Neonatal Syndrome
Multisystem Maladaptation

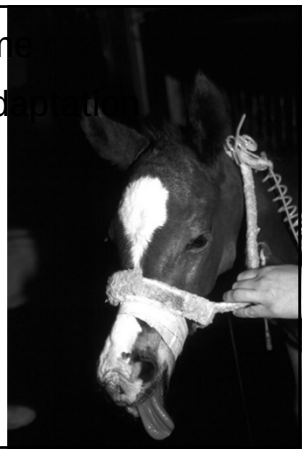
Hypoxic Ischemic Syndrome

Perinatal Asphyxia

Hypoxic Ischemic Asphyxial Syndrome

Neonatal Maladjustment Syndrome

Dummy Foals



Changes in Behavior

Neonatal Intensive Care

Hypoxic-Ischemic Syndrome

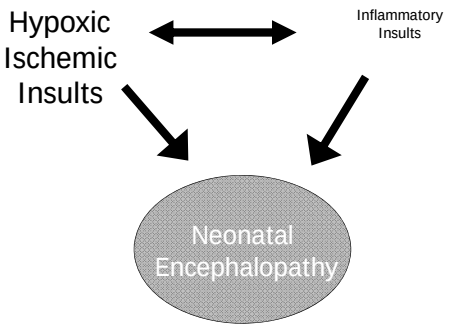
- Human Neonates - cerebral palsy
  - Prolonged Stage II
  - Lawsuits
  - Clinical studies on onset
    - Intranatal
    - Prenatal
    - Postnatal
- Experimental Studies
  - Hypoxic ischemic insults
  - Hypoxic ischemic encephalopathy (HIE)

Neonatal Problems Hypoxic Ischemic Asphyxial Disease

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

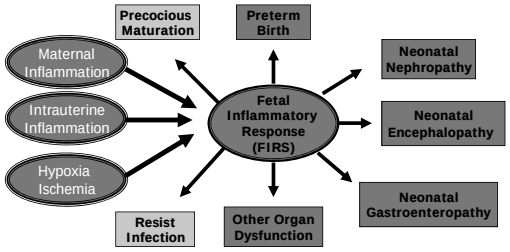
Neonatal Problems

- 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?



Role of Placentitis

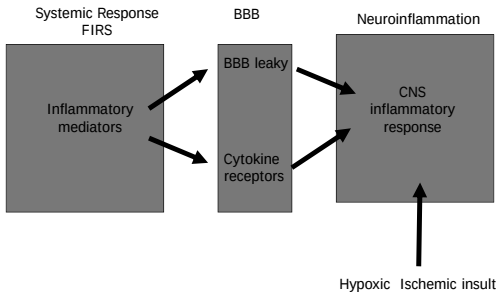
- Many neonatal diseases
  - Multiple etiologies
  - Disruption of fetal life
    - Predispose to neonatal disease
    - Origin of the neonatal disease
- Placentitis - untreated
  - Neonatal diseases
    - CNS, Renal, GI
- Placentitis - treated
  - Protects against neonatal diseases



Septic Encephalopathy

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

Septic Encephalopathy



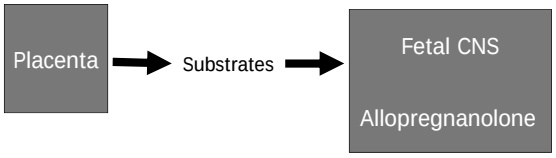
Neuroinflammation

- 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”

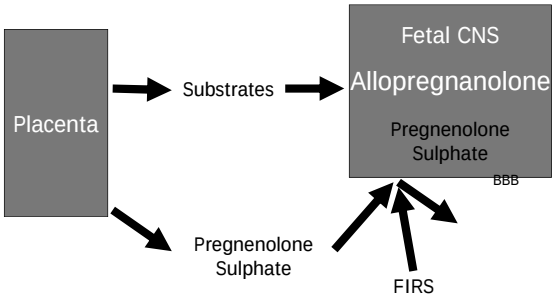
Neurosteroids

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

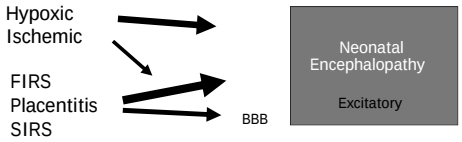
Neurosteroids

- 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

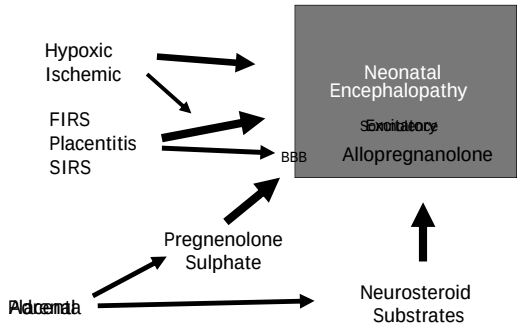
Neurosteroids



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 responsiveness

Changes in muscle tone

Changes in muscle tone

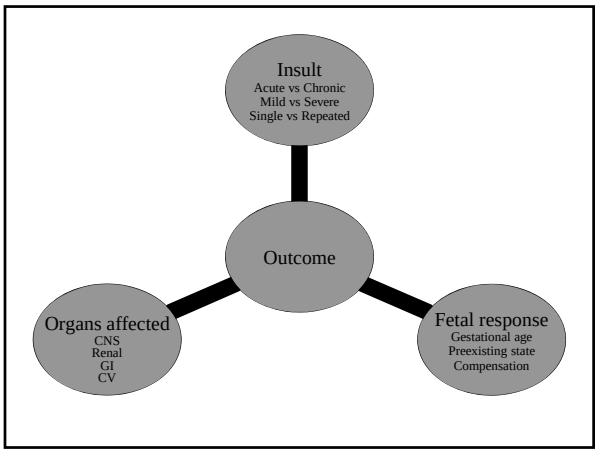
Changes in behavior

Brain stem damage

Seizure-like behavior

Terms
Generic Description of Signs

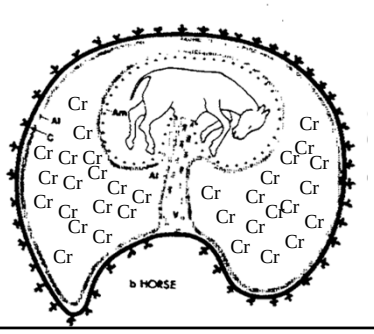
- Neonatal Encephalopathy (NE)
- Neonatal Gastroenteropathy (NG)
- Neonatal Nephropathy (NN)
- Neonatal Metabolic Maladaptation
- Neonatal Cardiovascular Maladaptation

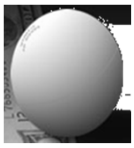


Intrauterine Challenge

- Indications at birth of intrauterine challenge
  - Cr level
  - Hypochloremic alkalosis
  - Low CV
  - Low birth blood glucose
  - 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

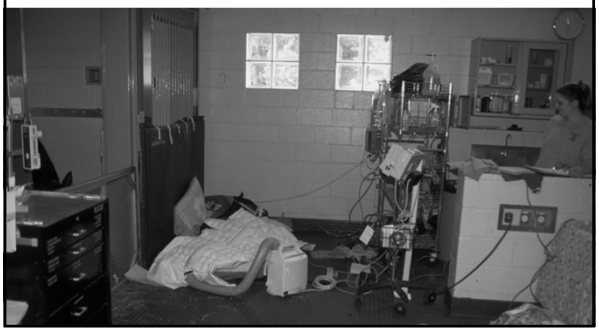
"Pong" History

- 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 Laboratory Data

	Admission	Normal
Fibrinogen	461 mg/dl	150 mg/dl
WBC	800 cells/ul	5-10,000
Neutrophil	62% 496 cells/ul	50-80%
Lymphocytes	38% 304 cells/ul	20-50%
Creatinine	6.46 mg/dl	2.5-4.0
Glucose	44 mg/dl	60 – 120
PCV	54%	30 – 45%
TPP	6.1 gm/dl	4.0 – 5.5

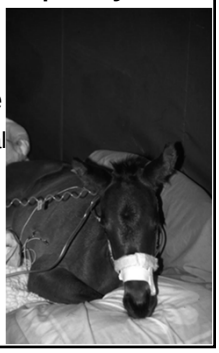
"Pong"
Admission Problems

- **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

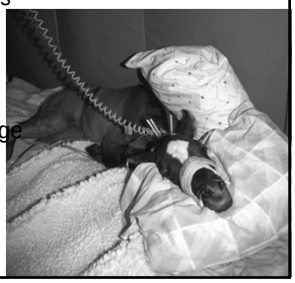
- Seizure like activity
  - Opisthotonus, tonic/clonic marching activity
  - Minimal nystagmus
- Lingual erythema
- Moderate nasal septum hyperemia
- Hyperresponsive to stimuli
- No suckle or searching

Neonatal Encephalopathy CNS Signs

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

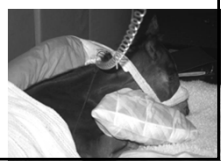
Neonatal Encephalopathy
Signs of CNS disease

- 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

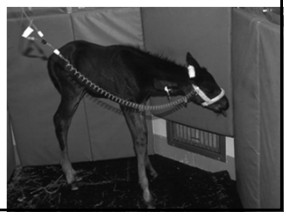
- Changes in muscle tone
  - Extensor tonus
  - Hypotonia
  - Neurogenic myotonia
  - Inability to protract legs

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

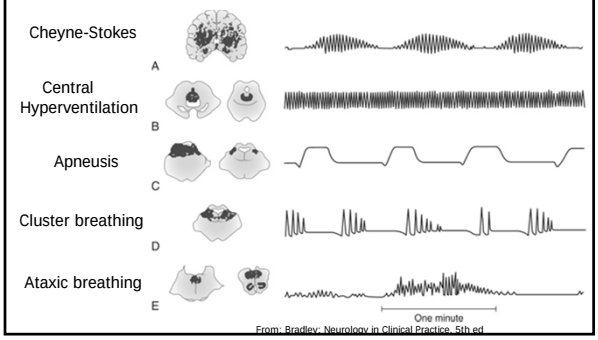

"Pong"
Neonatal Encephalopathy

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

Central Respiratory Patterns



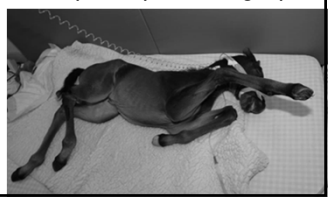
From: Bradley: Neurology in Clinical Practice, 5th ed

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
- Coma, death



"Pong" Neonatal Encephalopathy Treatment

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

"Pong" Neonatal Encephalopathy

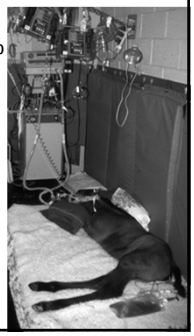
- Hospital day 2
  - Seizures – resolved with phenobarbital therapy
  - Began ventilation
- Hospital day 3 – standing
- Hospital day 5 – nursing from bottle, more aware
- Hospital day 6 – off intranasal oxygen
- Hospital day 9 – nursing from mare

"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 decrease GFR
  - 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 cardiopulmonary instability
- Predisposition to sepsis and SIRS
  - Translocation of bacteria through the GI tract

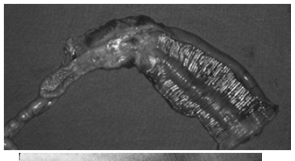
Neonatal Gastroenteropathy

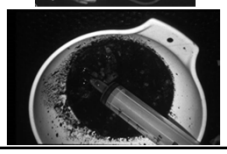
- Dysphagia
- Colic
- Abdominal distension
- Gastric reflux
- Diarrhea
- Constipation
- Dietary intolerance
  - Milk replacer
  - Other specie's milk
  - Frozen mare's milk
  - Fresh mare's milk

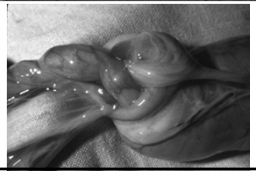
Neonatal Gastroenteropathy

- 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







Neonatal Syndrome Cardiovascular tract

- Less commonly affected – 10 %
- Poorly responsive peripheral vasculature
  - To hypovolemic challenges
  - To endogenous/exogenous adrenergic agents
- Cardiac disease
  - Inappropriate bradycardia
  - Premature ventricular contractions
  - Supraventricular tachycardia
  - Ventricular tachycardia
- Persistent fetal circulation/PPH
- Cardiovascular collapse
  - Refractory hypotension
  - Cardiovascular shock
  - Septic shock

"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

Neonatal Metabolic Maladaptation
Signs of Metabolic Disease

- Hypoglycemia
- Hyperglycemia
- Hypocalcemia
- Hypercalcemia
- Hyperlipemia/hyperlipidemia
- Slow response
  - To changing metabolic demands

Neonatal Syndrome

- NE - *Neonatal Encephalopathy*
- NN - *Neonatal Nephropathy*
- NG - *Neonatal Gastroenteropathy*
- NMM - *Neonatal Metabolic Maladaptation*
- NCM - *Neonatal Cardiovascular Maladaptation*
- NAM - *Neonatal Autonomic Maladaptation*
- NEM - *Neonatal Endocrine Maladaptation*

"Pong"
Problems

- Sepsis
  - Bacteremia - *Pantoea agglomerans*
- Septic 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 Syndrome
Clinical Course/Therapeutic Intervention

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

Neonatal Syndrome
Maintain Tissue Perfusion/Oxygen Delivery

- Adequate cardiac output/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

Neonatal Syndrome
Maintain Nutrition

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

NE
Therapy

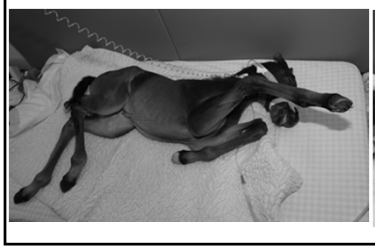
- Support cerebral perfusion
  - Insure volemia
    - Careful fluid replacement
  - Defend perfusion
    - Inopressor therapy
- Insure oxygen delivery
  - Achieve pulmonary O_2 loading
  - Avoid anemia
- Nutritional support
  - Permissive underfeeding

Therapy

- DMSO
- Mannitol
- Thiamine
- MgSO4
- Others

Seizure Control

Phenobarbital? Midazolam? Others?



Neonatal Nephropathy Therapy for Renal Dysfunction

- Avoid fluid overload
  - 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
  - Initiation of normal renal function

Neonatal Gastroenteropathy Treatment of GI Dysfunction

- Signs of damage lag behind other tissues
- Continued feeding with episodes of 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 1-2 oz 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
- Caffeine
- Positive pressure ventilation
- Parenteral Nutrition
- Trophic feedings
- Sucralfate
- Domperidone -- mare
- TMS , Cephalexin
- Bandaging

"Pong"