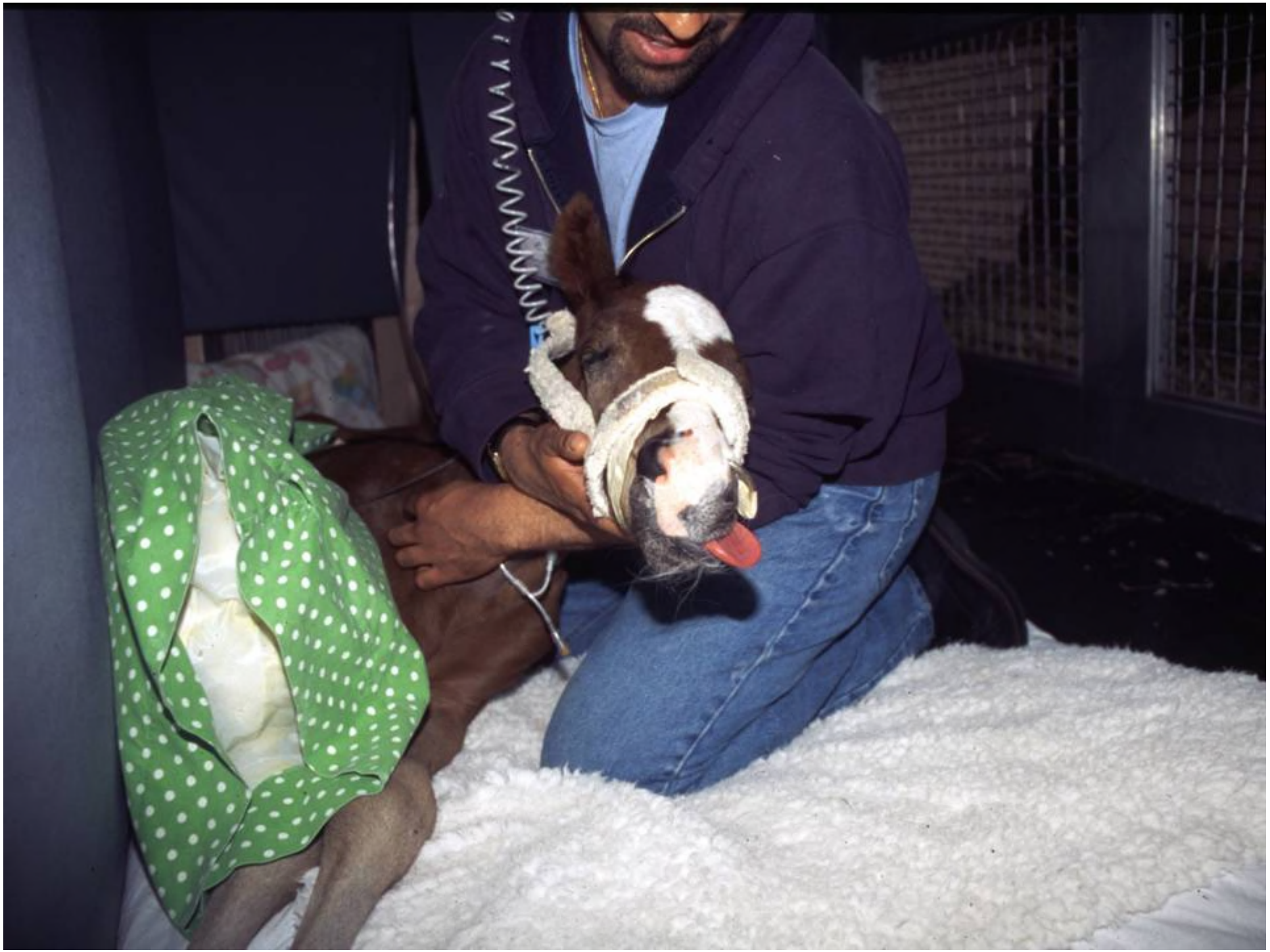
The Maladjusted Foal

Jon Palmer, VMD

Changes in Behavior



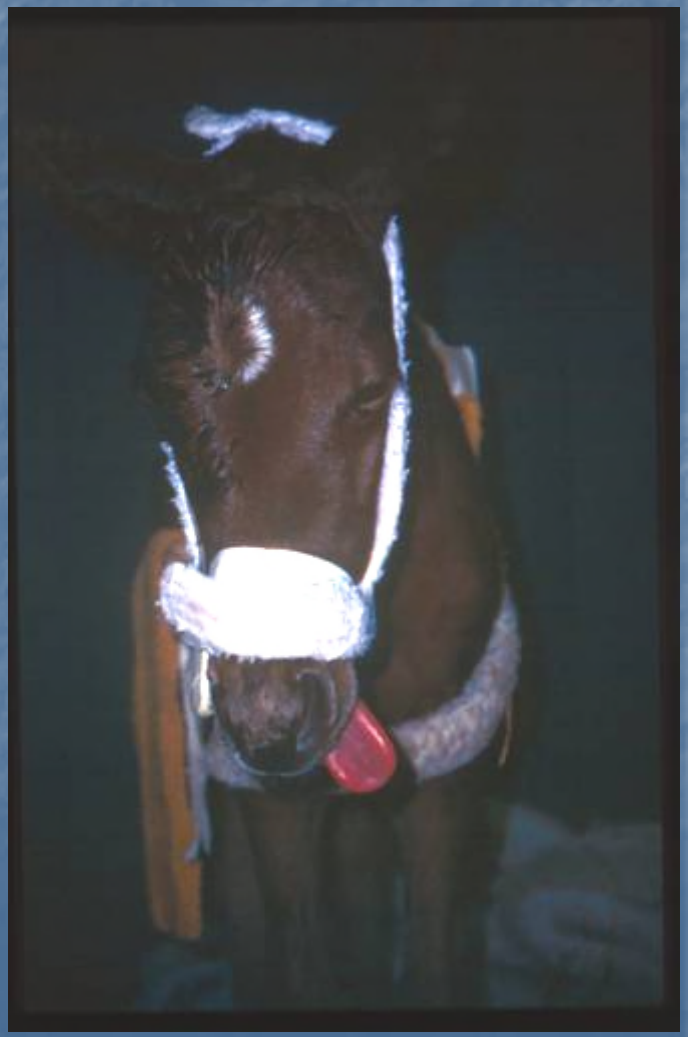
Neonatal Intensive Care

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

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

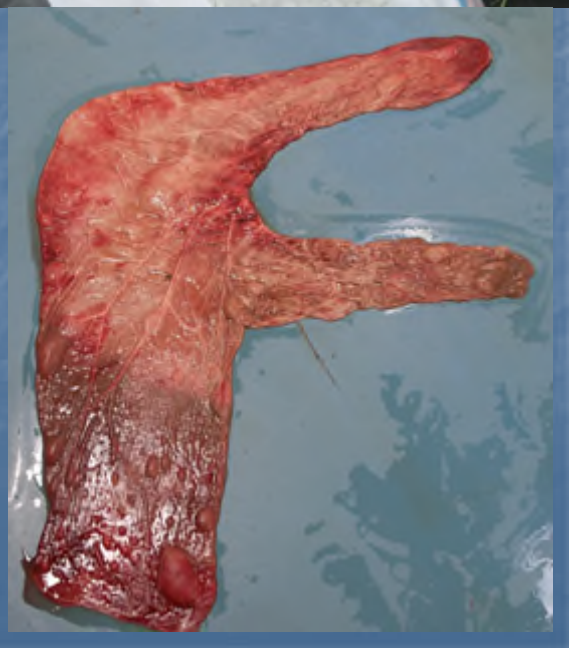


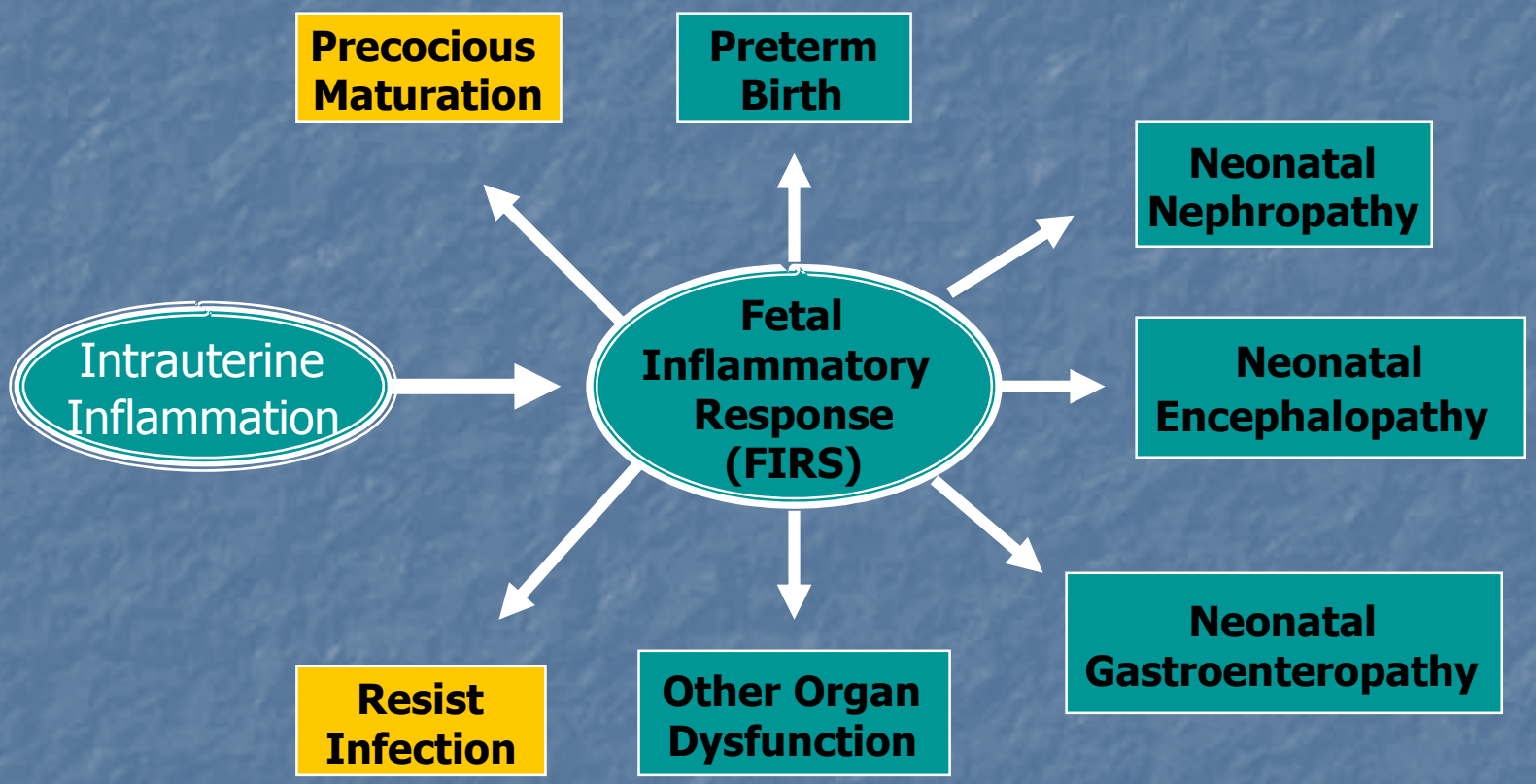
Neonatal Problems

- 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?

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

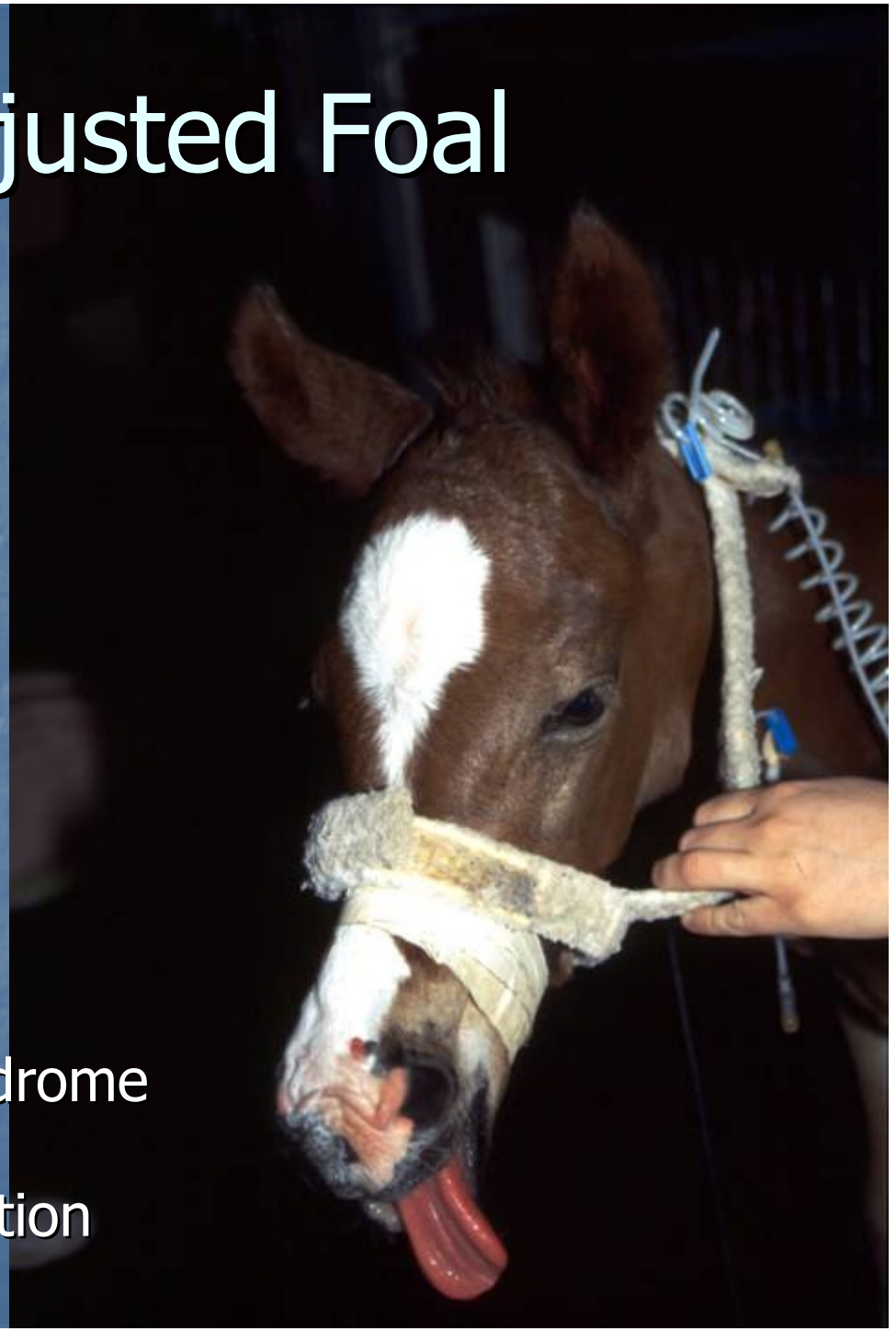



Precocious Maturation
Preterm Birth
Neonatal Nephropathy
Intrauterine Inflammation
Fetal Inflammatory Response (FIRS)
Neonatal Encephalopathy
Neonatal Gastroenteropathy
Resist Infection
Other Organ Dysfunction

The Maladjusted Foal

- Dummies
- Barkers
- Wanders

- Hypoxic Ischemic Syndrome
- Perinatal Asphyxia
- Hypoxic Ischemic Asphyxial Syndrome
- Neonatal Multisystem Maladaptation

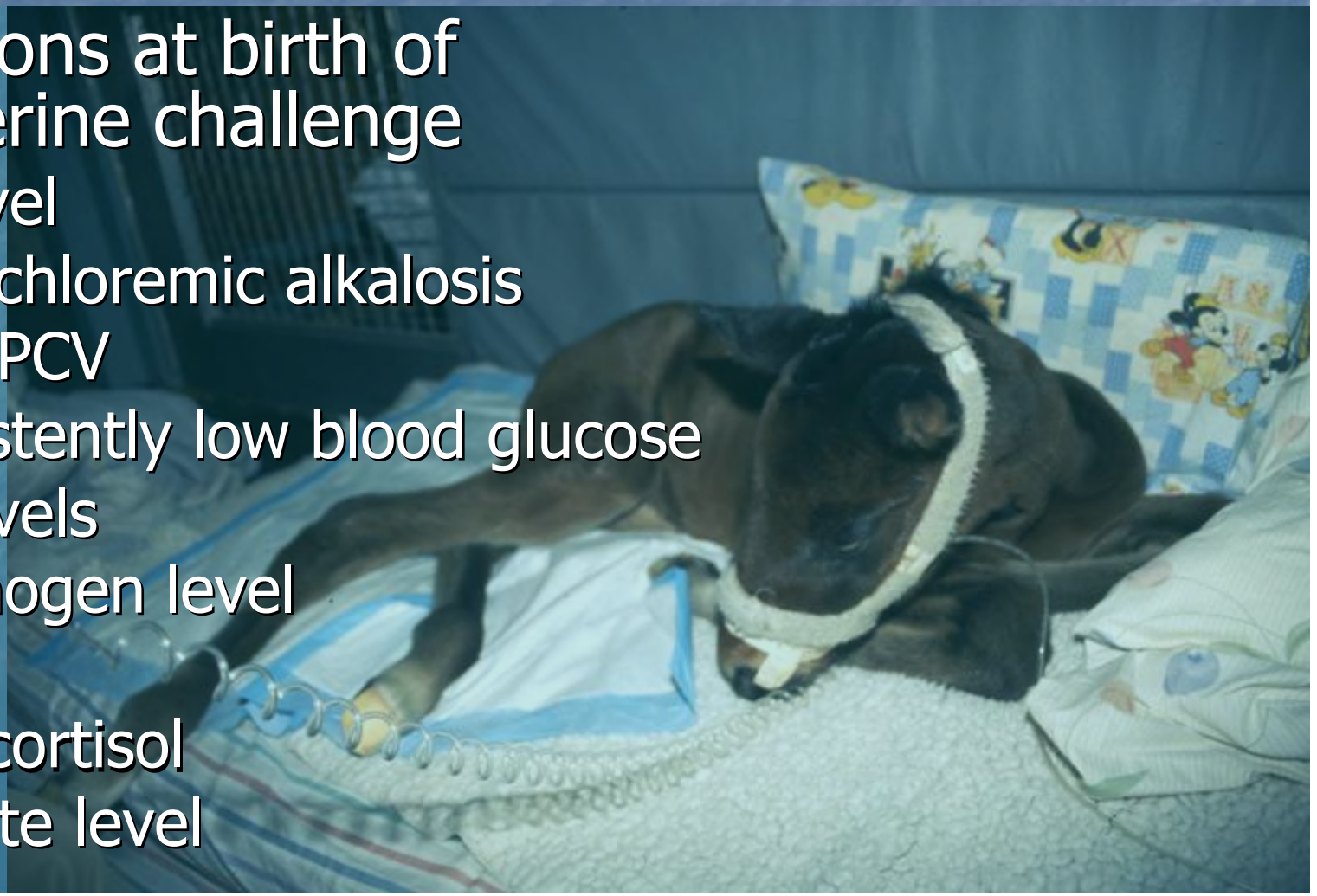


Terms
Generic Description of Signs

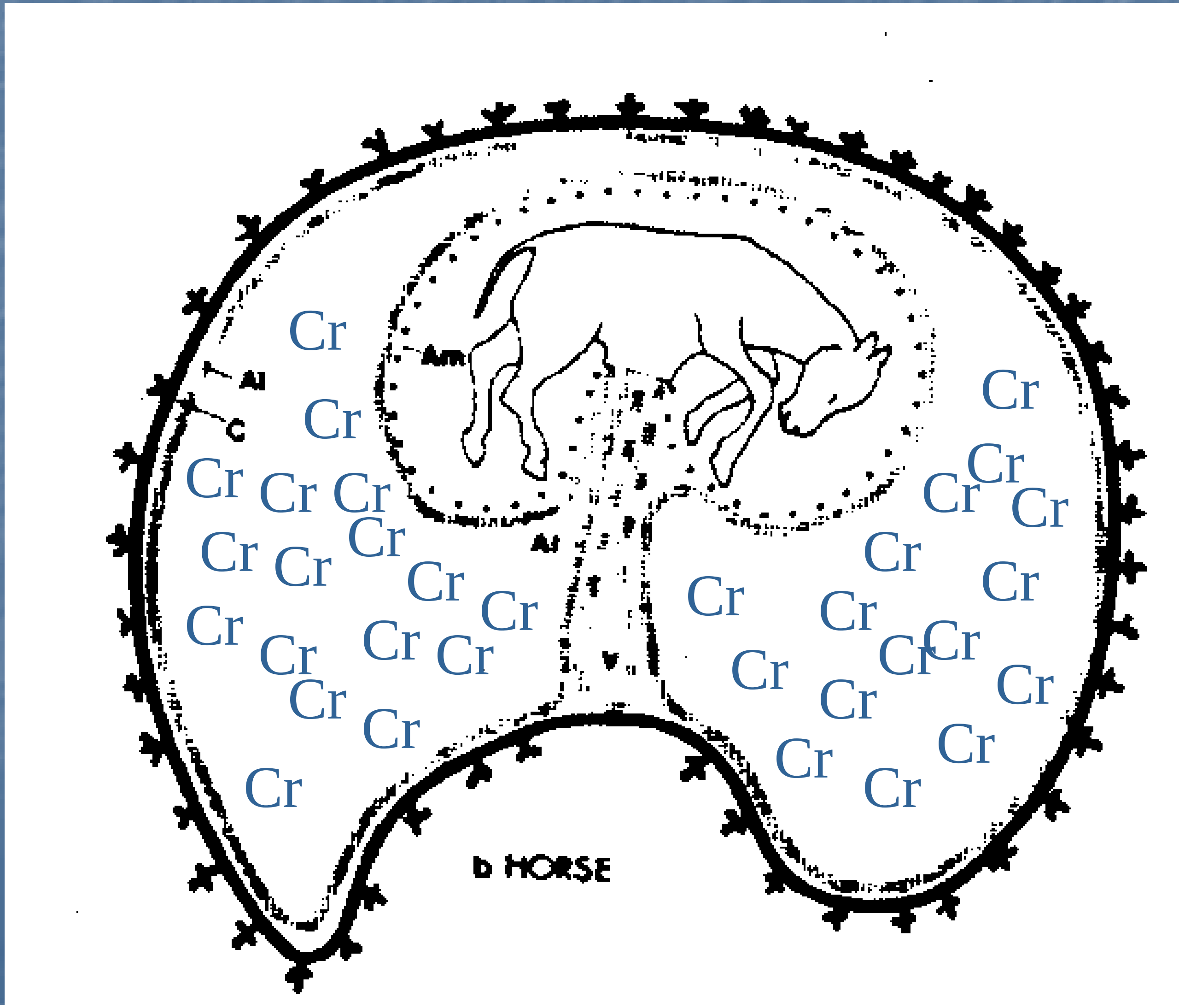
- Neonatal Encephalopathy (NE)
- Neonatal Gastroenteropathy (NG)
- Neonatal Nephropathy (NN)
- Neonatal Metabolic Maladaptation
- Neonatal Cardiovascular Maladaptation

Intrauterine Challenge

- Indications at birth of intrauterine challenge
  - Cr level
  - Hypochloremic alkalosis
  - High PCV
  - Persistently low blood glucose
  - Ca levels
  - Fibrinogen level
  - WBC
  - Low cortisol
  - Lactate level



Fetal foal floating in a sea of creatinine



"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

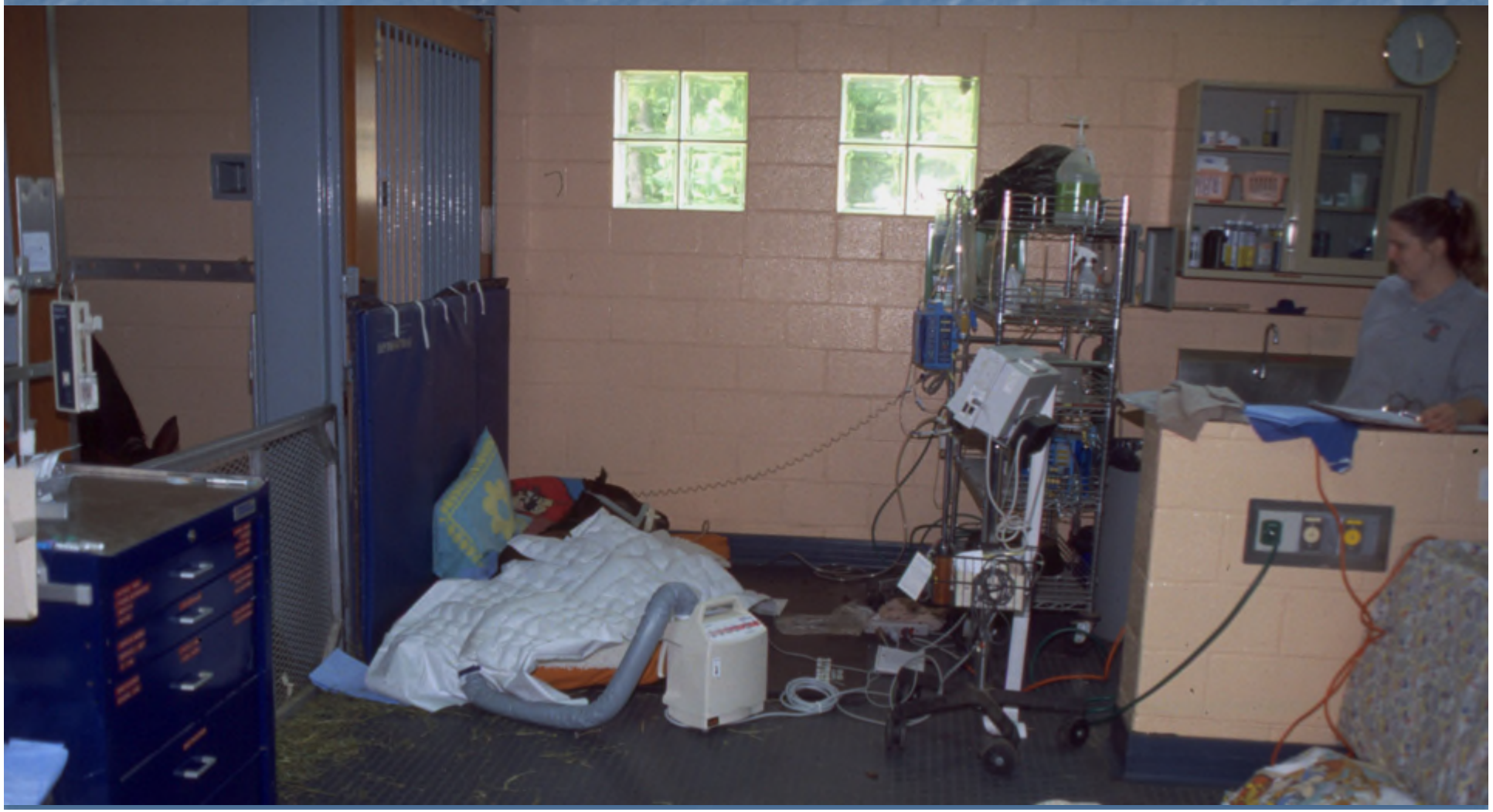
"Pong" History

- 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

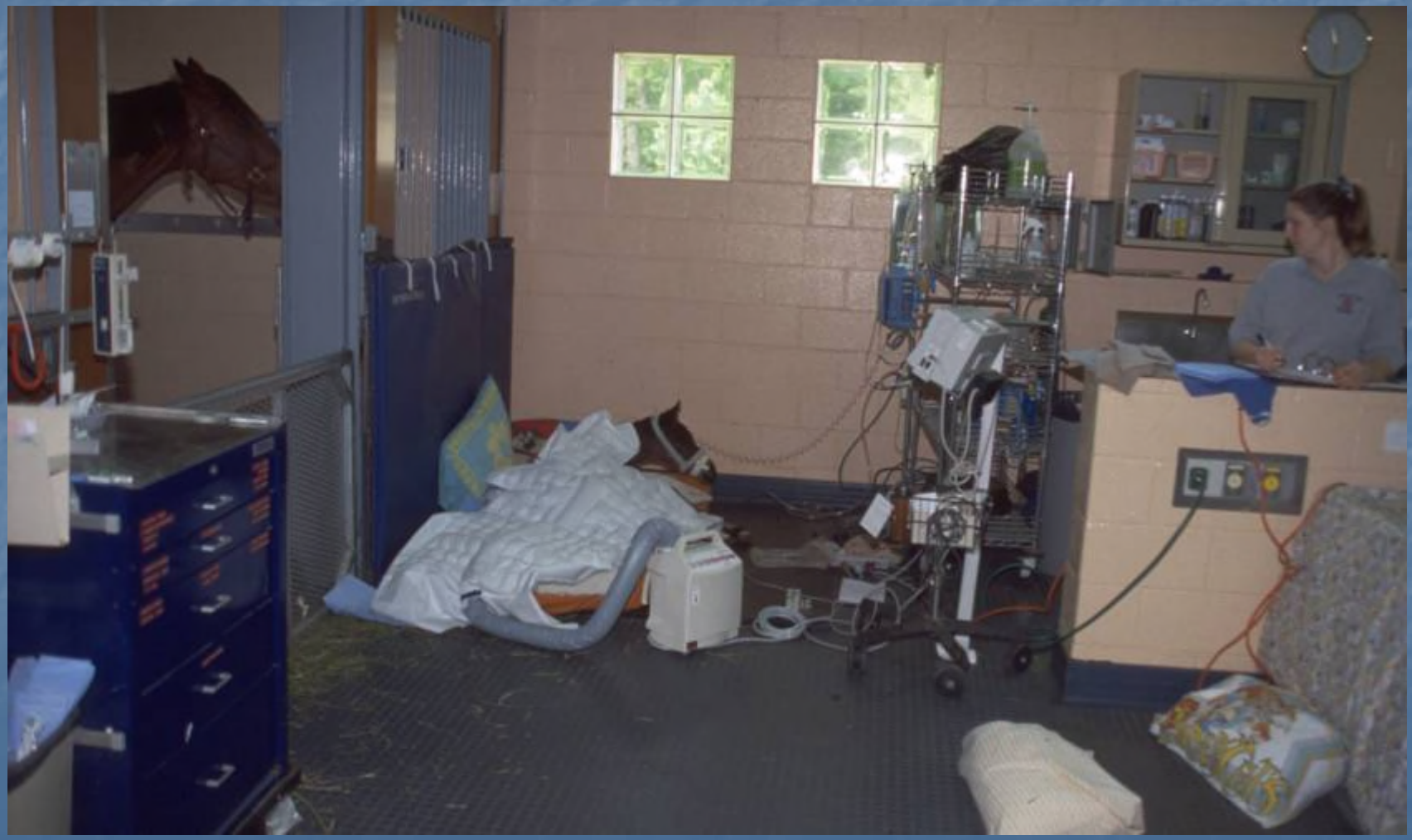
"Pong" Admission Physical



"Pong"
Admission Problems

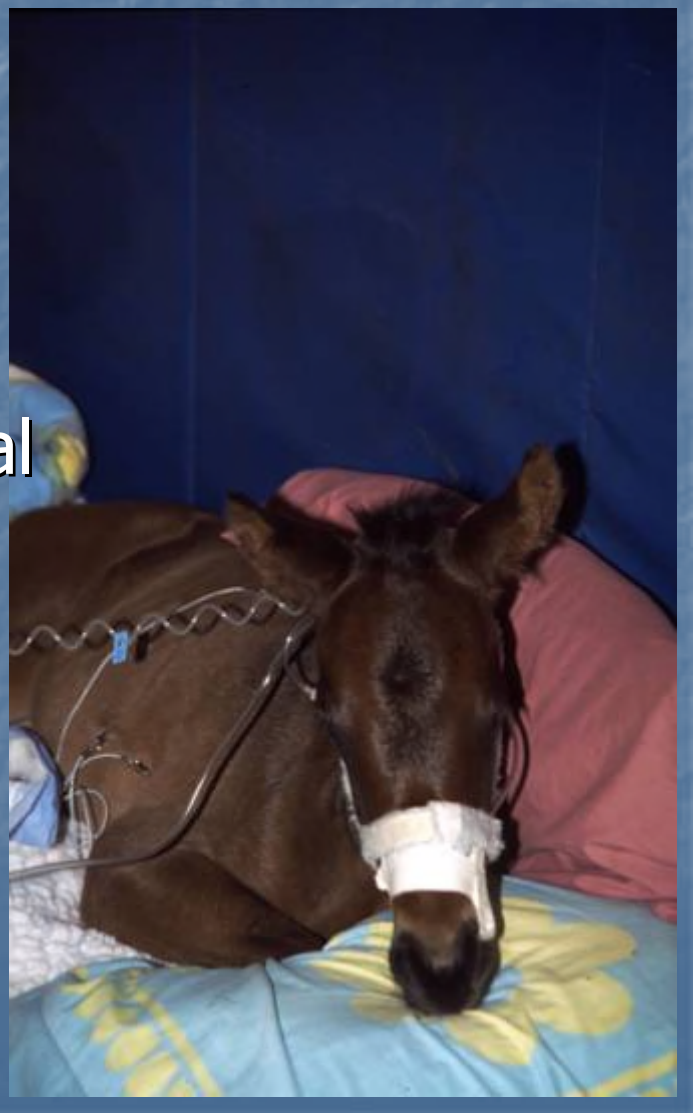
- Weakness, somnolence
- Not nursing
- Lingual erythema
- Injection
- Petechia
- Icterus
- Poor perfusion
- Diarrhea
- ↓ WBC, ↑fibrinogen
- ↑ PCV, ↑ TPP
- ↑ Creatinine
- Hypoxemia
- ↑ lactate

"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

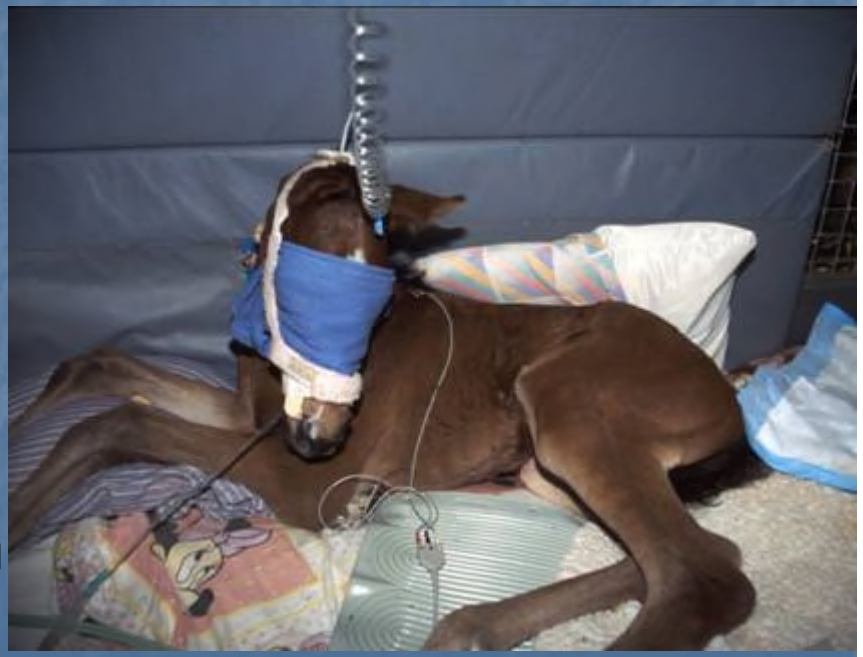
- Periodic apnea
  - Up to 60 sec
  - With clustered breathing
- Inappropriate central tachypnea
- Apneusis (apneustic respiration)
- Hypercapnia
  - Without apnea

"Pong"
Neonatal Encephalopathy

- Seizure like activity
  - Opisthotonus, tonic/clonic marching activity
  - Minimal nystagmus
- Hyperresponsive to stimuli
- No suckle or searching

Neonatal Encephalopathy CNS Signs

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

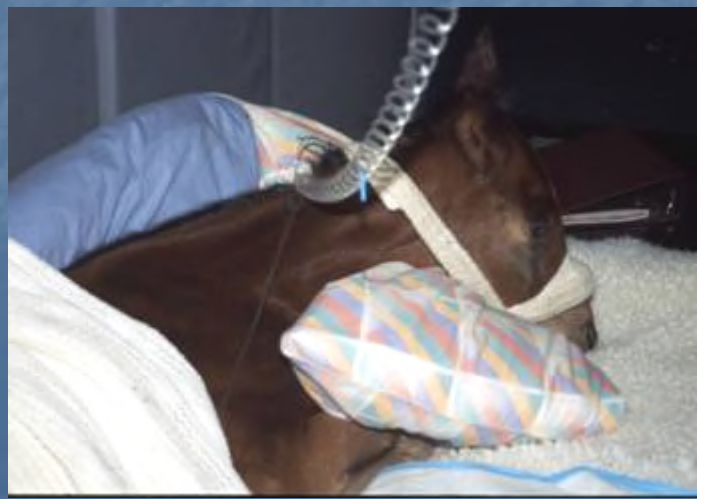


Neonatal Encephalopathy Signs of CNS disease

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

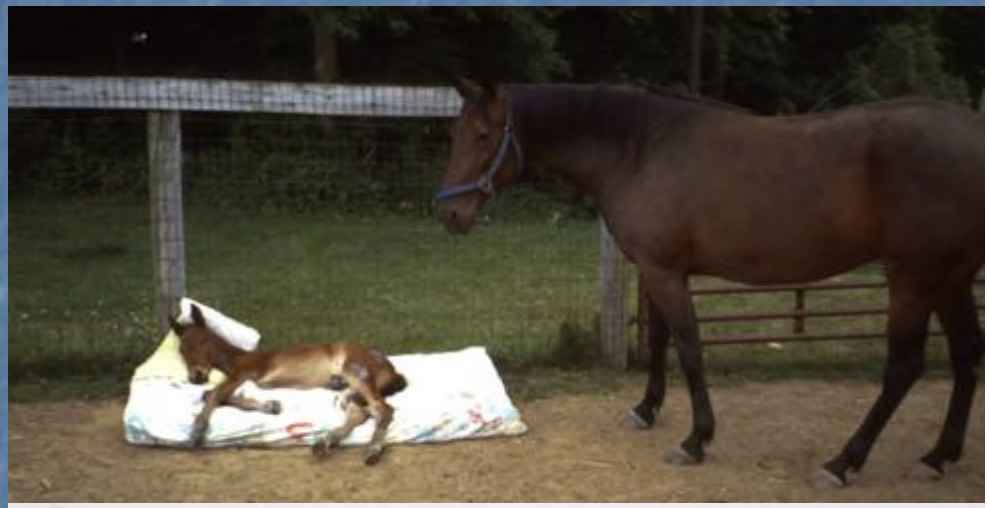
Neonatal Encephalopathy Signs of CNS disease

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



Neonatal Encephalopathy
Signs of CNS disease

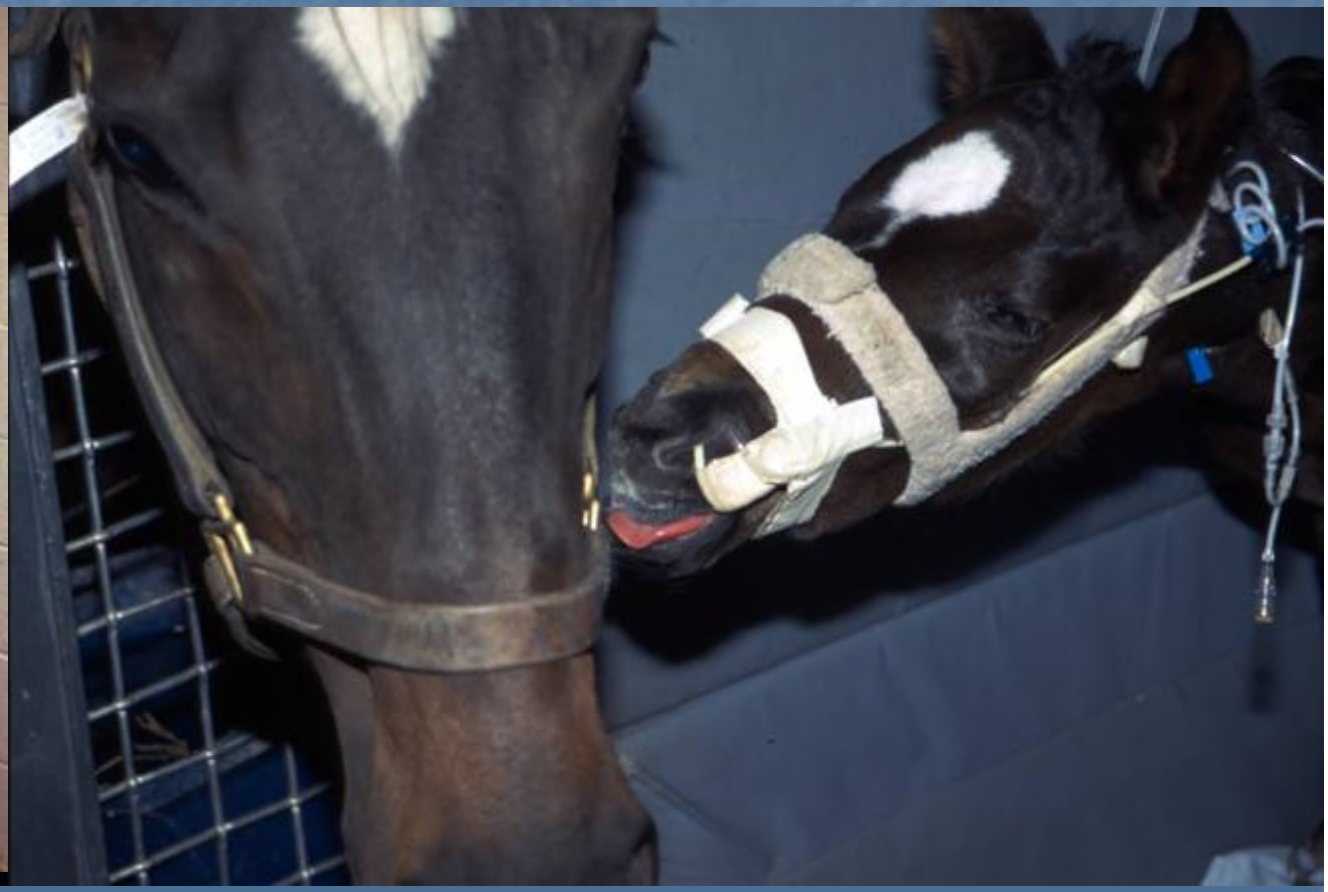
- Changes in muscle tone
  - Extensor tonus
  - Hypotonia
  - Neurogenic myotonia
  - Inability to protract legs



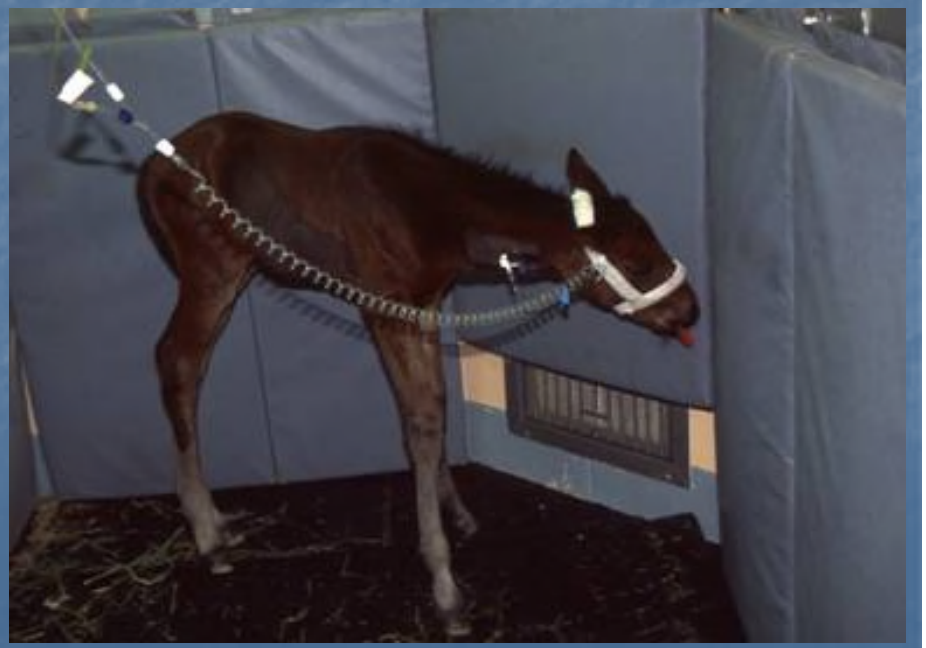
Neonatal Encephalopathy Signs of CNS disease

- 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

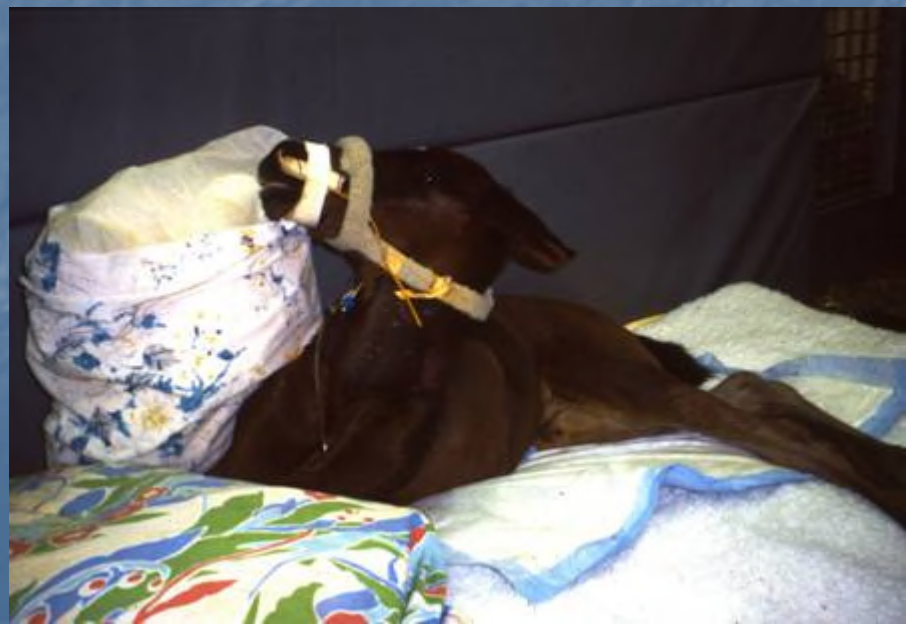
- Changes in respiratory patterns
  - Central tachypnea (midbrain)
  - Apneusis (pontine)
  - Apnea (> 20 seconds midbrain)
  - Cluster breathing (high medullary)
  - Ataxic breathing (medulla)
  - Cheyne-Stokes breathing - very rare
- Central hypercapnia

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
  - Marching type behavior
  - Abnormal extensor tone
  - Seizures
- Coma, death



"Pong" Neonatal Encephalopathy Treatment

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

"Pong"
Neonatal Encephalopathy

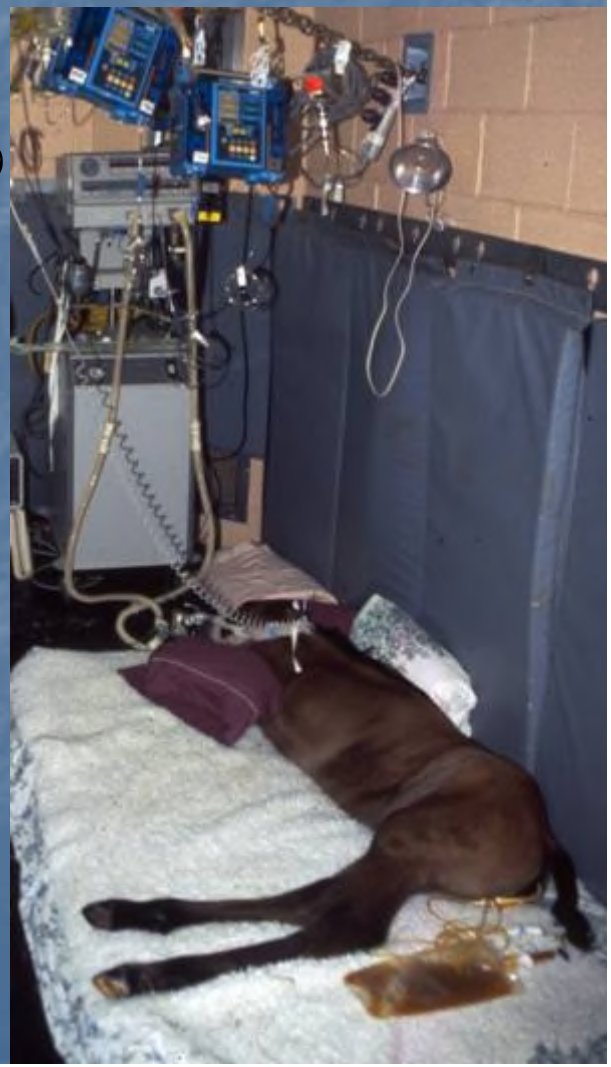
- Hospital day 2
  - Seizures – resolved with phenobarbital therapy
  - Began ventilation
- Hospital day 3 – standing
- Hospital day 5 – nursing from bottle, more aware
- Hospital day 6 – off intranasal oxygen
- Hospital day 9 – nursing from mare

"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

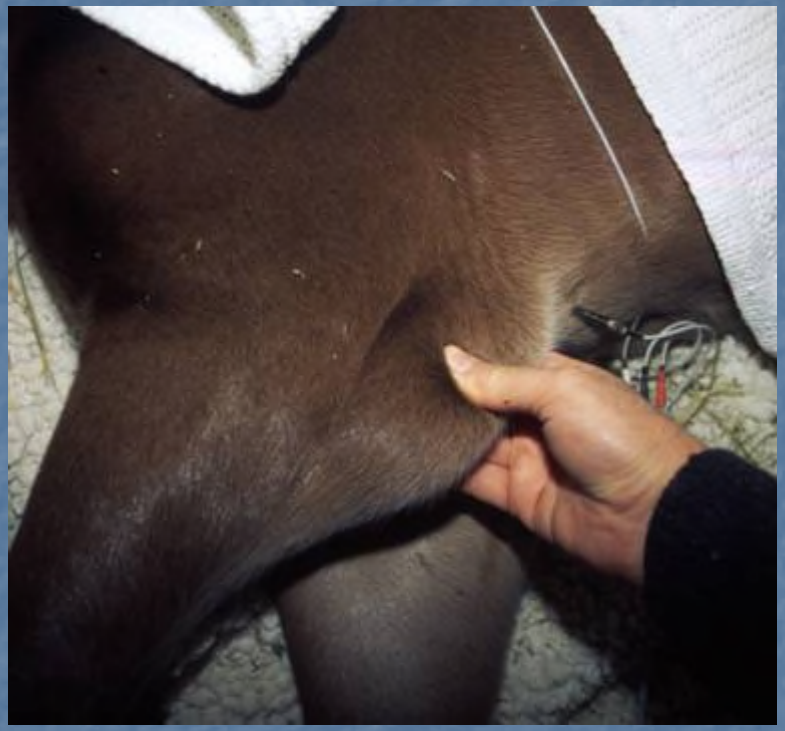
Neonatal Nephropathy

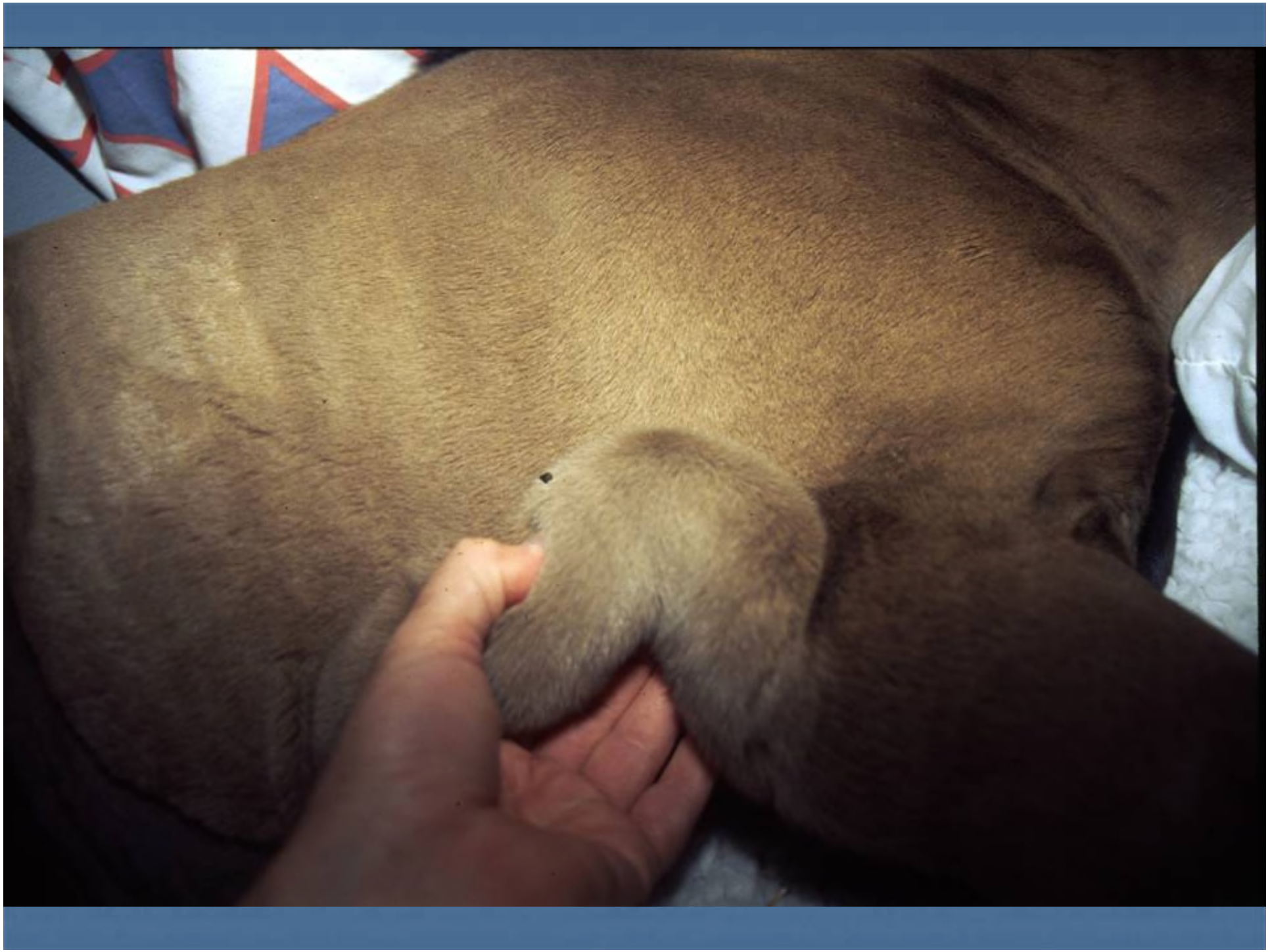
- Second most common target - 45%
- Common disease states
  - Mild acute tubular necrosis
  - Mild tubular dysfunction
  - Maldistribution of renal blood flow
- Less common disease states
  - Severe acute tubular necrosis
  - Irreversible acute damage
  - Chronic renal disease



Neonatal Nephropathy

- Oliguria
- Anuria
- Edema formation
- Fluid overload
- Weight gain
- Persistently elevated Cr
- Birth Cr slow to drop
- Abnormal fraction excretions
- High amikacin trough levels
- Slow response to fluid challenges





"Pong"
Neonatal Gastroenteropathy

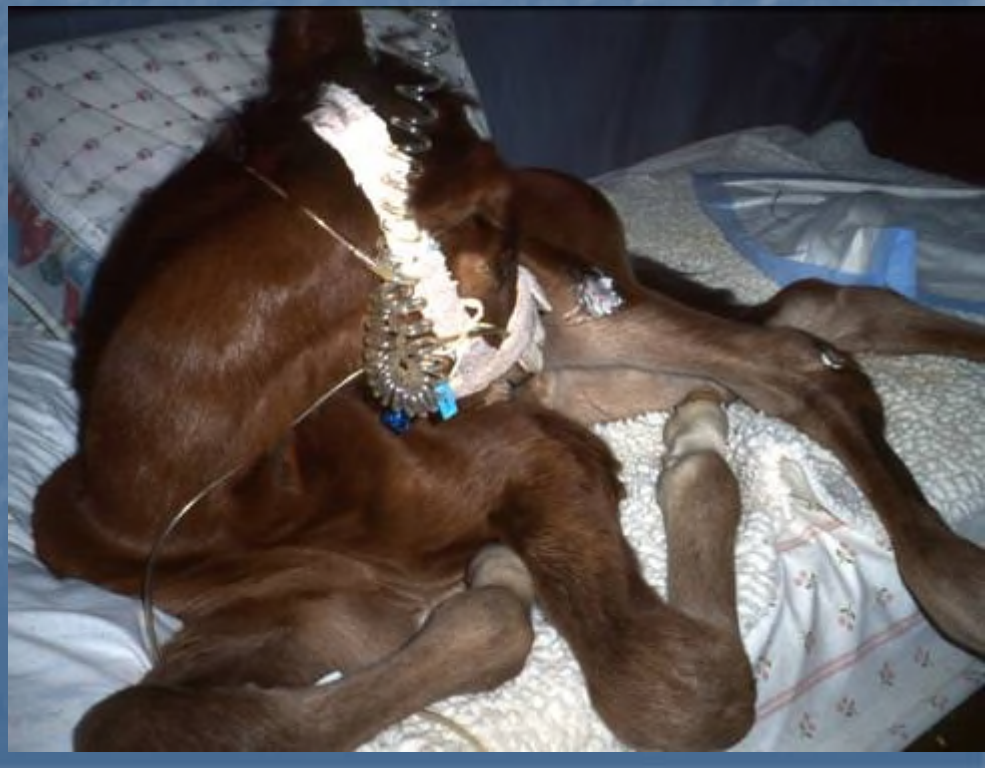
- Fetal/neonatal diarrhea
- Retained meconium
- Too much abdominal fill for not being fed
- Abnormal abdominal palpation
  - One loop of bowel thickened wall
- Day 7 began passing feces
  - Frequency > 24 hours
  - Enema dependent
- Day 17 resolved

Neonatal Gastroenteropathy

- Third most common target - 40%
  - Especially when metabolic demands (digestion) are superimposed on hypoxemic ischemic episodes
- Predisposition to sepsis and SIRS
  - Translocation of bacteria through the GI tract

Neonatal Gastroenteropathy

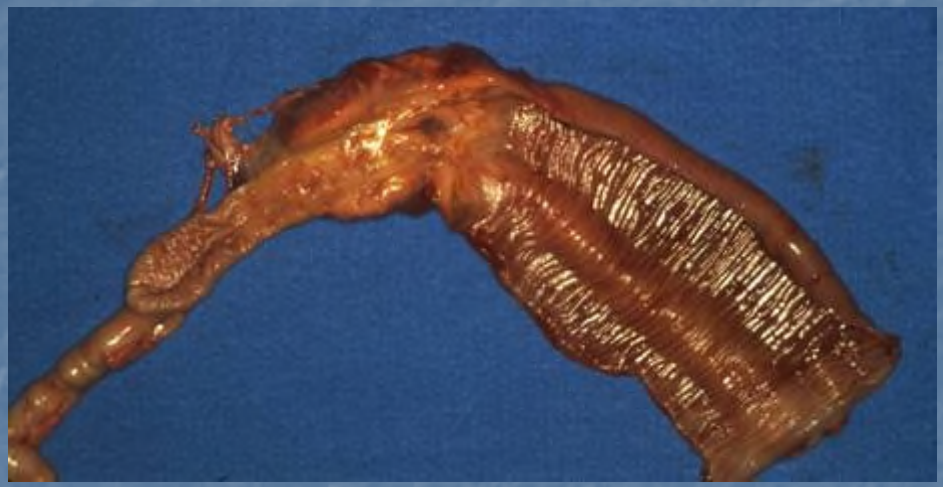
- Dysphagia
- Colic
- Abdominal distension
- Gastric reflux
- Diarrhea
- Constipation
- Dysmotility
- Dietary intolerance
  - Milk replacer
  - Other specie's milk
  - Frozen mare's milk
  - Fresh mare's milk

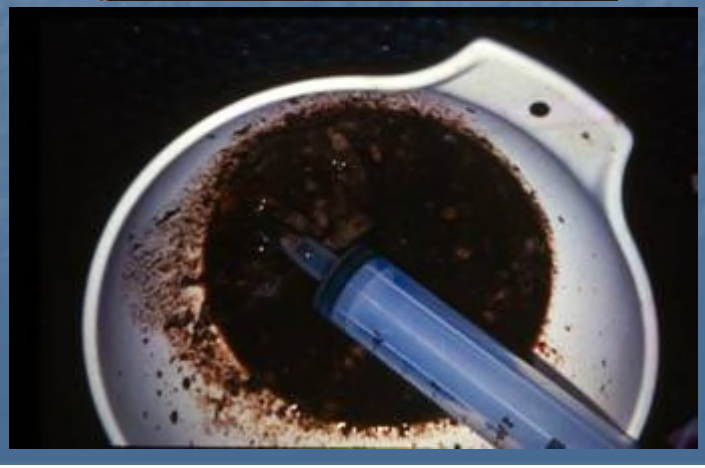


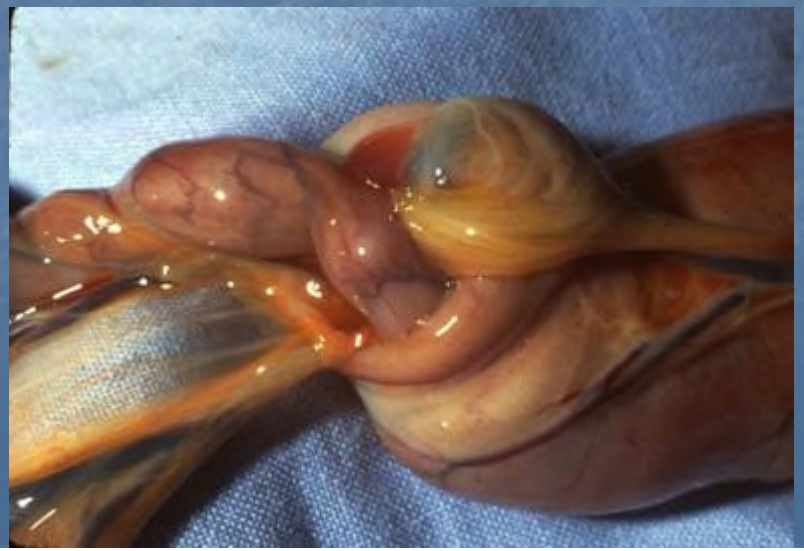
Neonatal Gastroenteropathy

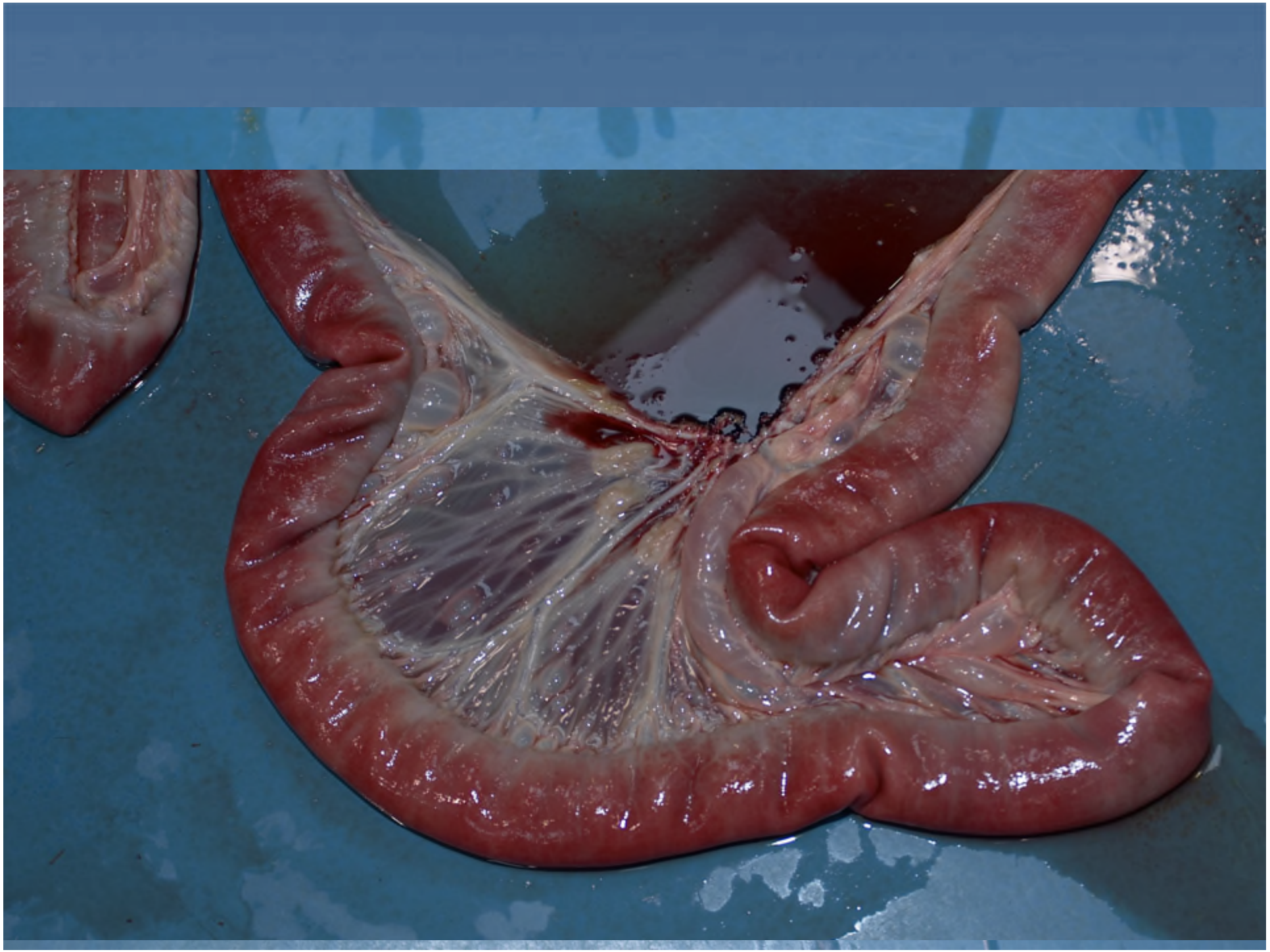
- Mild indigestion
- Failure to absorb colostrum and other nutrients
- Dysmotility
- Ileus
- Diapedesis of blood into the lumen
- Mucosal edema
- Epithelial necrosis
- Development of intussusceptions or structures
- Hemorrhagic gastritis or enteritis/colitis
- Pneumatosis intestinalis

Neonatal Gastroenteropathy









"Pong"
Metabolic Maladaptation

- Hypoglycemia at admission – 44 mg/dl
- Hyperglycemic on glucose infusion – 243 mg/dl
  - Glucose diuresis
  - Hyponatremia, hypochloremia, hypokalemia
    - Diuresis, plasma osmotic effects
- Insulin therapy
  - Constant infusion regular insulin IV
  - Begun hospital day 2, weaned day 4

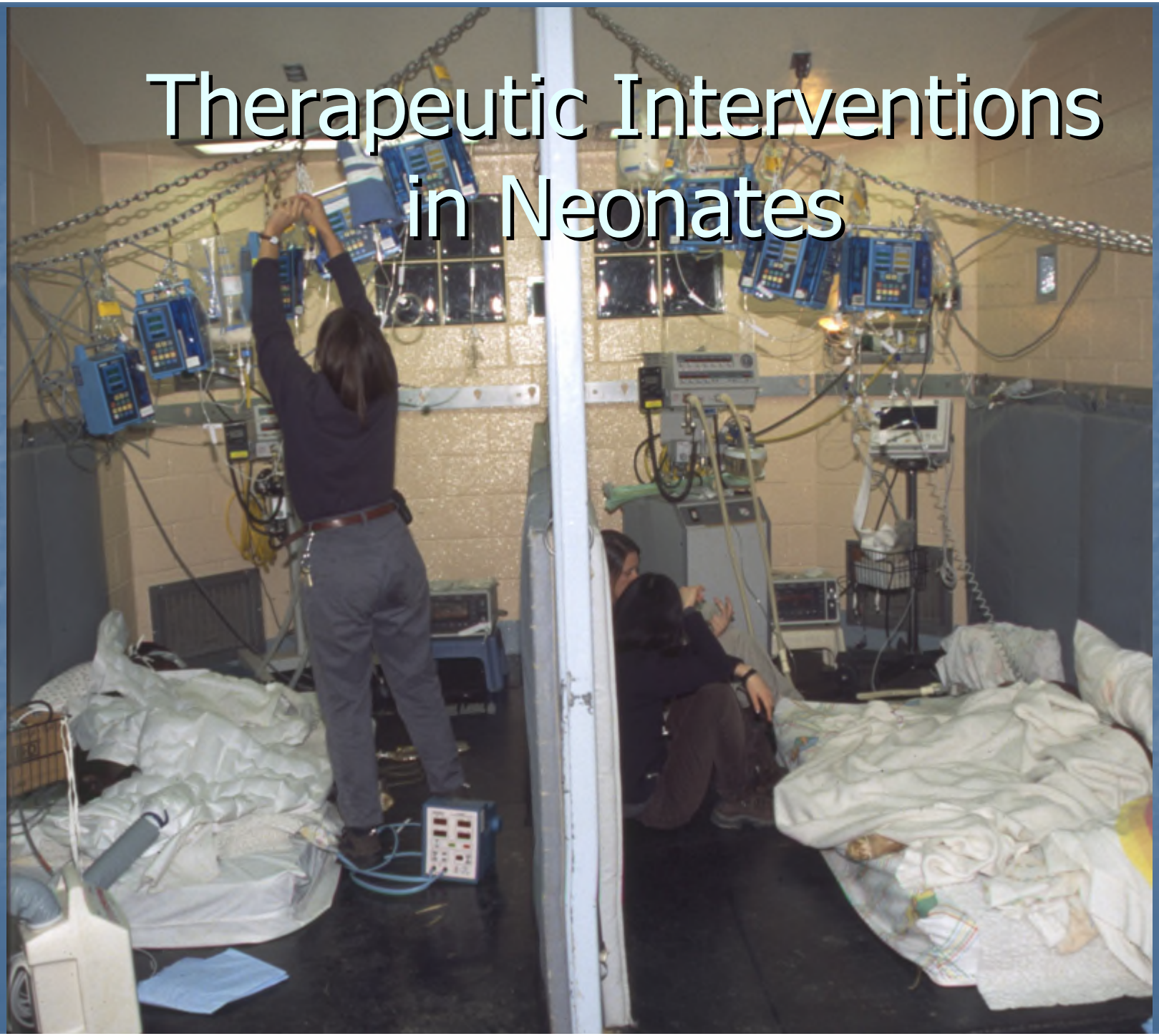
"Pong" Problems

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

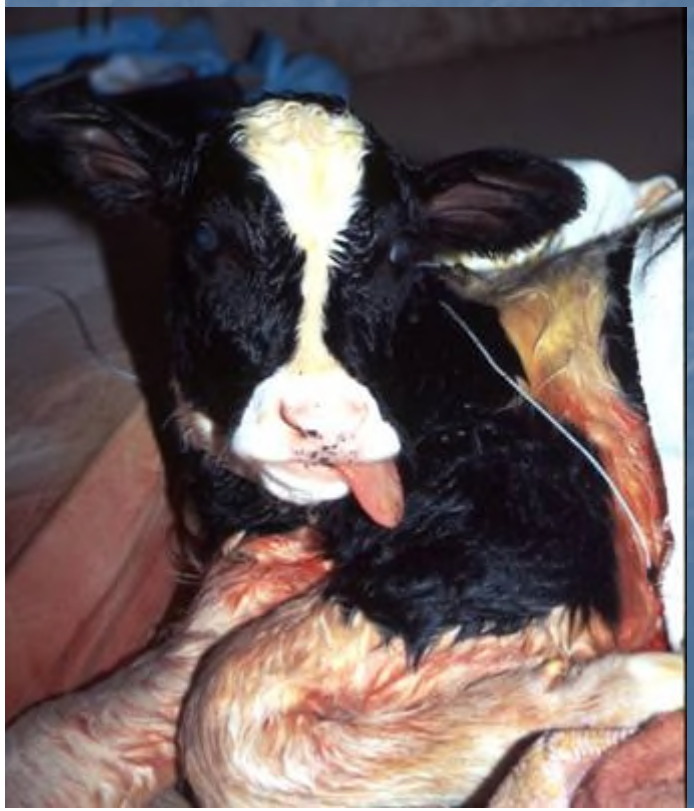
"Pong" Problems

- Neonatal Metabolic Maladaptation
- Edema
- Urachitis
- Hepatomegaly
- LDN
- Patent Urachus
- Over at knees

Therapeutic Interventions in Neonates



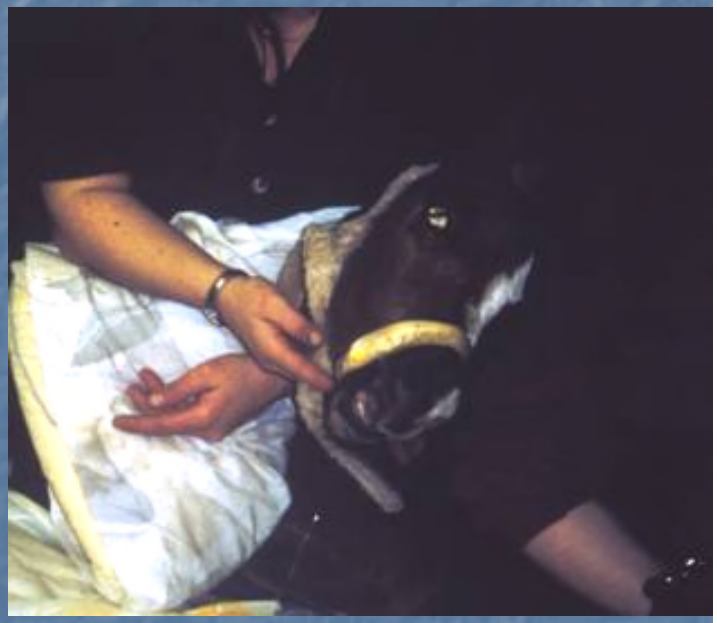
Neonatal Encephalopathy Therapy - CNS



- DMSO
- Mannitol
- Thiamine
- MgSO4

Neonatal Encephalopathy Therapy - CNS

- Control seizures
  - Phenobarbital
  - Diazepam
  - Midazolam
- Maintain cerebral perfusion
  - Careful fluid replacement
  - Maintaining blood pressure
  - Inotropes and pressors

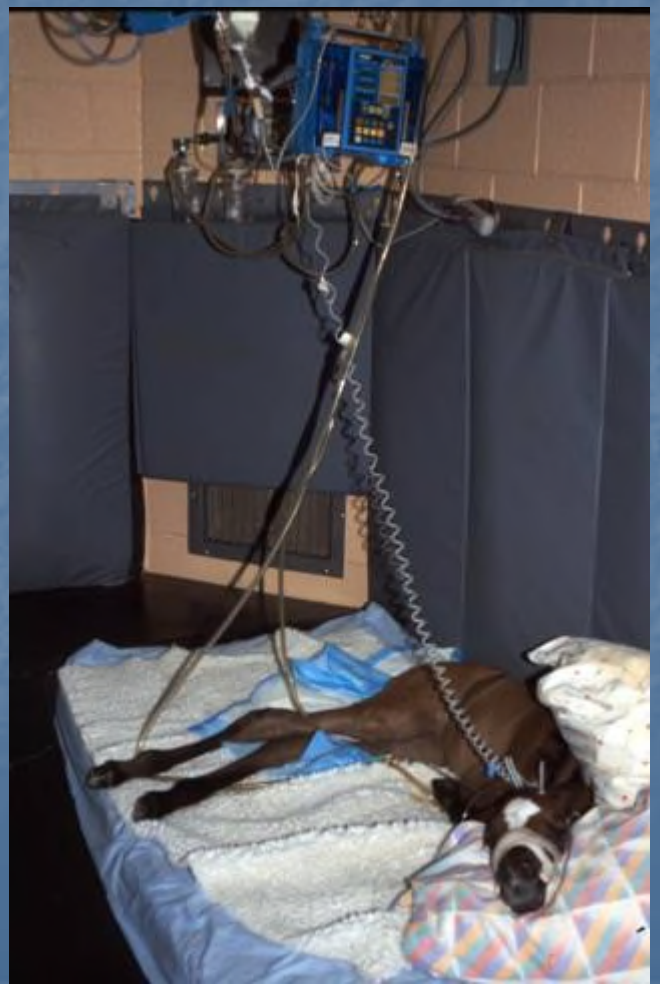


Neonatal Multisystem Maladaptation

- Treat hypoxemia
  - Intranasal Oxygen
  - Oxygen carrying capacity of blood
  - Oxygen delivery
- Normalized the pH, not CO2
  - Treat acidotic hypercapnia
    - Caffeine
    - Positive Pressure Ventilation
- Adequate perfusion
  - Avoid fluid overload

Neonatal Multisystem Maladaptation

- Maintain Nutrition
  - IV glucose
    - Avoid hyperglycemia
  - Parenteral nutrition
  - Enteral Nutrition
- Treat infections



"Pong"
Therapeutic interventions

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


"Pong"

THE MALADJUSTED FOAL

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Neonatology is a constantly evolving specialty. As our understanding of fetal and neonatal physiology and pathophysiology increase, our approach to therapy is modified and constantly refined. Approaches to therapy based on new ideas are introduced as those found to be based on incorrect assumptions are abandoned. One area currently undergoing reassessment is the pathogenesis is the neurologic disease and multiorgan maladaptation traditionally refered to as neonatal maladjustment syndrome.

Over the years, neonatal foals with neurologic signs have been referred to using various descriptive terms such as “barkers,” “wanderers,” “dummies,” and most persistently as having Neonatal Maladjustment Syndrome (NMS). More recently NMS has been abandoned in favor of Hypoxic Ischemic Encephalopathy (HIE) because the former focuses attention on the behavioral aspects colored by the use of the term maladjustment in mental health. 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.). HIE not only was felt to describe the etiology, it implied a more generalized neurologic disruption. As it turns out, HIE is also not an ideal term. Although a hypoxic ischemic insult may be responsible for some cases, in most the underlying etiology is uncertain. We have followed the lead of MD neonatologists in simplifying the terminology to describe the organ system involved and the age group and not implying an etiology. Thus the term we use to describe neonatal foals with neurologic signs is Neonatal Encephalopathy (NE). We use the same convention for disorders of other organ systems: Neonatal Nephropathy (NN), Neonatal Gastroenteropathy (NG), etc. Hopefully this terminology will survive further expansion of our understanding of the underlying pathophysiology and will not need to be changed in the future.

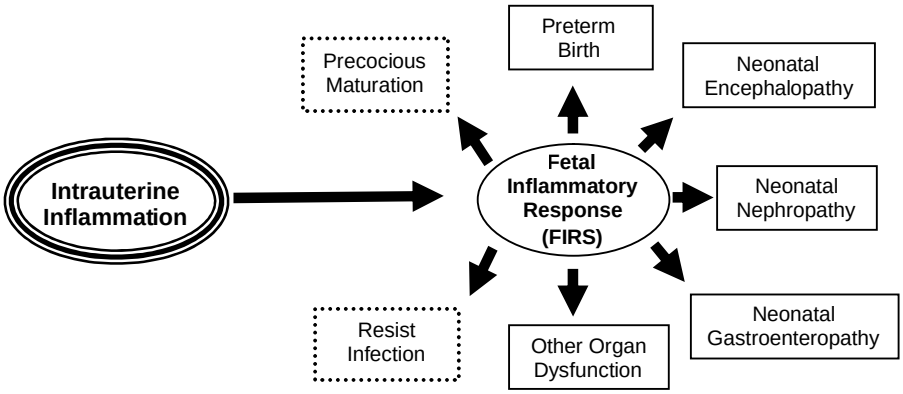
Foals with Neonatal Encephalopathy (NE) may show changes in responsiveness, muscle tone, behavior, show evidence of brain stem damage or seizure-like behavior. Changes in responsiveness include hyperesthesia, hyperresponsiveness, hyperexcitability, hyporesponsiveness, periods of somnolence or unresponsiveness. 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 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, 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 amikacin 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.

Neonatal Gastroenteropathy (NG) can be manifested by a wide spectrum of signs ranging from mild indigestion with dysmotility and enema dependence 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, 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, affected foals have the triad of Neonatal Encephalopathy, Neonatal Nephropathy and Neonatal Gastroenteropathy. 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 may be fetal inflammation and not always fetal hypoxia ischemia. There is a connection between placentitis and many neonatal diseases and there is a protective effect of treatment. For many years we have suspected that the occurrence of placentitis is important in predisposing to neonatal diseases. In human medicine, intrauterine sepsis has been connected to early termination of pregnancy (prematurity) and experimental models have recently reinforced this connection. But the connection between placentitis and neonatal problems goes far beyond prematurity based on preliminary data from an ongoing study. Disruption of the intrauterine environment may be the initiator of many serious neonatal diseases. The inflammatory response may directly affect placental sufficiency or the inflammatory cascade accompanying the placentitis may have secondary adverse consequences for the fetus. On the other hand, the up-regulation of the fetal inflammatory response may help to hasten maturation and prepare of the fetus not only for neonatal life but modify its response to septic challenges.



In a preliminary analysis of an observational retrospective study of the relationship between occurrence of placentitis and neonatal diseases and the effect of therapy we have found a significant connection between neonatal diseases and untreated placentitis. There is a strong association of placentitis and NE, NN and NG. This strong association supports the hypothesis that placentitis is the cause of these diseases. In addition prepartum treat of the mare for placentitis appears to protect against development of these diseases. The commonly utilized therapy of antimicrobials, NSAIDs and progestins all seemed to contribute to this protective affect. Surprisingly, treatment, independent of the presence of placentitis, showed a trend to protect against sepsis suggesting that something other than placentitis which responded to treatment could predispose the foal to sepsis. Alternately, treatment of the mare might decrease the exposure of the neonatal foal to factors that predispose to sepsis. This trend will be explored further as more cases are added to this data set. Although bacteremia was more likely in foals from mares with untreated placentitis, prepartum treatment of the mares did not protect from sepsis. Treatment of mares with placentitis significantly increased the odds of having a foal without any of the neonatal problems.

So the bad news is placentitis, a prevalent, recurring problem in many of our mares, is a major cause of some of the most serious neonatal diseases we treat. It may not be the only cause of these diseases but it significantly contributes to morbidity in our foals. The good news is that the commonly utilized therapy of placentitis in mares will protect foals from these diseases. So the take home message is that mares with suspect placentitis should be treated prepartum with the traditional therapy of TMS, ReguMate® and flunixin to

prevent development of common neonatal diseases in their foals. It is nice to have clinical impressions reinforced by clinical studies.

So how should we treat foals with this complex syndrome? Maintaining cerebral perfusion, achieved by careful fluid replacement and by the careful use of inopressors are the most important goals of therapy. It is also vital to maintain oxygen delivery and prevent catabolism. 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 (be careful to avoid overhydation), oxygen, glucose and occasionally inotropes and pressors.

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 rational grounded in evidence for most of them. 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 or so of the insult it will not help. Clinicians often treat cerebral edema that "must be present." My experience parallels that of MDs who note that cerebral edema, when present, is an 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 use DMSO or mannitol routinely. I stopped using these treatments more than a decade ago. I did look back at about 300 cases and found using no treatment was 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 levels of dextrose are given especially in the face of hypermetabolism.

In the past I treat NE foals with $MgSO_4$, however its efficacy is unproven and $MgSO_4$ may be, in fact, contraindicated. The MgSO4 story is very interesting. It was originally suggested as a therapy to prevent NE in babies when a retrospective study showed that women preeclampsia who were treated with MgSO4 near the end of their pregnancy had a lower risk of having babies with NE. Its possible therapeutic use is bolstered by the knowledge that it will block Ca channels which will in theory prevent neurocyte damage secondary to hypoxic ischemic insults. However, several prospective therapeutic trials of the use of MgSO4 in late pregnancy in women have found that the use of magnesium increases the risk of severe neurologic disease in babies. It is actually preeclampsia which has the protective effect. It is possible that in smaller doses MgSO4 may have a protective effect against damage caused by hypoxic ischemic insults but in using it in foals we are not sure what dose might be toxic and which may be protective and as in human medicine, I have questioned how many foals with NE actually suffer from a hypoxic ischemic insult. So I no longer use MgSO4 to treat NE (*primum non nocere*).

With the recent idea that the underlying etiology is FIRS it is logical to consider anti-inflammatory drugs. As I believe that the insult occurs prenatal and the turned on inflammatory state helps the neonate resist antenatal infections, I don't currently use anti-inflammatory drugs in these cases. With a recovery rate of 85-90% with supportive care alone, any additional therapy would have to be very good or significantly shorten the course to make its use worthwhile.

Seizure-like activity should be prevented to minimize the possibility of ongoing damage. Phenobarbital is my standard therapy, despite its side effects which if anticipated can be minimized. Phenobarbital will cause a drop in core body temperature, a decrease in respiratory drive sometimes inducing hypercapnia and it may potentiate hypotension resulting in deterioration of perfusion. All of these side effects can be minimized by early intervention. Phenobarbital can be given repeatedly until seizures are controlled, infused over 15-20 minutes with a peak activity at 45 minutes. Once the seizures are controlled, in rare cases it may be necessary to repeat the dose in 6 to 12 hours. The half-life of phenobarbital in some foals may be >200 hours (others may have faster clearance) making maintenance unnecessary and even contraindicated. The degree of sedation achieved may be prolonged. If phenobarbital fails, phenytoin may be tried. Recently it has been suggested that midazolam might make a better choice. I have not adopted this therapy primarily because it is my goal to insure cerebral perfusion and it is well known that midazolam decreases cerebral perfusion significantly within minutes of administration. There is enough concern about midazolam's adverse effects in human neonatology that it has been recommended that it only be used in experimental trials. My feeling again is *primum non nocere*.