Neonatal Syndrome
Multisystem Maladjustment

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
Intrauterine Inflammation

Maternal Inflammation

Intrauterine Inflammation

Hypoxia Ischemia

Resist Infection

Other Organ Dysfunction

Fetal Inflammatory Response (FIRS)

Neonatal Birth

Neonatal Nephropathy

Neonatal Encephalopathy

Neonatal Gastroenteropathy

Precocious Maturation

Septic Encephalopathy

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

Septic Encephalopathy

Systemic Response

FIRS

Inflammatory mediators

BBB leak

Cytokine receptors

Neuoinflammation

CNS inflammatory response

Hypoxia Ischemia insult
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

- Placenta ➔ Substrates ➔ Fetal CNS
  - Allopregnanolone
- 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
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 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
  - High PCV
  - High 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

- Cardiovascular
  - Cold hooves, cold legs
  - Very weak pulses
  - Poor arterial fill, poor arterial tone

- Neurologic signs
  - Somnolent with occasional struggling
  - Struggling appeared meaningful

“Pong”
Admission Laboratory Data

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Normal</th>
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<tbody>
<tr>
<td>Fibrinogen</td>
<td>461 mg/dl</td>
<td>150 mg/dl</td>
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<tr>
<td>WBC</td>
<td>800 cells/ul</td>
<td>5-10,000</td>
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<tr>
<td>Neutrophil</td>
<td>69% cells/ul</td>
<td>50-80%</td>
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<tr>
<td>Lymphocytes</td>
<td>38% cells/ul</td>
<td>20-50%</td>
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<tr>
<td>Creatinine</td>
<td>6.46 mg/dl</td>
<td>2.5-4.0</td>
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<tr>
<td>Glucose</td>
<td>44 mg/dl</td>
<td>60 - 120</td>
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<tr>
<td>PCV</td>
<td>54%</td>
<td>30 - 45%</td>
</tr>
<tr>
<td>TPP</td>
<td>6.1 gm/dl</td>
<td>4.0 - 5.5</td>
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</tbody>
</table>
“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

- Cheyne-Stokes
- Central Hyperventilation
- Apneusis
- Cluster breathing
- Ataxic breathing

Neonatal Encephalopathy

Signs of CNS disease

- Signs of brain stem damage
  - Loss of thermoregulatory control
  - Weakness
  - Anisocoria (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 excrections
- High amikacin trough levels
- Slow response to fluid challenges
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

"Pong"

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 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

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“Pong” Problems

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

Therapeutic Interventions in Neonates

- Prevent hypoxic ischemic episodes
- Support organ system function
  - Allow recovery
  - Prevent secondary sepsis
  - Prevent other complications

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 state
    - Perfusion of bowel - GI function
  - Inotropic 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
    - Inotropic therapy
- Insure oxygen delivery
  - Achieve pulmonary O₂ 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”