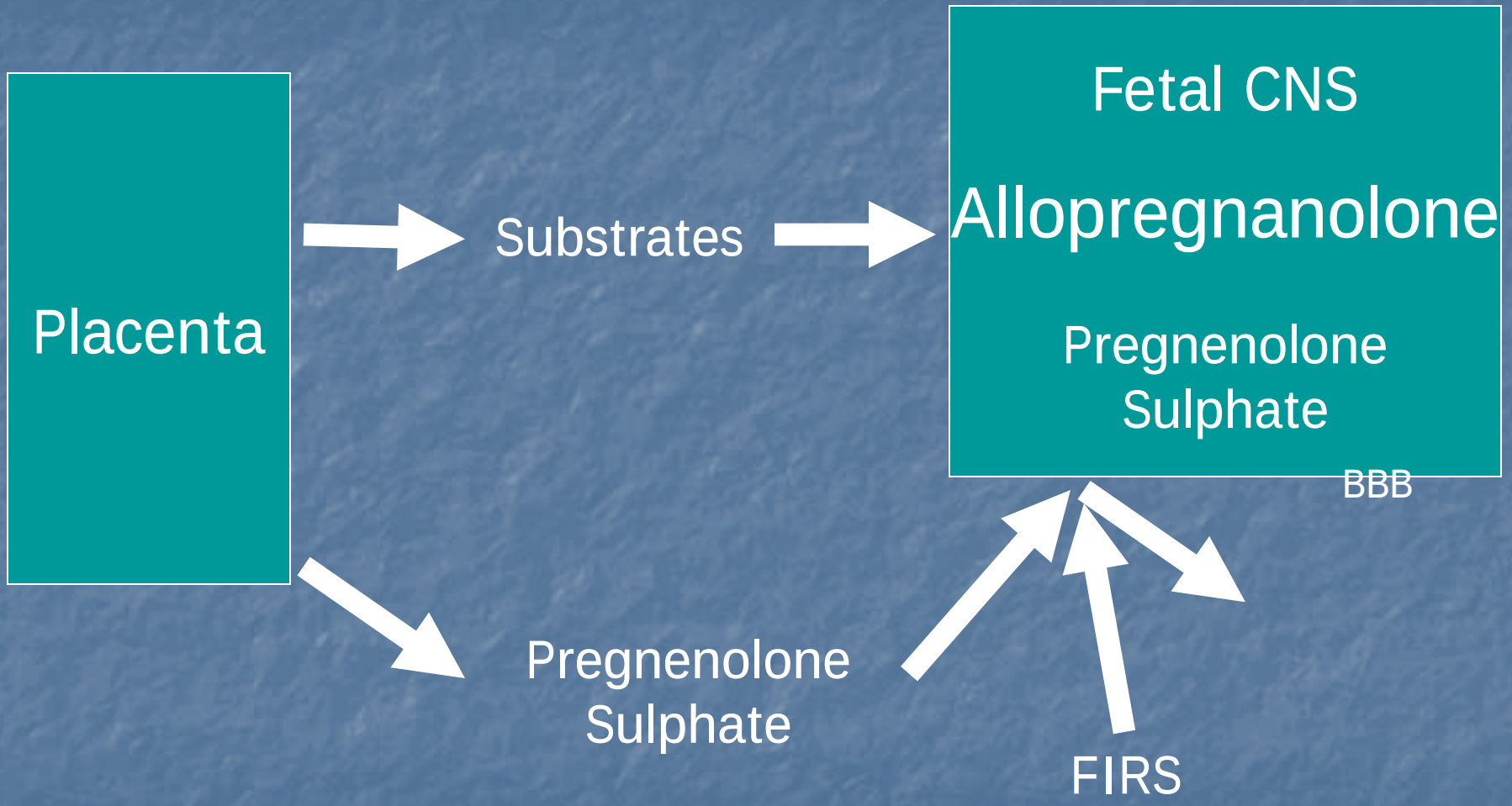
Neurosteroids

- Allopregnanolone
  - Brain levels induced by
    - Inflammatory mediators
    - Hypoxic ischemic insults
  - Protect against neuroexcitatory toxicity
  - Marked anti-seizure actions
  - Raise seizure threshold
  - Induces somnolence

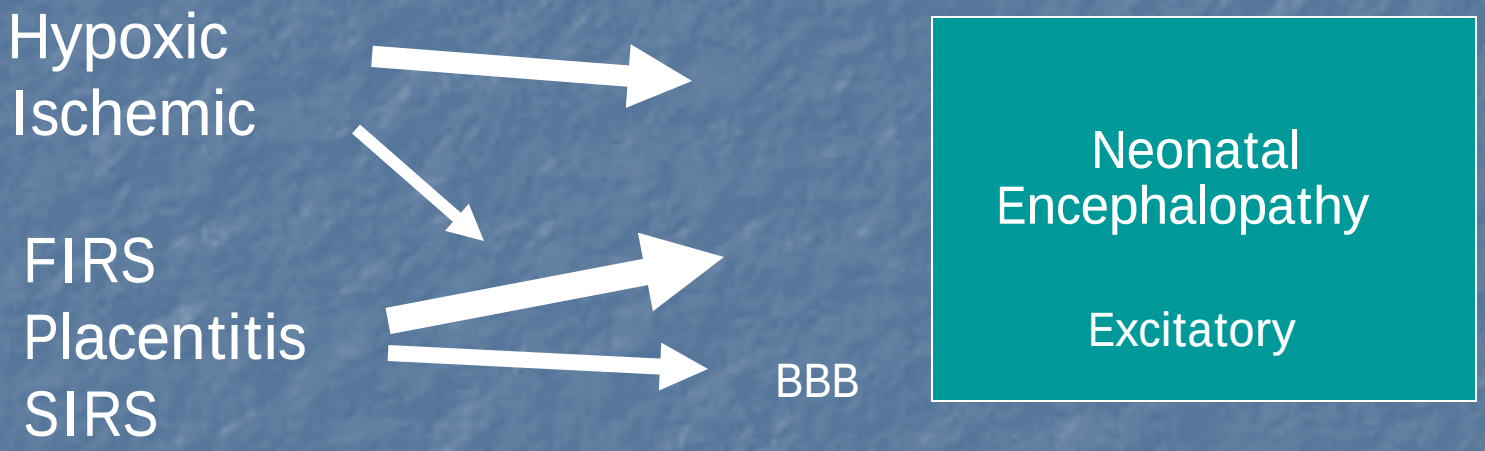
Neurosteroids

- Pregnenolone and pregnenolone sulphate
  - Placenta also secretes
  - Excitatory action in the brain
  - Cross the blood brain barrier
    - Normal – slow
    - Abnormal BBB – rapid transfer
    - Inflammation
    - Hypoxic ischemic insult

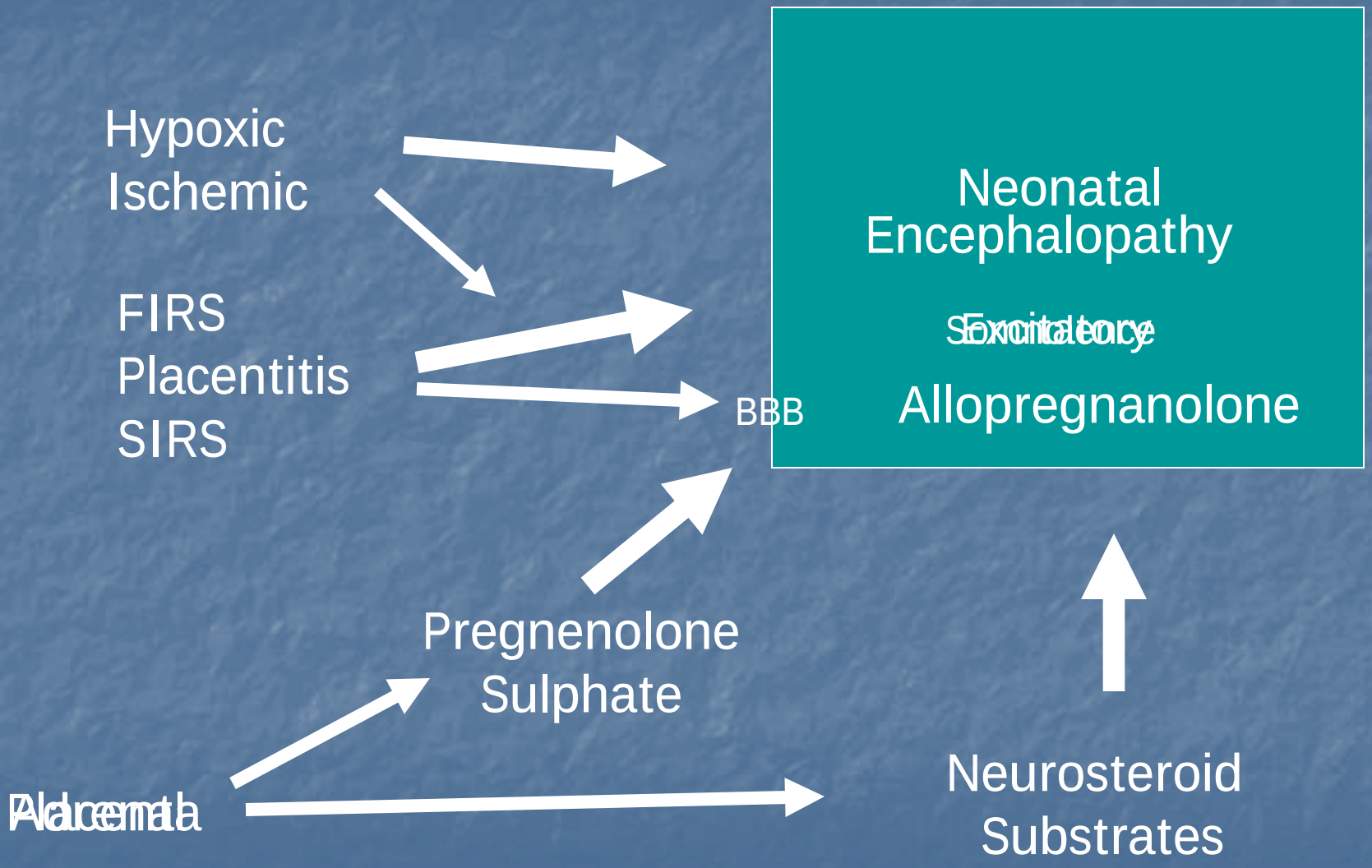
Neurosteroids



Neonatal Encephalopathy



Neonatal Encephalopathy



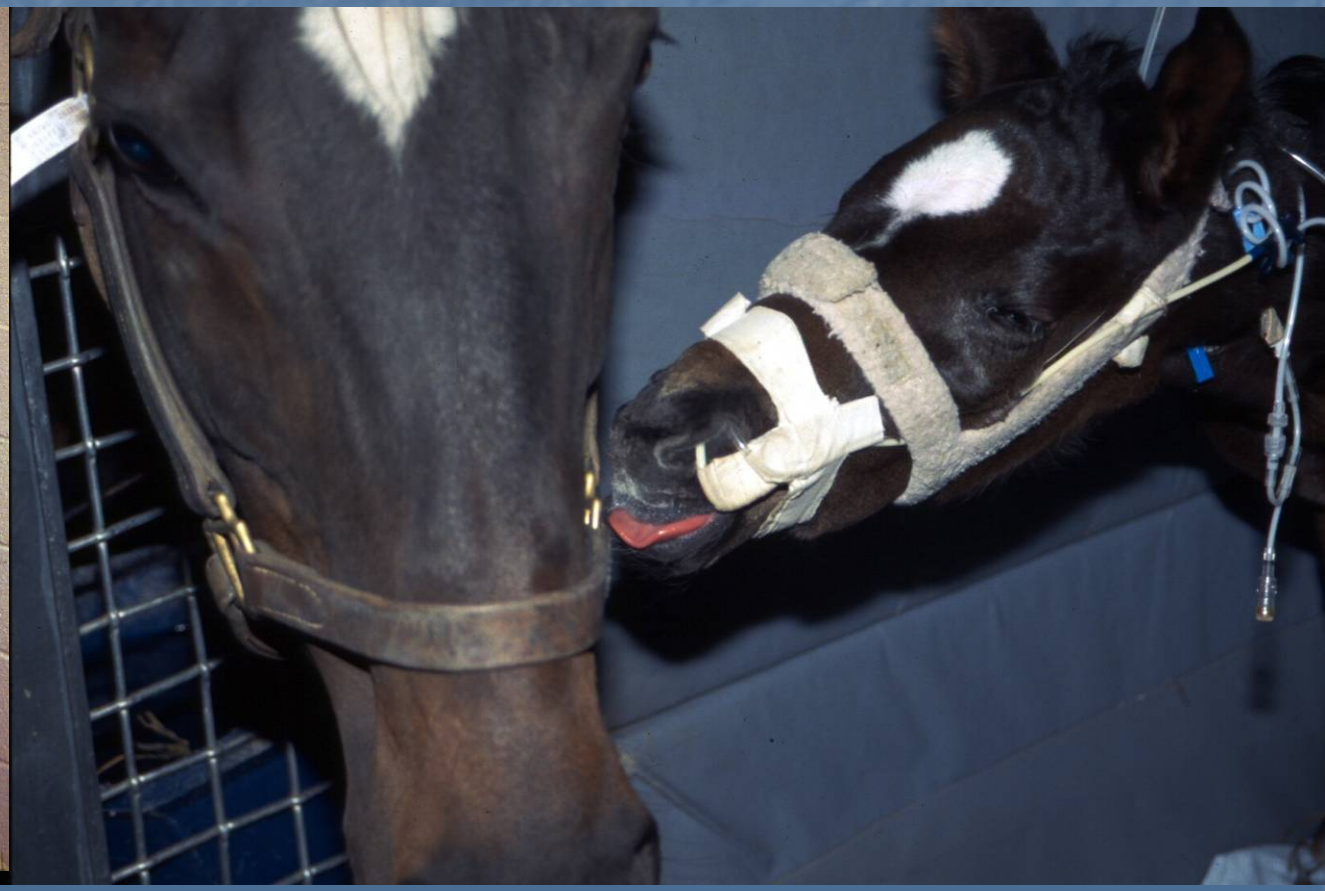
Typical Clinical Course

- Born near normal behavior
- Initial signs – excitatory
  - Constant activity – wandering, not lie down
  - Hyper-responsiveness
  - Hypertonus
  - Culminating in tonic-clonic seizure-like behavior
- Onset of somnolent phase
  - Stress induced adrenal steroidogenesis
  - Neuroinflammation induces neurosteroids
  - Healing period
- Recovery

Typical Clinical Course

- Born seizure-like behavior
  - Less placental steroidogenesis
    - Lower levels protective neurosteroids
  - Inflammatory mediators
    - Induced blood brain barrier deficits
    - Allow sulfated neurosteroids into CNS
- With neonatal stress onset of somnolent phase
  - Stress induced adrenal steroidogenesis
  - Neuroinflammation induced CNS neurosteroids
  - Healing period

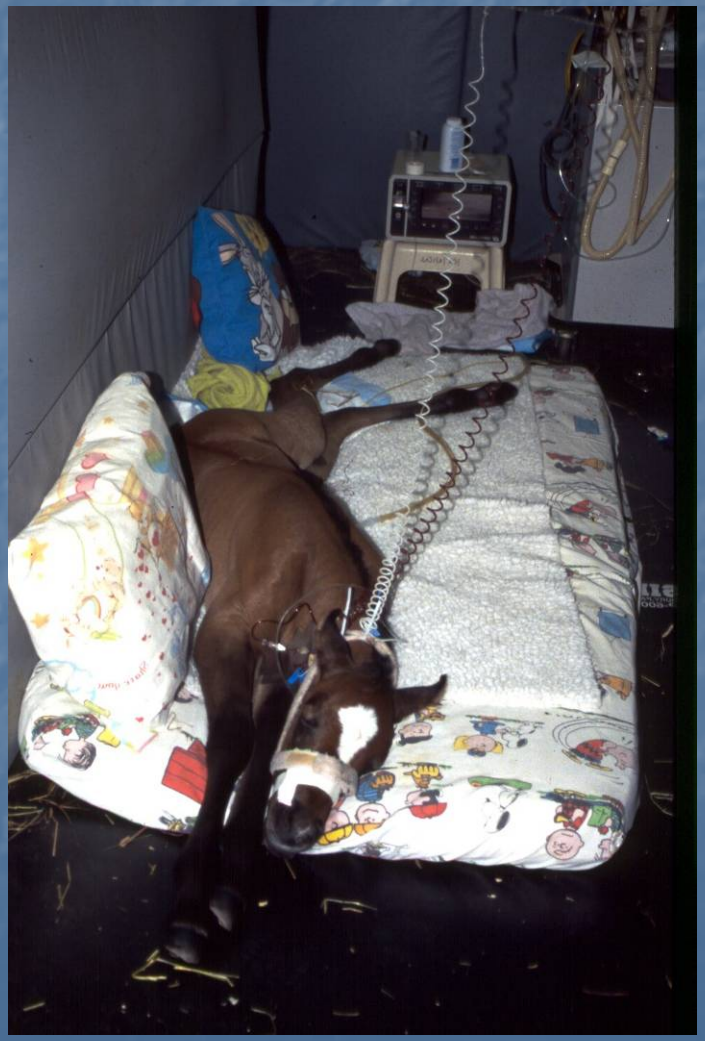
Changes in behavior



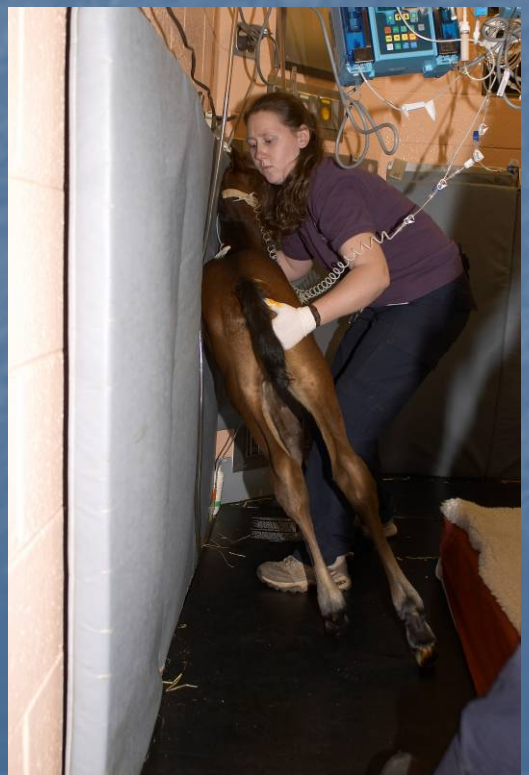
Changes in responsiveness

Changes in muscle tone

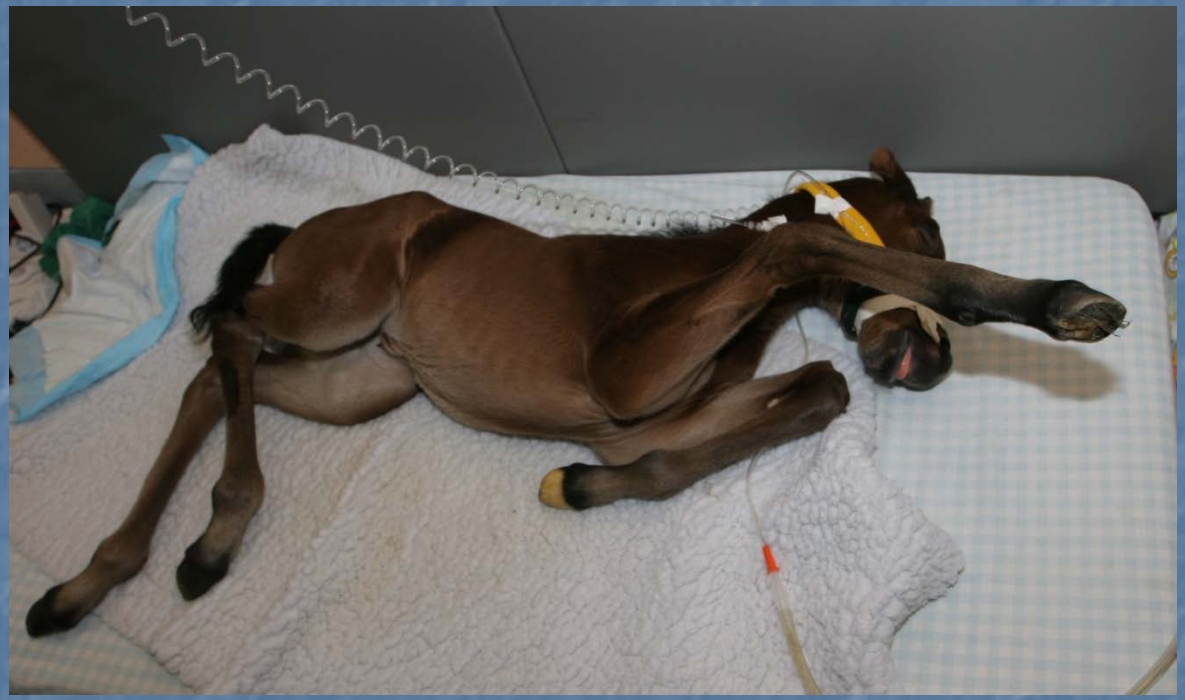
Changes in muscle tone



Brain stem damage



Seizure-like behavior



Intrauterine Challenge

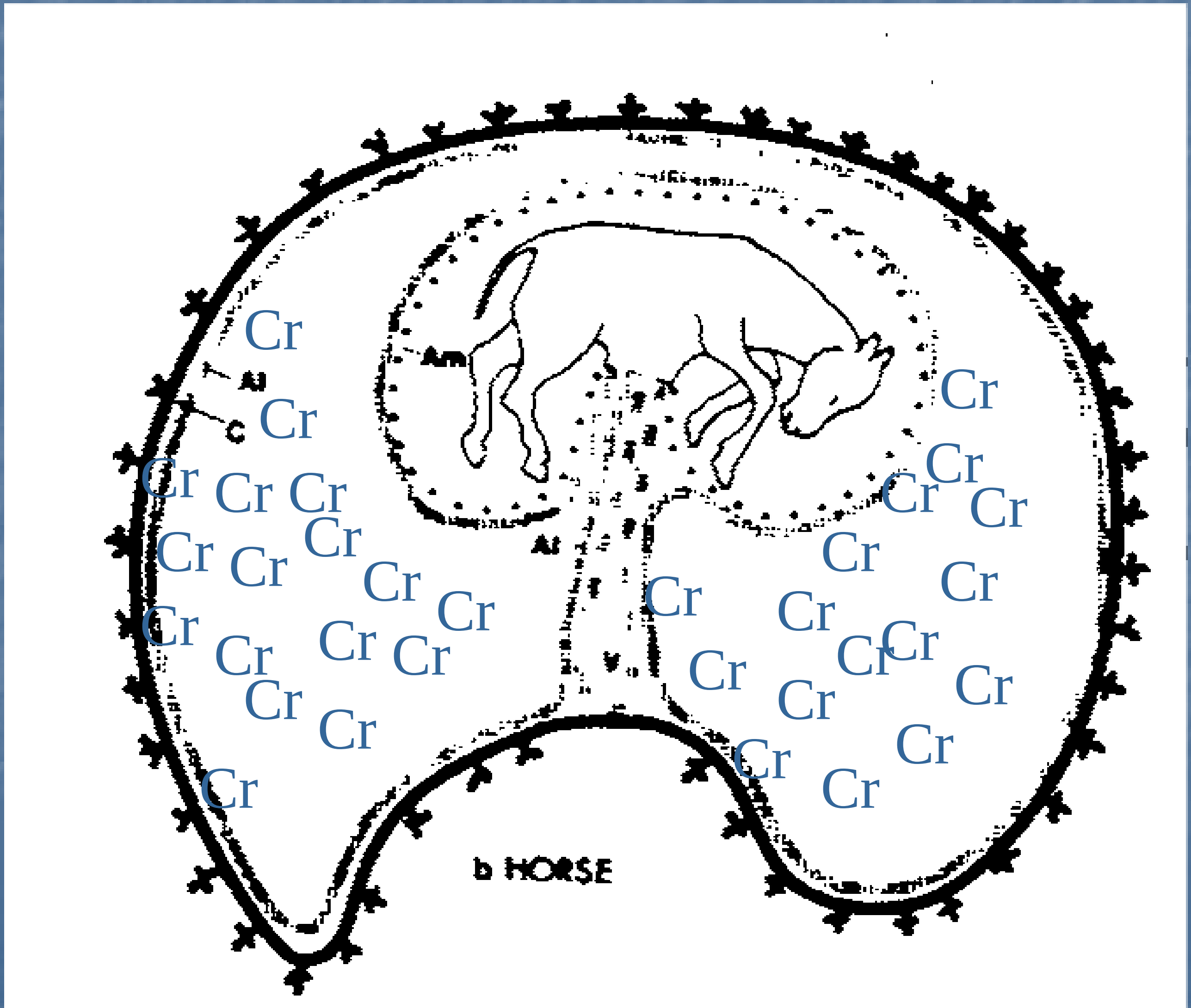
- Indications at birth of intrauterine challenge
  - Cr level
  - Hypochloremic alkalosis
  - High PCV
  - Glucose dysregulation
  - Ca dysregulation
  - Fibrinogen level
  - WBC
  - Low cortisol
  - Lactate level

Fetal foal floating in a sea of creatinine

Allantoic fluid
10,000 – 14,000

Amnionic fluid
700 – 1,000

Birth ≤350
48 hr ≤ 100



“Pong”

Thoroughbred foal
Born: May 7 at 6 PM
Admitted: May 8 at 8:53 AM
15 hrs old

“Pong” History

- Term birth to a multiparas mare
- Normal gestation
- Stage 1 - not observed
- Stage 2 - 10 minutes or less
- Stage 3 - 1 hour
- Assisted to stand after 1.5 hours
  - Nursed from the mare

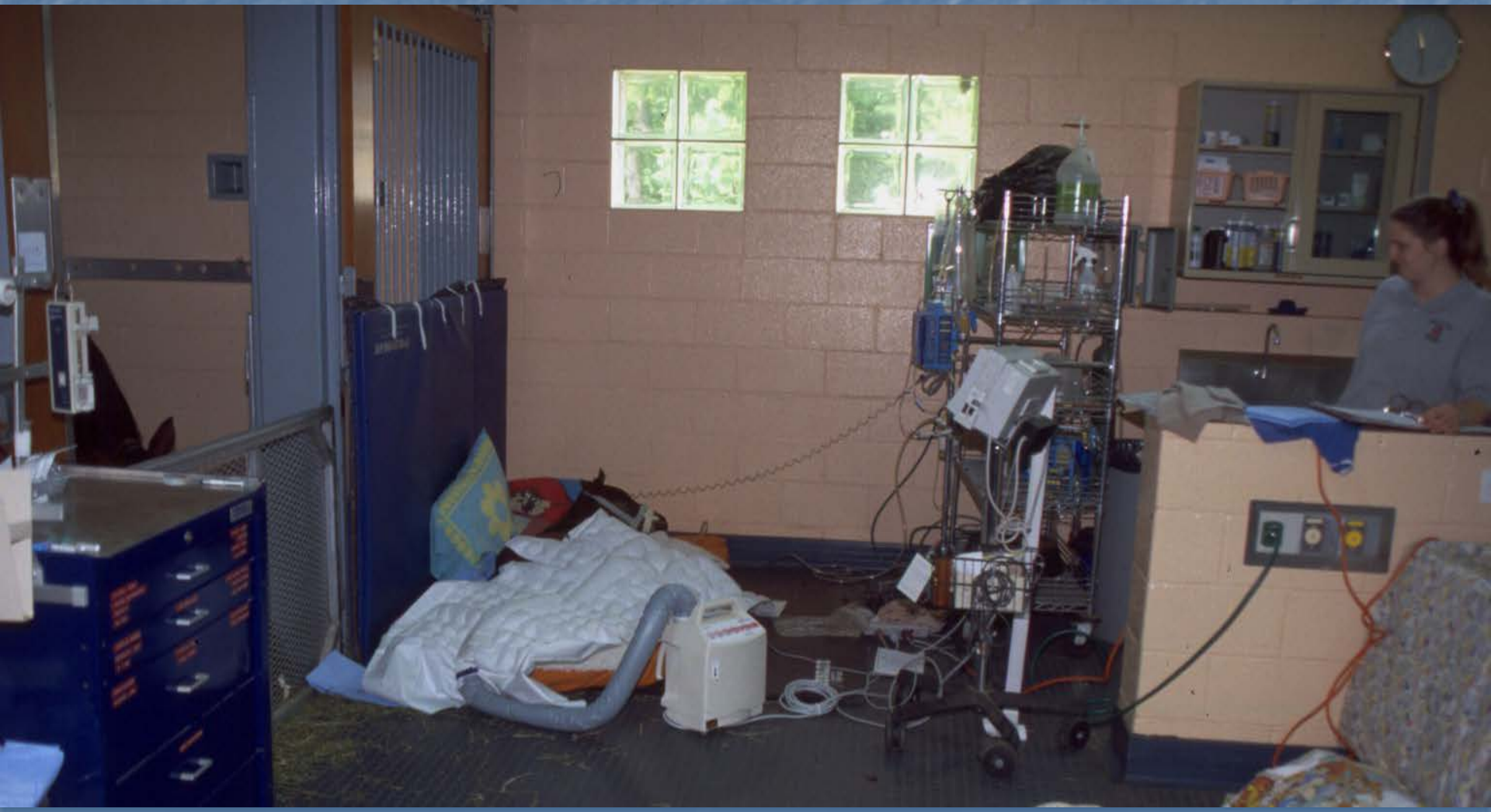
“Pong” History

- Never vigorous
- Got up once during night
  - Only for short time
  - Did not nurse
- Bottle-fed 8 oz. of colostrum
- Referred for intensive care
  - Weak
  - Inability to stand

“Pong” Admission Physical

- Marked oral, nasal, scleral, aural icterus
- Oral, nasal, scleral, aural injection
- Multiple oral petechia
- Marked lingual erythema
- Abdomen
  - Meconium in the right dorsal colon
  - Few borborygmi
  - Fetal/neonatal diarrhea

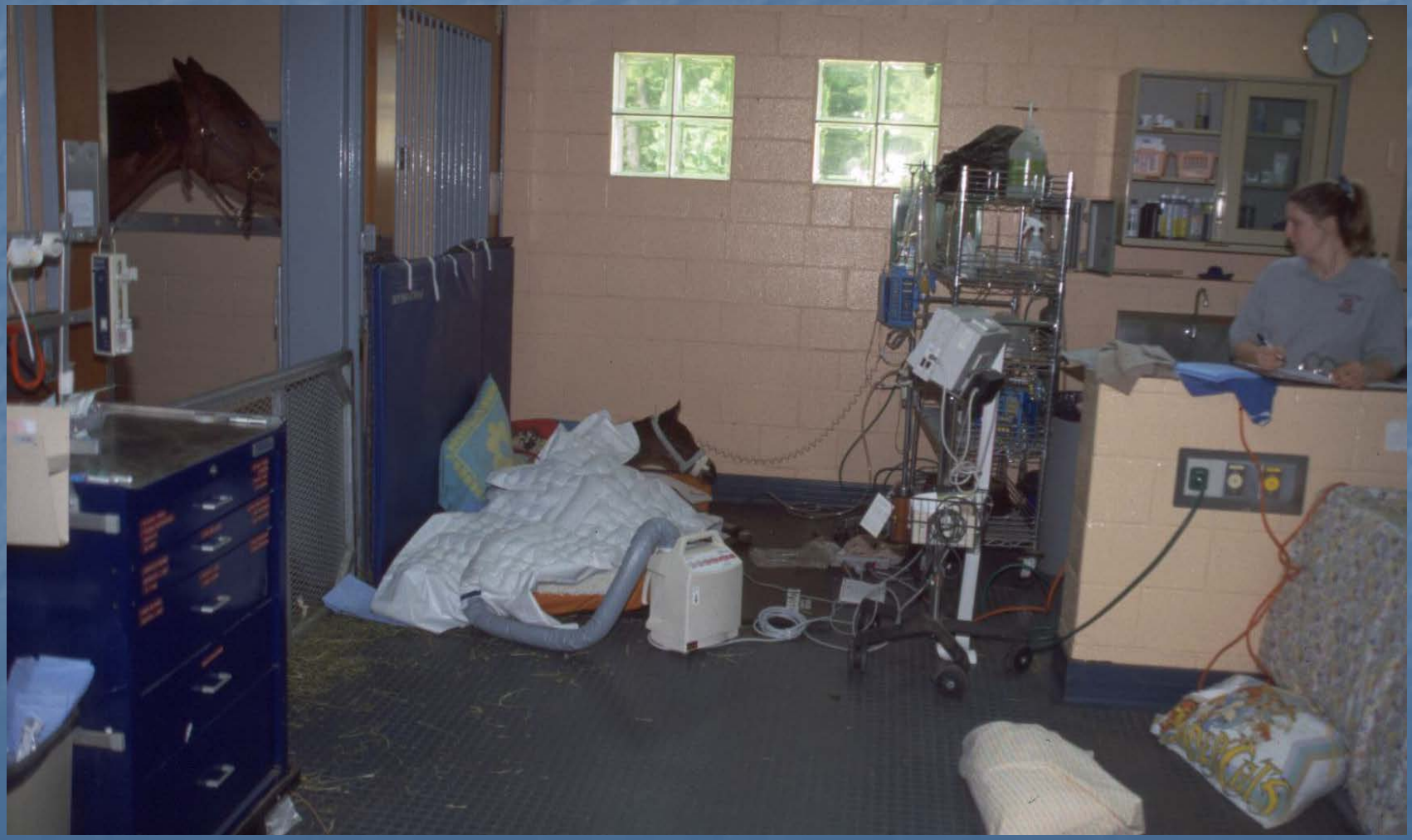
“Pong” Admission Physical



“Pong” Admission Problems

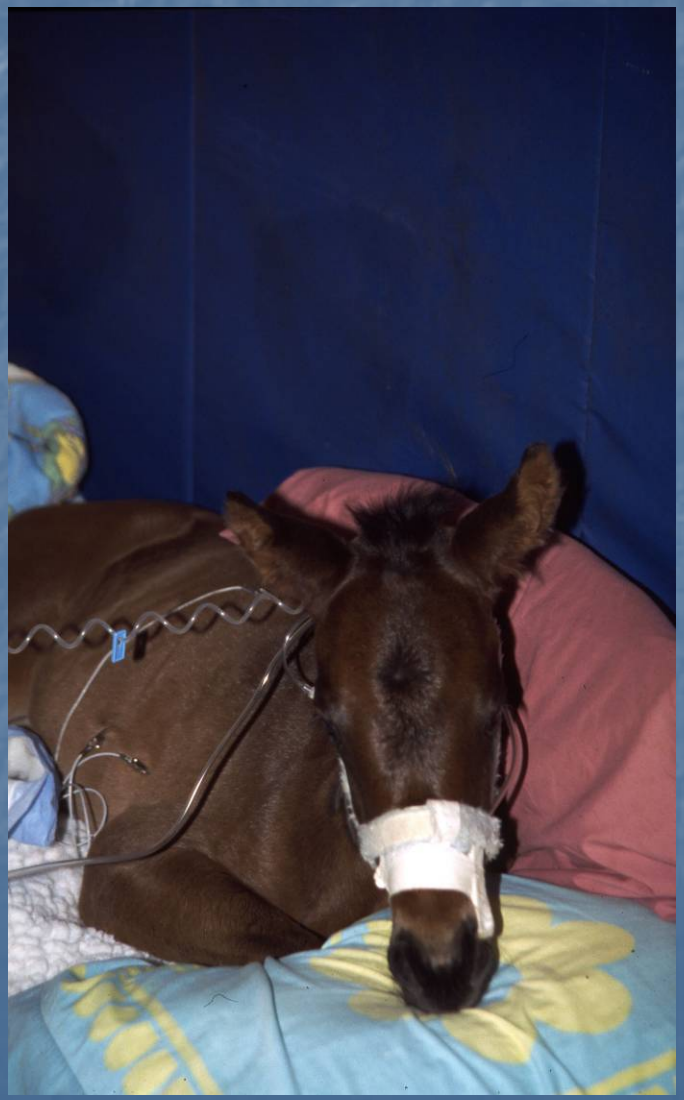
- Weakness, somnolence
- Not nursing
- Lingual erythema
- Injection
- Petechia
- Icterus
- Poor perfusion
- Diarrhea
- ↓ WBC
- ↑ fibrinogen
- ↑ PCV, ↑ TPP
- ↑ Creatinine
- Hypoxemia
- ↑ lactate

“Pong”
Major Problems



“Pong”
Neonatal Encephalopathy

- Periods - bright and active
- Sudden onset of somnolence
  - Somnolence/periods of arousal
- Apparent facial paresis
  - Right ear moves slowly
- Generalized weakness



“Pong” Neonatal Encephalopathy

- Periodic apnea
  - Up to 60 sec
  - With clustered breathing
- Inappropriate central tachypnea
- Apneusis (apneustic respiration)
- Hypercapnia
  - Without apnea

“Pong” Neonatal Encephalopathy

- Seizure like activity
  - Opisthotonus, tonic/clonic marching activity
  - Minimal nystagmus
- Lingual erythema
- Moderate nasal septum hyperemia
- Hyperresponsive to stimuli
- No suckle or searching

Neonatal Syndrome
Neonatal Encephalopathy

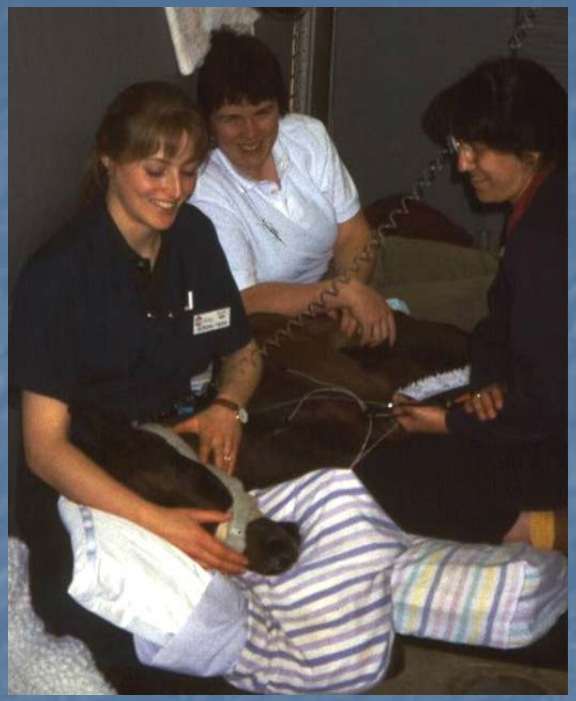
- Most common and noticeable
  - Signs occur predictably - 90%
- Mild central insult
  - Multifocal lesions
  - Selective neuronal dysfunction
  - Slow maturation of coordination

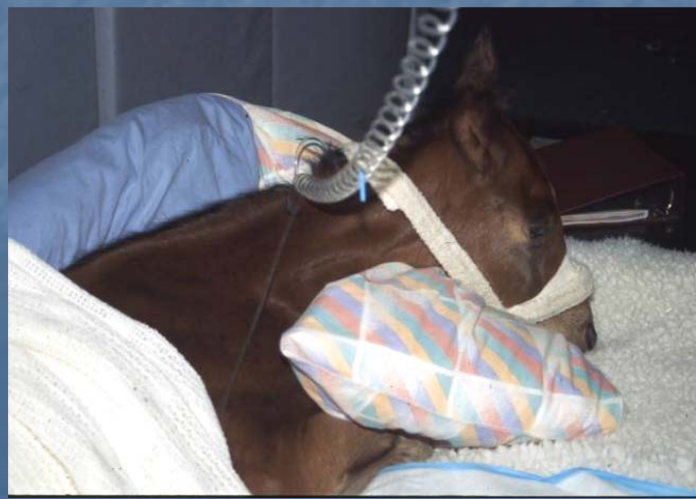
Neonatal Encephalopathy Signs of CNS disease

- Changes in responsiveness
- Changes in muscle tone
- Changes in behavior
- Signs of brain stem damage
- Seizure-like behavior
- Coma, death

Neonatal Encephalopathy Signs of CNS disease

- Changes in responsiveness
  - Hyperesthesia
  - Hyperresponsiveness
  - Hyperexcitability
  - Hyporesponsiveness
  - Periods of somnolence
  - Unresponsiveness





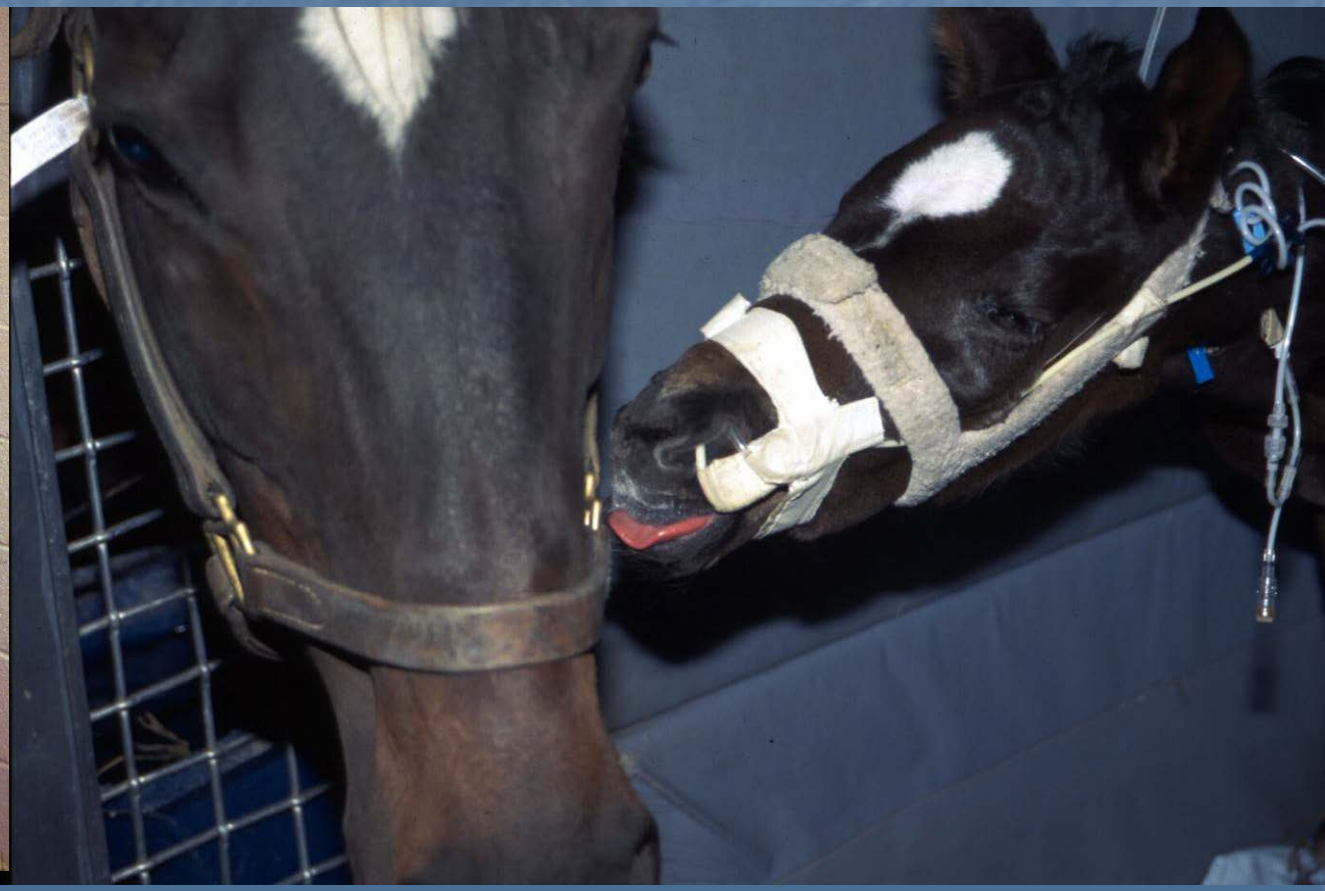
Neonatal Encephalopathy
Signs of CNS disease

- Changes in muscle tone
  - Extensor tonus
  - Hypotonia
  - Neurogenic myotonia
  - Inability to protract legs

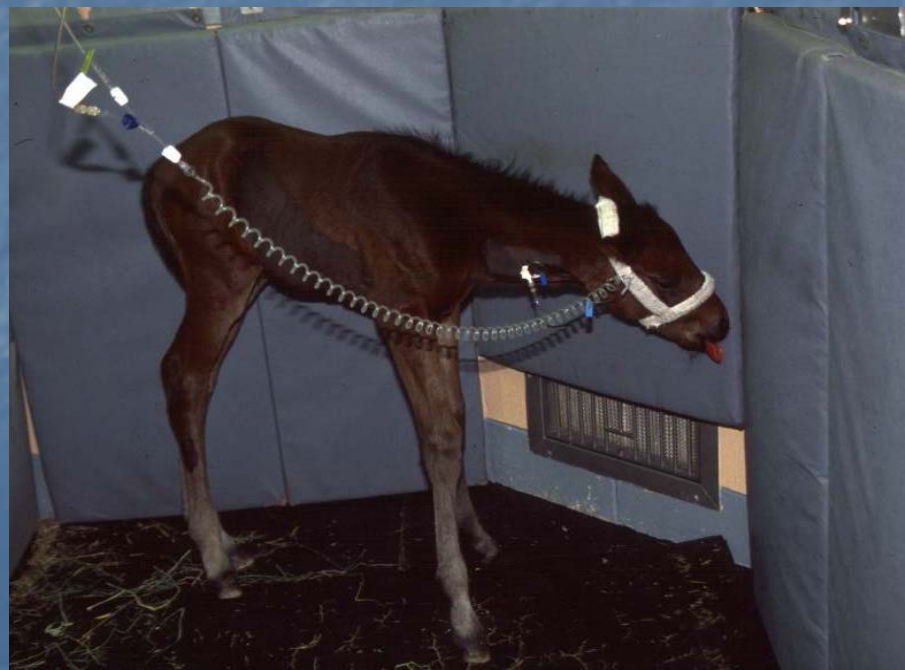
Neonatal Encephalopathy Signs of CNS disease

- Changes in behavior
  - Loss of suckle response
  - Loss of tongue curl
  - Loss of tongue coordination
  - Disorientation especially relative to the udder
  - Aimless wandering
  - Blindness
  - Loss of affinity for the dam
  - Abnormal vocalization ("barker")

Changes in behavior



“Pong”
Neonatal Encephalopathy



Neonatal Encephalopathy Signs of CNS disease

- Changes in respiratory patterns
  - Central tachypnea (midbrain)
  - Apneusis (pontine)
  - Apnea (> 20 seconds midbrain)
  - Cluster breathing (high medullary)
  - Ataxic breathing (medulla)
  - Cheyne-Stokes breathing - very rare
- Central hypercapnia

Central Respiratory Patterns

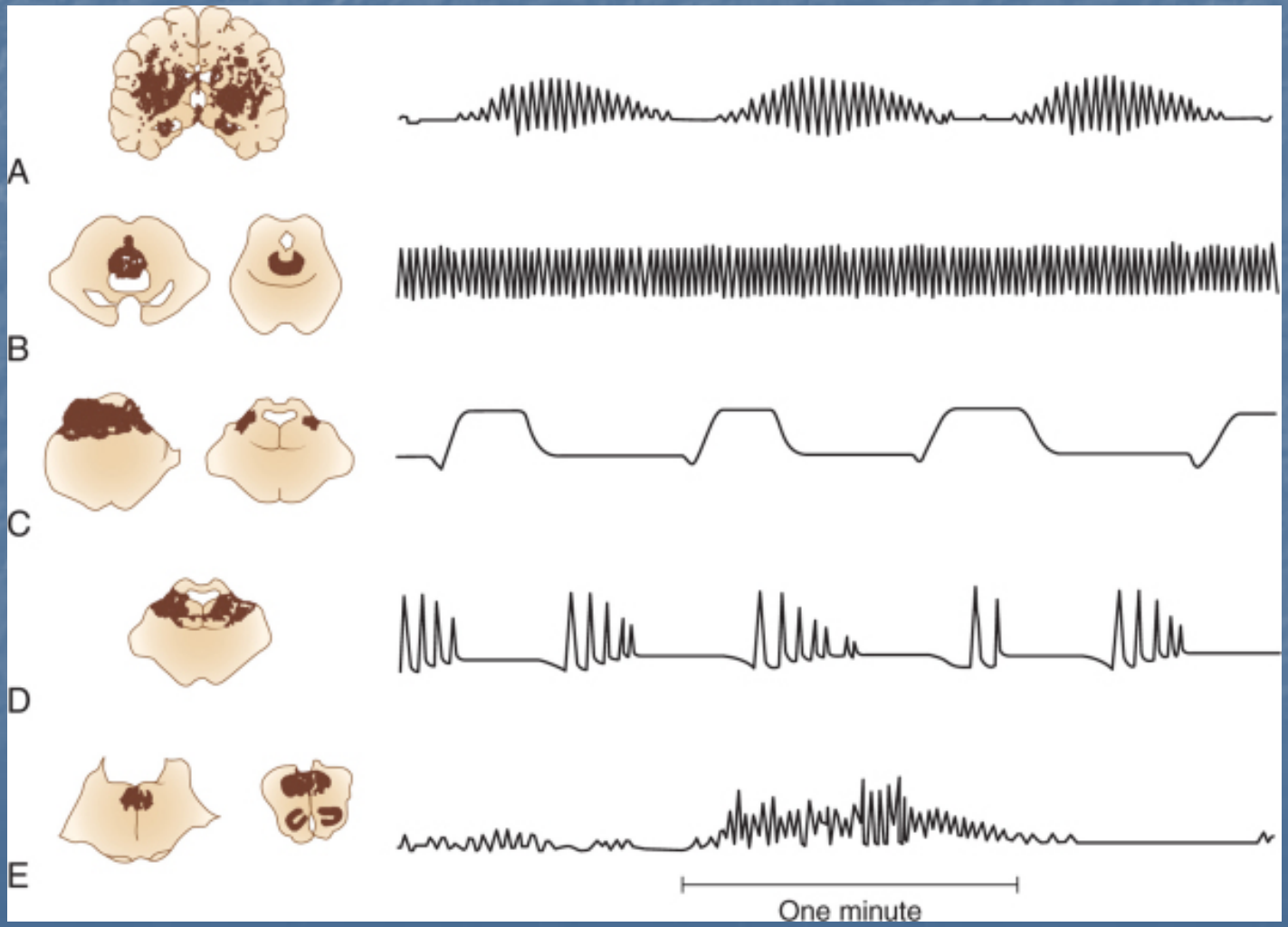
Cheyne-Stokes

Central Hyperventilation

Apneusis

Cluster breathing

Ataxic breathing



From: Bradley: Neurology in Clinical Practice, 5th ed

Neonatal Encephalopathy Signs of CNS disease

- Signs of brain stem damage
- Loss of thermoregulatory control
- Weakness
- Anisicoria (3rd nerve, one side)
- Pupillary dilation (midbrain)
- Pinpoint pupils (pontine)
- Hypotension
- Loss of consciousness (reticular formation)
- Vestibular signs - circling, head tilt
- Facial nerve paresis

Neonatal Encephalopathy Signs of CNS disease

- Seizure-like behavior (tonic/clonic generalized)
  - Marching type behavior (clonic, partial or gen)
  - Abnormal extensor tone (tonic, partial or gen)
  - Seizures
- Focal seizures

“Pong” Neonatal Encephalopathy Treatment

- Nutrition
  - Not nursing
  - Trophic feeding
  - Parenteral Nutrition
- Respiratory
  - Intranasal oxygen
  - Positive Pressure Ventilation
- Seizures
  - Phenobarbital

“Pong” Neonatal Encephalopathy

- Hospital day 2
  - Seizures – resolved with phenobarbital therapy
  - Began ventilation
- Hospital day 3 – standing
- Hospital day 5 – nursing from bottle, more aware
- Hospital day 6 – off intranasal oxygen
- Hospital day 9 – nursing from mare

“Pong”
Neonatal Nephropathy

- Creatinine level slow to drop
  - Above normal until hospital day 11
- High fractional excretion of Na
  - As high as 2.18% - normal for neonatal foal <0.3%
  - Still > 1% at discharge (day 20)
- Development of significant edema
  - Persisted until day 6

Neonatal Syndrome
Neonatal Nephropathy

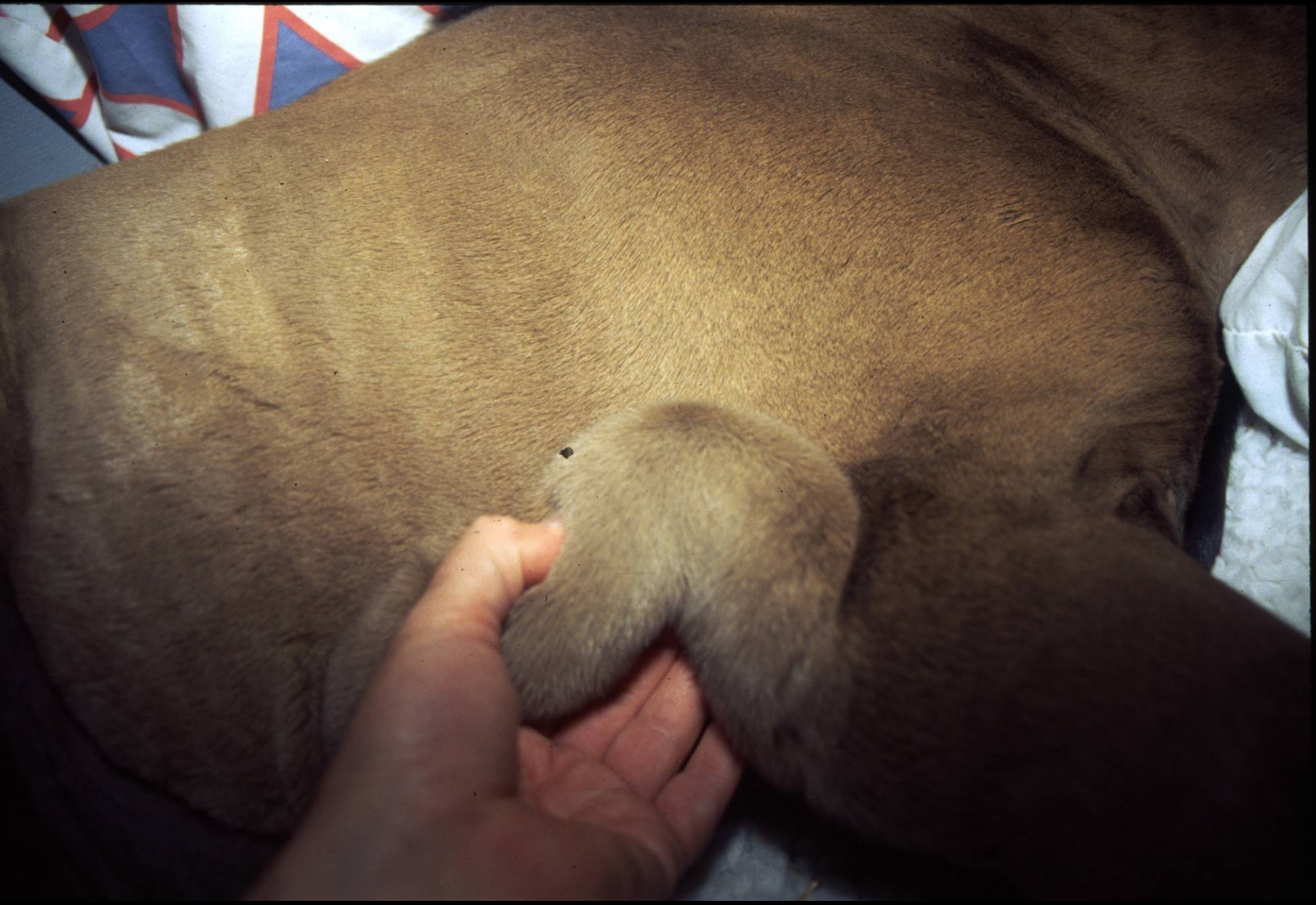
- Second most common target - 45%
- Common disease states
  - Neonatal Vasogenic Nephropathy
  - Mild acute tubular necrosis
  - Mild tubular dysfunction
- Less common disease states
  - Severe acute tubular necrosis
  - Irreversible acute damage
  - Chronic renal disease
    - Increased Cr for 6 m to 1 yr

Neonatal Vasogenic Nephropathy

- GFR and RBF
  - Balance afferent/efferent tone
  - Vasoconstrictors
    - Angiotensin II, Adrenergics
  - Vasodilators
    - PG, NO
  - NVN = imbalance afferent/efferent
- Signs
  - Oliguria
  - Concentrated urine
  - Slow Cr decrease (rarely increase)
  - Water weight gain
    - Usually no edema

Neonatal Vasogenic Nephropathy

- Therapy
  - Volume trial – volume restriction
  - Inotrope/pressor trial - caution
  - Furosemide trial - increase local PG
  - **Time**
- Consequences
  - Usually no parenchymal damage
    - Increase/failure to decrease Cr
  - Fluid/water overload
  - Na overload –(usually no Na waisting)
  - Impaired acid/base correction?



“Pong” Neonatal Gastroenteropathy

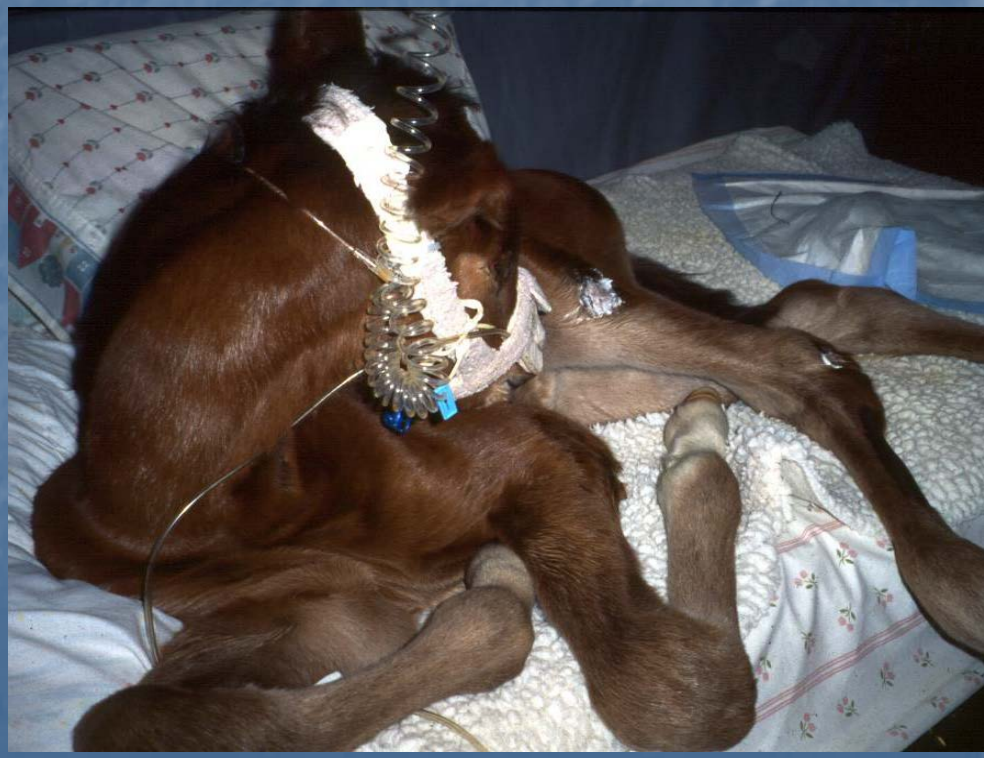
- Fetal/neonatal diarrhea
- Retained meconium – dysmotility
- Too much abdominal fill for not being fed
- Abnormal abdominal palpation
  - One loop of bowel thickened wall
- Day 7 began passing feces
  - Frequency > 24 hours
  - Enema dependent
- Day 17 resolved

Neonatal Gastroenteropathy

- Third most common target - 40%
  - Functional abnormalities – dysmotility
  - Severe damage – Necrotizing Enterocolitis
- Predisposition to sepsis and SIRS
  - Translocation of bacteria through the GI tract

Neonatal Gastroenteropathy Signs

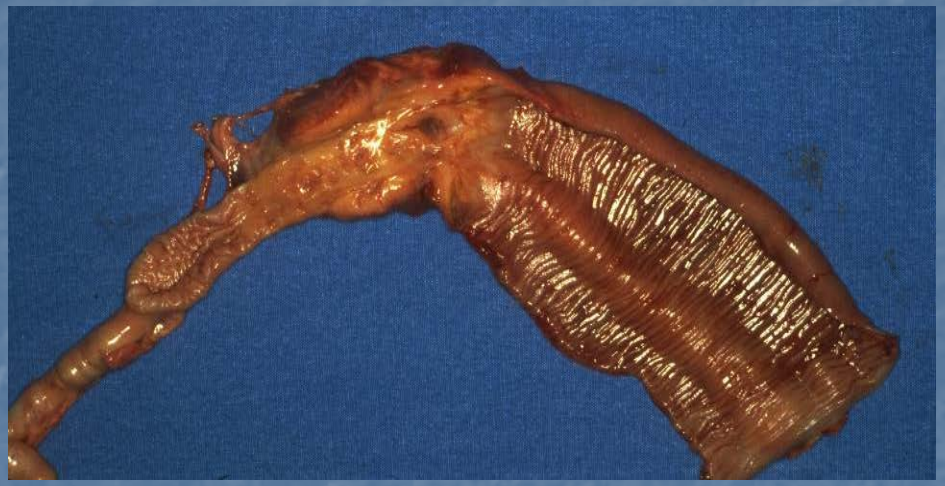
- Dysphagia
- Colic
- Abdominal distension
- Gastric reflux
- Diarrhea
- Fecal retension
- Dietary intolerance
  - Milk replacer
  - Other specie's milk
  - Frozen mare's milk
  - Fresh mare's milk

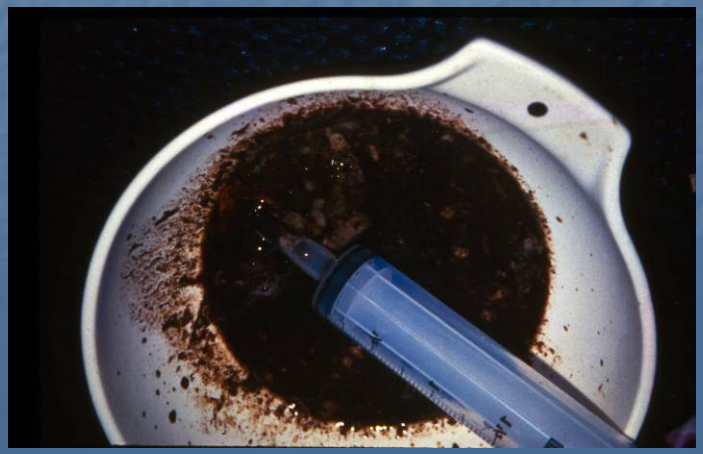


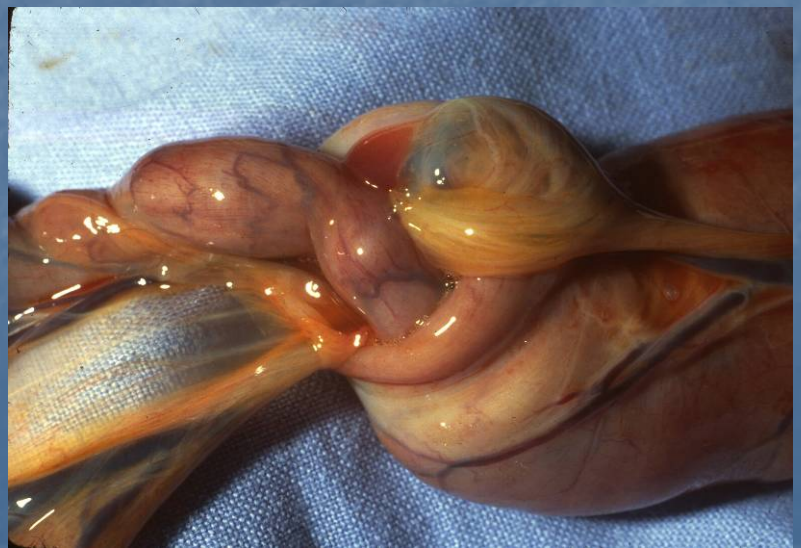
Neonatal Gastroenteropathy

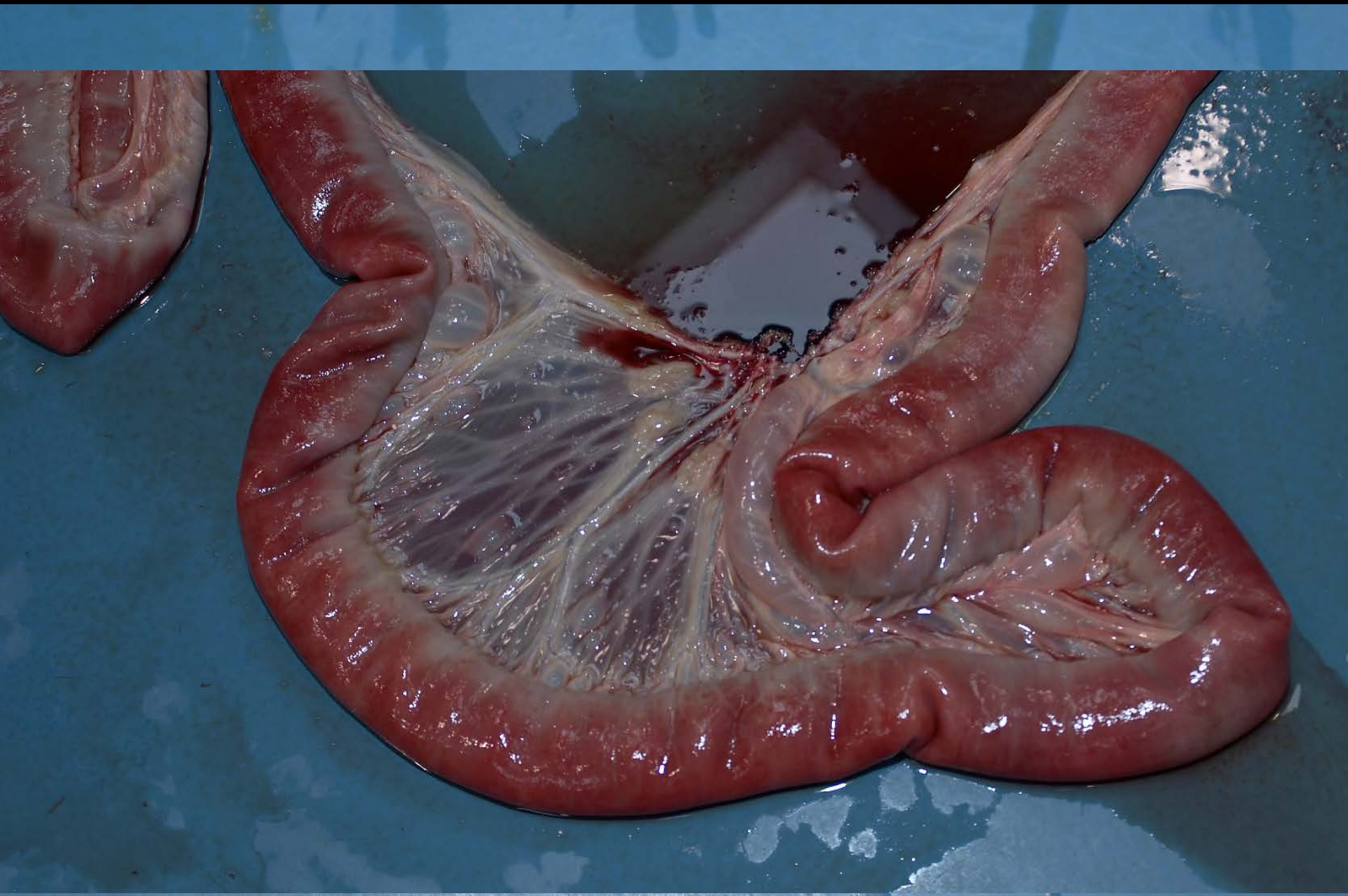
- Mild indigestion
- Dysmotility
- Ileus
- Diapedesis of blood into the lumen
- Mucosal edema
- Epithelial necrosis
- Development of intussusceptions or structures
- Hemorrhagic gastritis or enteritis/colitis
- Pneumatosis intestinalis

Neonatal Gastroenteropathy





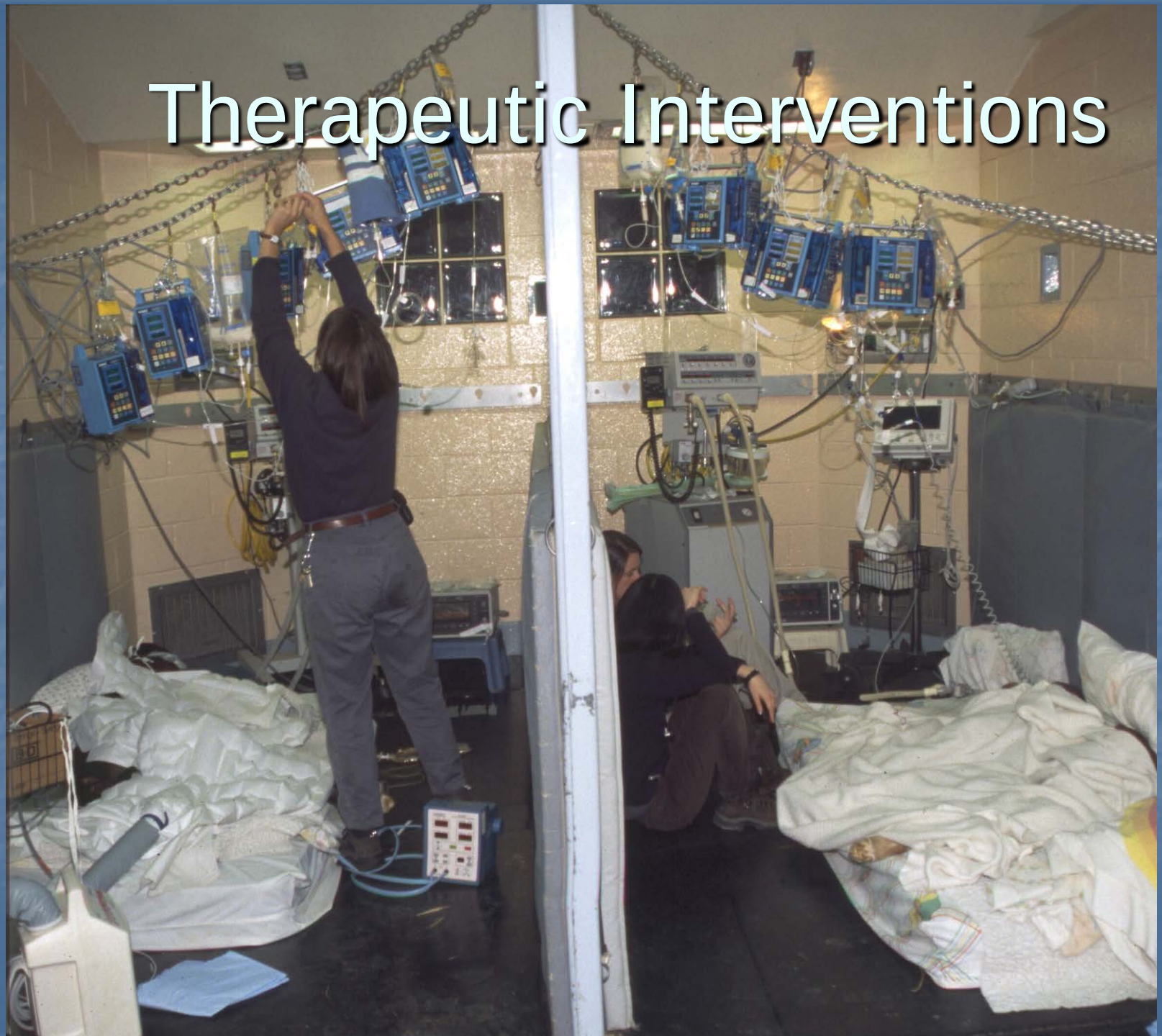




“Pong”
Major Problems

- Sepsis
  - Bacteremia - *Pantoea agglomerans*
- Septic shock
- Neonatal Encephalopathy
  - Central Respiratory failure – ventilation therapy
- Neonatal Nephropathy
- Neonatal Gastroenteropathy

Therapeutic Interventions



Therapy?

Evidence Based

Traditions

Beliefs

Experience Based

Neonatal Syndrome
Clinical Course/Therapeutic Intervention

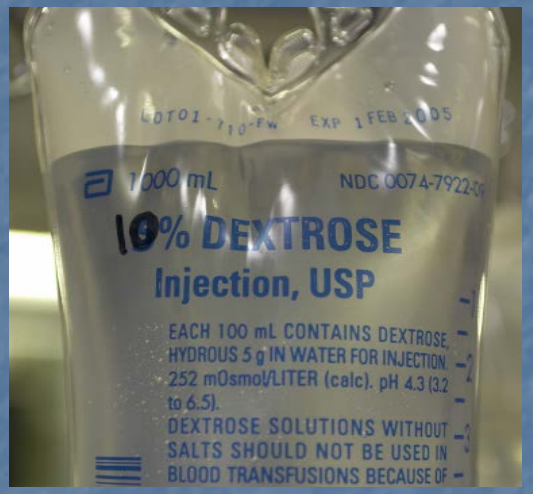
- As severe organ dysfunction develops
  - Oxygen delivery to the tissues interrupted
  - Sepsis – mediator damage to tissues
  - Progression of more severe disease
- Therapeutic intervention
  - Prevent hypoxic ischemic episodes
  - Prevent/control sepsis
  - Support organ system function
    - Allow recovery
  - Prevent other complications

Neonatal Syndrome
Maintain Tissue Perfusion/Oxygen Delivery

- **Adequate** CO/perfusion
  - No magic blood pressure value
  - Adequate perfusion reflected by?
    - Maintaining urine output
    - Perfusion of the limbs
    - Perfusion of the brain - mental status
    - Perfusion of bowel - GI function
  - Inotrope and pressor therapy
    - Goal: make livable – not normal

Neonatal Syndrome
Maintain Nutrition

- Avoid
  - Catabolic state
  - Hypoglycemia
    - Hypermetabolism
- All compromised neonates
  - Will benefit from glucose therapy
- Hyperglycemia
  - Insulin therapy
- Enteral Nutrition
- Parenteral Nutrition

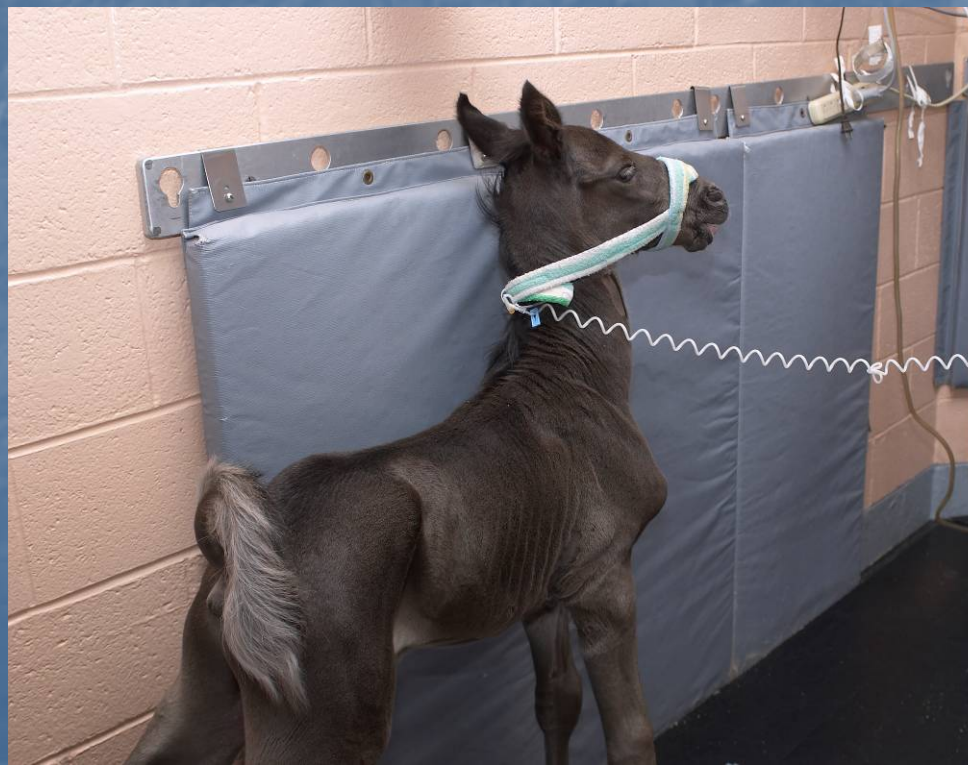


Neonatal Syndrome Therapy

- Support cerebral perfusion
  - Insure volemia
    - Careful fluid replacement!!!
  - Defend perfusion
    - Inopressor therapy – sparingly
- Insure oxygen delivery
  - Achieve pulmonary O_2 loading
  - Avoid anemia
  - Avoid hyperoxia
- Nutritional support
  - Permissive underfeeding

Neonatal Encephalopathy Therapy

- DMSO
- Mannitol
- Thiamine
- MgSO4
- Others

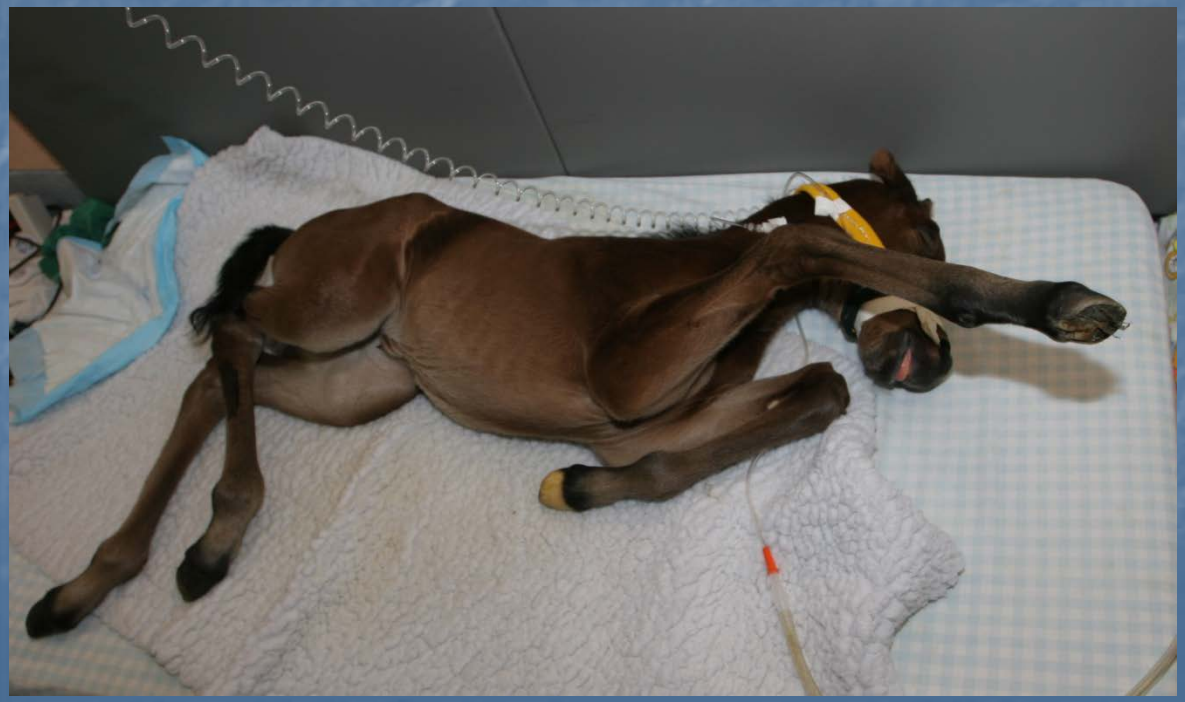


200 Cases of Neonatal Syndrome

- All treated with only supportive therapy
- 78% survived
- 22% nonsurvivrors:
  - 7% died
  - 15% euthanized
- Failures: 44 cases
  - Sepsis – 24 cases (12%)
  - NEC – 7 cases (3.5%)
  - NE – 5 firm cases – 2.5%
  - Congenital defects – 4 cases
  - Renal failure , kernicterus, arrhythmia , cardiac tamponade

Seizure Control

Phenobarbital? Midazolam? Others?



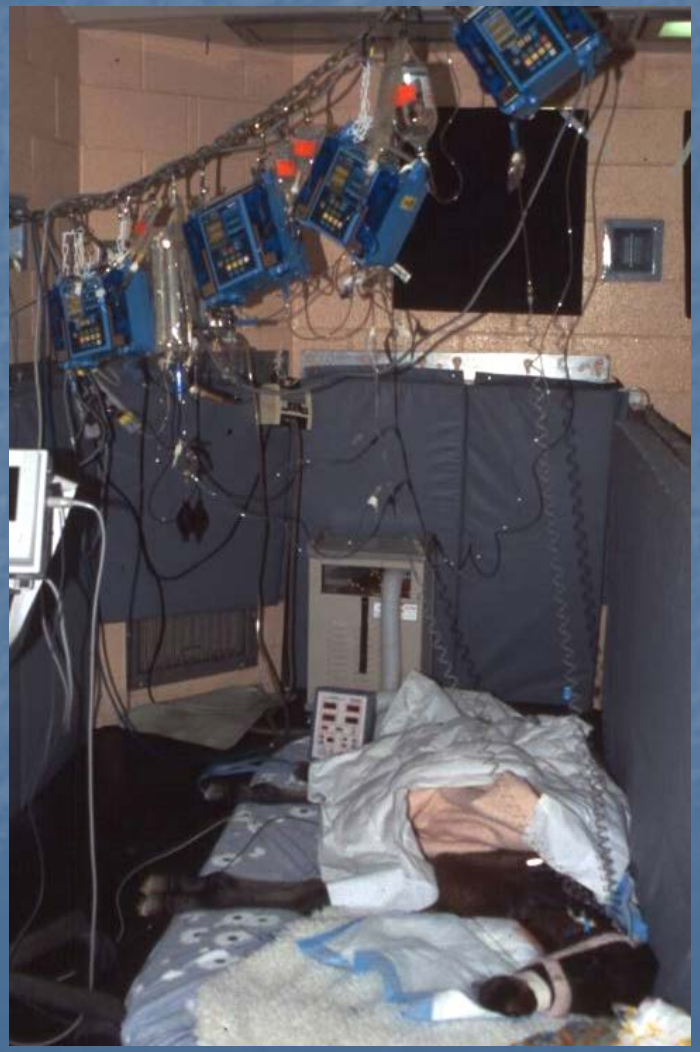
Neonatal Nephropathy Therapy for Renal Dysfunction

- Avoid fluid overload – how to tell?
  - Ventral edema
    - Between front legs ("jelly belly")
    - Proximal limbs
    - Back
    - Generalized
  - Monitor body weight at least SID
- Avoid NSAIDs

Neonatal Nephropathy Therapy for Renal Dysfunction

Fluid restriction

- Most important management tool
- Deliver maintenance fluids or less
  - "Run them dry"
  - Balance nutritional needs/fluid overload
- Watch for onset of diuresis
  - Transition to high output renal failure
    - Very rare
  - Initiation of normal renal function



Neonatal Gastroenteropathy Treatment of GI Dysfunction

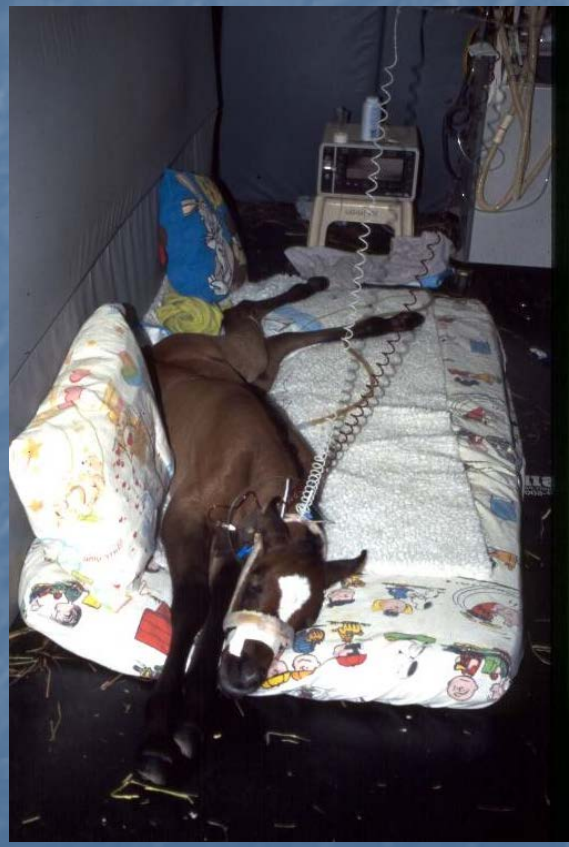
- Signs of damage lag behind other tissues
- Continued feeding with hypovolemia/hypoxemia
  - May result in further damage
  - Oral feeding undertaken with great care
  - Full nutritional requirements cannot be met enterally
  - Partial parenteral nutrition

Neonatal Gastroenteropathy Treatment of GI Dysfunction

- Important trophic substances in colostrum
  - Only small amounts needed for effect
- Luminal nutrition important to enterocyte health
  - Not feeding increases likelihood of translocation
- Small feedings 30 – 60 ml QID
  - Fresh colostrum - not refrigerated - best
  - Fresh mare's milk
  - Frozen colostrum or mare's milk
  - Don't use milk replacer

Neonatal Syndrome
Recognition/Early Treatment of Secondary Infections

- Very susceptible to infections
- Monitor
  - For localizing signs of infection
  - Repeated blood cultures
- Repeat measurements of IgG
  - Repeated plasma transfusions



“Pong” Therapeutic interventions

- INO2
- Fluid boluses
- Dobutamine
- Ticarcillin, clavulanic acid
- Plasma transfusion
- CRI glucose fluids
- Insulin
- Phenobarbital
- Positive pressure ventilation
- Parenteral Nutrition
- Trophic feedings
- Sucralfate
- Domperidone -- mare
- TMS , Cephalexin
- Bandaging

“Pong”

Equine Neonatology
Neonatal Syndrome

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Neonatology is a constantly evolving specialty. One area currently undergoing reassessment is the pathogenesis of the neurologic disease traditionally referred to as Neonatal Maladjustment Syndrome and which I refer to as Neonatal Encephalopathy (NE). NE is part of a multiorgan maladaptation syndrome we recognize that commonly involves not only neurologic signs but also renal and gastrointestinal signs. More rarely it may also include signs of other organ dysfunction. This discussion will begin with a review of recently proposed pathogenesis of the neurologic aspect of the syndrome followed by a more general discussion of the syndrome.

PATHOGENSIS OF NEONATAL ENCEPHALOPATY

Currently the best evidence suggests that NE is a result of Septic Encephalopathy (SE), Hypoxic Ischemic Encephalopathy (HIE) or the interaction of the two, modified by innate protective mechanisms. SE may be mediated by inflammatory mediators originating from maternal systemic inflammatory response syndrome (SIRS) or from fetal inflammatory response syndrome (FIRS). Maternal SIRS may be the result of maternal placentitis or other maternal inflammatory focus and FIRS is most commonly a result of fetal placentitis. In fetal circulation proinflammatory cytokines, prostaglandins, or lipopolysaccharide may change the blood brain barrier permeability resulting in the "leak" of mediators and other metabolites into the brain or the mediators may attach to cytokine receptors in areas devoid of the blood brain barrier resulting in up-regulation of proinflammatory cytokines and activation microglia/macrophages resulting in fetal brain SIRS (neuroinflammation). In central inflammation, microglia activation is a key feature, which will lead to the release of cytokines as well as trophic factors. The neuroinflammatory response depends on level and mix of inflammatory messengers. Low levels of messengers may result in "preconditioning" leading to protection for repeat exposure to higher levels of mediators or for hypoxic ischemic insults but more commonly the result is "sensitization" (sometimes referred to as negative preconditioning) which makes the neonate more susceptible to the effects of repeat exposure of inflammatory messengers or to even mild hypoxic ischemic insults.

Previously NE has been thought to be almost exclusively caused by hypoxic ischemic insults. Indeed, many practitioners continue to refer to NE as HIE. However there is little evidence that most neonates with NE have had a prenatal or intranatal hypoxic ischemic insult. In fact there is a better correlation of inflammatory insults and NE in neonates without overt evidence of birth asphyxia or early neonatal asphyxia. We have found a significant connection between placentitis and the occurrence of NE. The strength of the association supports the hypothesis that placentitis is a cause of NE in many foals. There is no doubt that those neonates that have intranatal or post natal asphyxia such as prolonged stage 2 labor, cord compression, birth apnea or cardiopulmonary failure will have true hypoxic ischemic encephalopathy. Hypoxic ischemic insults are strong inducers of neuroinflammation. But it should be kept in mind that although all cases of NE may have similar clinical signs, as the etiology and thus the pathogenesis and response to therapy may differ, it may be dangerous to refer to them all as cases of HIE and expect them all to respond uniformly.

High concentrations of neurosteroids, especially alloprenanolones, protect the brain during fetal life. The placenta provides substrates (primarily progesterones) allowing maintenance of high levels of alloprenanolone in the fetal brain. These high levels are largely responsible for the somnolence which subdues the fetus. At birth, with the removal of the placental source, the levels drop rapidly, allowing the fetus to "awake up."

Allopregnanolone and its synthetic analogues have marked anti-seizure actions and raise seizure threshold and protect against neuroexcitatory toxicity. They primarily work through potentiating $GABA_A$ receptor mediated neuroinhibitory responses. Inflammatory mediators and hypoxic ischemic insults are powerful inducers of brain production of allopregnanolones before and after birth. The placenta also secretes pregnenolone and pregnenolone sulphate into the fetal circulation. These steroids have an excitatory action in the brain again primarily through their

effect on $GABA_A$ receptors. They block $GABA_A$ inhibitory responses. Passage of sulphated steroids across the blood brain barrier is slow compared with the suppressive steroids. Normally the fetus has a blood brain barrier which excludes sulphated steroids so they will not enter the fetal brain in sufficient quantities to influence excitability. But under the influence of fetal infection, compromise of the blood brain barrier may allow the entry of these sulphates causing adverse effects. Similar effects may occur with hypoxic ischemic insults.

So there is a complex interaction with remote or local sepsis initiating encephalopathy which may be exacerbated by even mild hypoxic ischemic insults or by the entrance through the damaged blood brain barrier of excitatory sulfated steroids or inflammatory mediators. In addition, these processes simultaneously induce high levels of neuroprotective allopregnanolones. Loss of placental precursors at the time of birth may lead to decreased brain neurosteroids levels resulting in a window of increased vulnerability. But the accompanying stress of neonatal disease leads to increases in adrenal steroidogenesis leading to the release of neurosteroid precursors (deoxycorticosterone e.g. DOC) replacing the placental supply of precursors to the CNS. This may restore the appropriate balance of neurosteroid action in the brain after birth and the transition from largely allopregnanolone before birth to allopregnanolone and TH-DOC (5a-tetrahydro-deoxycorticosterone) mediated neuroprotective pathways after birth. Adrenal insufficiency may lead to a decrease neurosteroid availability allowing more severe NE. The effects of neurosteroids results from enhancing (neuroprotective) or blocking (neuroexcitatory) $GABA_A$ receptor-mediated post-synaptic hyperpolarization and interfering with glutamatergic transmission with an overall effect of modifying excitation.

These interactions can explain the common clinical observation that foals with NE secondary to placentitis may initially appear normal, followed by develop clinical signs often associated with excitation (constant activity, hyper-responsiveness, hypertonus) followed by onset of seizure-like activity and finally followed by a period of somnolence and recovery. Before and just after birth the effects of NE may be dampened by placental derived neurosteroids. As the protective neurosteroid levels wane, the clinical signs of NE emerge culminating in tonic clonic seizure-like activity. The stress of the disease induces adrenal steroidogenesis providing precursor for neurosteroids production and the neuroinflammatory response, itself, induces high levels of protective neurosteroid production resulting in somnolence and recovery. Foals with severe placental damage secondary to widespread placentitis may have less placental steroidogenesis and lower levels of protective neurosteroids or inflammatory mediator induced blood brain barrier deficits allowing sulphated steroids access to the CNS. In either case early onset of clinical signs, prenatal or intranatal, or more commonly within an hour of birth could be expected to occur. Although this pathogenesis is purely speculative, it could have significant implications with the development of therapeutic neurosteroids.

CLINICAL SIGNS

The signs seen in Neonatal Syndrome are remarkably similar between cases following predictable patterns even though all cases do not necessarily encompass all possible signs. The neurologic disease of neonatal foals not only involves behavioral abnormalities but also other neurologic signs including changes in respiratory patterns/function, changes in muscle tone, changes in responsiveness, vestibular signs and autonomic disruption (loss of vascular control, loss of thermoregulation, inappropriate bradycardia, etc.). The renal signs show less variation but include inappropriate antidiuresis, sodium wasting, other tubular abnormalities and rarely tubular necrosis. The GI signs have a large spectrum from failure to pass feces for days to weeks without colic, to GI bleeding with few other signs, to severe colic or diarrhea secondary to intestinal necrosis.

Foals with NE may show changes in responsiveness, muscle tone, behavior, evidence of brain stem damage or seizure-like behavior. Changes in responsiveness include hyperesthesia, hyperresponsiveness, hyperexcitability, hyperkinesis, hyporesponsiveness, periods of somnolence or unresponsiveness. Often foals go through a period of increased responsiveness followed by a period of decreased responsiveness. Changes in muscle tone include increased extensor tonus, hypotonia and other less common changes such as neurogenic myotonia or failure to protract front or hind legs. Changes in behavior are very common and include loss of suckle response, loss of tongue curl, loss of tongue coordination, disorientation especially relative to the udder, aimless wandering, loss of affinity for the dam and abnormal vocalization. Although blindness is commonly assumed based on collisions with obstacles, I find that most foals can see but don't process what they see and thus run into obstacles. Foals with NE commonly have changes in respiratory patterns with central tachypnea, apneusis, apnea, cluster breathing, ataxic breathing, Cheyne-Stokes breathing or central hypercapnia. Other signs of brain stem damage include loss of thermoregulatory control, generalized weakness, anisocoria, pupillary dilation, pinpoint pupils, central hypotension,

inappropriate bradycardia (autonomic disruption), decreased responsiveness, difficult to arouse, loss of consciousness, vestibular signs (circling, head tilt), facial nerve paresis and a variety of other signs. Foals with NE have a wide variety of signs and degrees of severity. More than 90% of affected foals are normal within 10 days.

Foals may also develop Neonatal Nephropathy (NN). There is a wide spectrum of disease seen in cases of NN including incomplete transition from fetal renal physiology, water/sodium retention, mild tubular dysfunction (sodium wasting), abnormal excretion of drugs (e.g. high aminoglycoside trough levels), acute tubular necrosis or decreased GFR. Often the signs of dysfunction are subtle and easily overlooked unless anticipated. Although almost always transient, on occasion significant acute damage may lead to chronic renal disease. These foals often have a decreased GFR as reflected by a slow decrease birth creatinine or decreased creatinine clearance, delayed water excretion with edema formation and weight gain and slow response to fluid challenges. Many foals develop signs similar to the syndrome in human neonates called Neonatal Vasogenic Nephropathy which results in inappropriate antidiuresis. This syndrome is marked by infrequent urination of small volumes of concentrated urine leading to fluid overload. It can easily go unnoticed without care observation and monitoring urine output and urine specific gravity.

Neonatal Gastroenteropathy (NG) can be manifested by a wide spectrum of signs ranging from mild indigestion with dysmotility and fecal retention to moderate disease with ileus, diapedesis of blood into the lumen and mucosal edema to severe disease with epithelial necrosis, intussusceptions, structures, hemorrhagic gastritis/enteritis/colitis, full thickness necrosis and pneumatosis intestinalis. Even mild forms predispose to sepsis and SIRS with increased likelihood of translocation of bacteria. Like NN, often the signs of dysfunction are subtle and easily overlooked unless anticipated. The most common manifestation is dysmotility with meconium retention and lack of fecal passage for days (range 2-30 days). Despite fecal retention, an important aspect is lack of discomfort. Classically, foals with dysmotility will not return enema fluid or strain associated with rectal distension.

Often, foals affected with Neonatal Syndrome have the triad of NE, NN and NG. Other problems seen include metabolic maladaptation, autonomic failure and other systemic problems. Most of these foals have no clear history of an intrauterine hypoxic ischemic insult but certainly have had some intrauterine challenge. This intrauterine challenge often proves to be fetal inflammation secondary to placentitis. There is a connection between placentitis and the Neonatal Syndrome and there is a protective effect of treatment. Placentitis is a risk factor for these neonatal diseases.

THERAPY

So how should we treat foals with this complex syndrome? As we have no evidence based information on therapy of foals with NE, treatment of the disease is largely based on traditions and beliefs. Beliefs are usually based on rational extrapolation of information gleaned from experimental models and clinical trials in man. But as we have no solid evidence, treatment is somewhat arbitrary and there is no right or wrong approach. As intrauterine insults appear to result in “sensitization” resulting in even mild hypoxic ischemic insults causing significant exacerbation of NE, my main goal is to support cerebral perfusion and oxygen delivery. In many mild cases these are not limiting but in the more severe case (recumbent foal) this is achieved by insuring normovolemia with careful fluid management, use of inopressor as needed and insuring oxygen delivery by maintaining pulmonary oxygen loading and avoiding anemia. It is also vital to prevent catabolism by careful nutritional management. These goals should be achieved by delivering intranasal oxygen insufflation when necessary, enhancing pulmonary gas exchange with postural support, maintaining hematocrit above 20%, maintaining perfusion as above, supplying adequate exogenous glucose initially and if enteral nutrition is not possible within 24 hours, parenteral nutrition. So these foals may need fluids (being careful to avoid fluid overload), oxygen, glucose and occasionally inotropes and pressors. It should be noted that the goal of therapy is not to make the foal “normal” but to partially correct extreme values when needed. For instance, it’s probably not necessary to place the foal on intranasal oxygen insufflation unless the Pao_2 is < 60 and maybe wise to try to keep the Pao_2 < 80 to avoid negative consequences of oxygen therapy.

There have been a number of other favorite therapies used and although I have tried many, I have never been overly impressed and I feel we have little rationale grounded in evidence for most of them. With a recovery rate of neurologic disease of >90% with supportive care alone, any additional therapy would have to be very good or significantly shorten the course to make its use worthwhile. Free radical scavengers (DMSO, mannitol) have been used to minimize reperfusion injury, and they may be appropriate within minutes after relieving a dystocia during birth resuscitation but if treatment is not given within an hour of the insult it will not help. Clinicians often treat

cerebral edema that "must be present." My experience parallels that of human medicine, which notes that cerebral edema, when present, is epiphenomena. It is a byproduct of severe disease and not part of the genesis. In survivable disease it doesn't seem to play a role. When a hypoxic ischemic insult is the cause, it may result in cellular edema and not cerebral edema unless it is very severe and the primary damage is fatal. Many clinicians have used DMSO or mannitol routinely. I stopped using these treatments more than 20 years ago. I did look back at about 300 cases and found using only supportive therapy was as effective or even a little better (as gauged by survival to discharge) than using either of these drugs. Thiamine has been used for its cerebral protective effect, but I don't think it aids recovery. Its supplementation is probably more useful as an aid to metabolism when high infusion rates of dextrose are given especially in the face of hypermetabolism which sometimes accompanies severe sepsis.

Another proposed treatment of NE in foals is $MgSO_4$ administration, however its efficacy is unproven and $MgSO_4$ may in fact be contraindicated. The $MgSO_4$ story is very interesting and has followed many twists and turns in the past 2 decades. Its complete discussion goes beyond the scope of this talk but as based on the results of antenatal and neonatal studies in man (many have been published) showing either very slight benefit, slight to moderate detriment and equivocal results and the high recovery rate of neurologic disease (>90%) with no specific therapy I suggest *primum non nocere* and think $MgSO_4$ therapy should be avoided.

Complete discussion of the therapy for renal and gastrointestinal dysfunction which may occur in Neonatal Syndrome goes beyond the scope of this presentation. Briefly, the guiding principle for renal support is to avoid fluid overload through fluid restriction and careful attention to balancing the foal's electrolytes and acid base. Gastrointestinal support include avoiding aggressive feeding but rather begin with carefully controlled trophic feeding watching for GI intolerance and guaranteeing adequate nutrition with parenteral therapy as needed. The most important adjunct therapy is monitoring for and treating sepsis as most treatment failures are secondary to poorly controlled sepsis.