Therapeutic Hypothermia & Neonatal Neurocritical Care

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Objectives

- What is therapeutic hypothermia in the newborn?

- How does one provide brain-oriented neonatal care?

- What is the future of neonatal neurocritical care?
WHAT IS THERAPEUTIC HYPOTHERMIA?
What is Hypoxic Ischemic Encephalopathy?

- **Hypoxia**
  - Diminished amount of oxygen in the blood supply

- **Ischemia**
  - Diminished amount of blood perfusion to the brain

- **Asphyxia**
  - Impairment in the exchange of respiratory gases

- **Encephalopathy**
  - Altered mental state; disease of the brain
Mechanism of Brain Cell Death

- Hypoxic-ischemic insult
- Failure of ATP-dependent Na⁺/K⁺ pump
- Membrane depolarization
- Glutamate release
- Glutamate transporter
- NOS, lipase, protease, nucleases
- Impaired energy production: ATP↓
- Cell death (late, apoptosis > necrosis)

Phases of Cerebral Injury

Insult:
- Hypoxic depolarization
- Cell lysis
- Excitotoxins
- Calcium entry

Hypothermia:
- Latent: 6 to 15 h
- Secondary: From 6 h to >3 days
  - Recovery of oxidative metabolism vs residual mitochondrial injury
  - Apoptotic cascade
  - 2nd Inflammation
  - Receptor hyperactivity

Reperfusion:
- Deteriorating mitochondrial function
- Seizures
- Cytotoxic edema
- Excitotoxins
- Final cell death

Lai & Yang
2011 J Biomedicine and Biotechnology

Drury, Bennet, Gunn
2011 Seminars in Fetal & Neonatal Med
Vulnerability of the Early Immature Brain to HI Injury

- Period of maximal susceptibility to excitotoxic neuronal injury
- Period of maximal susceptibility to epileptogenic effects
- Incomplete maturation of inhibitory transmission
- Preoligodendrocyte or immature oligodendrocyte have intrinsic vulnerability to glucose and oxygen deprivation
- AMPA-kainate glutamate receptors may be involved in oligodendroglia death
What is Therapeutic Hypothermia?

- Lowering brain temperature to reduce extent of injury

- 500 B.C. – Hippocratic School of Cos – cold water for febrile convulsions, sprains, hemorrhages

- 19th Century – anesthesia for amputations

- 20th Century – pain relief, tumor reduction

Thoresen 2000; Swan 1973
How cold is hypothermia?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Temperature (°C)</th>
<th>Temperature (°F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild hypothermia</td>
<td>35°C</td>
<td>95°F</td>
</tr>
<tr>
<td>Moderate hypothermia</td>
<td>33.5°C</td>
<td>92°F</td>
</tr>
<tr>
<td>Deep hypothermia</td>
<td>18°C</td>
<td>64°F</td>
</tr>
<tr>
<td>Head coil water</td>
<td>10°C</td>
<td>50°F</td>
</tr>
<tr>
<td>Initial mattress water</td>
<td>5°C</td>
<td>41°F</td>
</tr>
<tr>
<td>Our NICU</td>
<td>25°C</td>
<td>77°F</td>
</tr>
<tr>
<td>Refrigerator</td>
<td>3°C</td>
<td>37°F</td>
</tr>
<tr>
<td>Freezer</td>
<td>-18°C</td>
<td>0°F</td>
</tr>
</tbody>
</table>
Mechanism of Hypothermia

- Cerebral metabolism is reduced by 5-7% for each 1°C reduction in body temperature (Laptook et al 1995; Erecinska 2003)
- Anti-convulsant properties by inhibition of glutamate (excitatory)
- Anti-inflammatory
- Anti-apoptotic

Shintani, Terao, Ohta 2011
Stroke Research and Treatment
From Cell Injury to Cell Death

Volpe 2000
Who does one cool – Neonatal Encephalopathy

- Defined as an abnormal neurobehavioral state beginning within the first 72 hrs of life (VON)
  - Altered sensorium
  - Abnormal neuromuscular tone or sucking
  - Seizure, abnormal respiratory control, abnormal reflexes

- Suggest a direct insult to the brain has occurred

- Caused by a variety of known etiologies
  - Uterine rupture and/or placental abruption
  - Cord prolapse, tight nuchal cord, tight knot in cord
  - Shoulder dystocia
  - Chorioamnionitis

- No intrapartum risk factors seen in up to 70% of NE cases*

* Badawi 1998 BMJ
Immediate Markers of Potential Brain Injury

- History of a sentinel event during labor
  - Uterine rupture, placental abruptin, maternal trauma/shock/death, cord prolapse

- Severely depressed infant with need for resuscitation
  - Apgar score < 5 at 10 minutes of life (AAP 2006 Apgar Statement)

- Evidence of fetal acidosis in cord arterial gases
  - pH < 7.0 or base deficit $\geq 16$ mEq/L

- Abnormal neurologic exam (mental state) or seizures

- Gross placental abnormality
  - Abruptation, thrombosis, inflammation
<table>
<thead>
<tr>
<th></th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mental State</strong></td>
<td>Hyperalert</td>
<td>Lethargic or obtunded</td>
<td>Stuporous</td>
</tr>
<tr>
<td><strong>Cranial nerves</strong></td>
<td>Weak suck</td>
<td>Weak or absent</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Tone &amp; Posture</strong></td>
<td>Normal tone</td>
<td>Mild hypotonia</td>
<td>Flaccid</td>
</tr>
<tr>
<td></td>
<td>Mild distal flexion</td>
<td>Cortical thumbing</td>
<td>Intermittent decerebration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strong distal flexion</td>
<td></td>
</tr>
<tr>
<td><strong>DTRs</strong></td>
<td>Mildly brisk</td>
<td>Brisk</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Primitive Reflexes</strong></td>
<td>Weak suck</td>
<td>Weak or absent suck</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Strong Moro</td>
<td>Weak &amp; incomplete Moro</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overactive Doll’s &amp; Tonic neck</td>
<td></td>
</tr>
<tr>
<td><strong>Autonomic Reflexes</strong></td>
<td>Sympathetic activation</td>
<td>Parasympathetic activation</td>
<td>Both systems suppressed</td>
</tr>
<tr>
<td></td>
<td>Pupils – increase</td>
<td>Pupils – small</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Profuse secretions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase GI motility</td>
<td></td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>None</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>EEG</strong></td>
<td>Normal</td>
<td>Early - low voltage delta &amp; theta</td>
<td>Early – periodic with burst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Late – periodic pattern</td>
<td>suppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seizure – focal or multi-focal</td>
<td>Late - isoelectric</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Less than 24hrs</td>
<td>2-14 days</td>
<td>Hours to weeks</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Less than 24 hrs</td>
<td>Good prognosis if recovery within 5 days</td>
<td>Microcephaly, MR, CP, seizures</td>
</tr>
<tr>
<td></td>
<td>No sequelae</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Whole Body Hypothermia Criteria*

**ABSOLUTE CRITERIA**
- > 36 Weeks gestation
- > 1,800 Grams at birth
- < 6 Hours of age

**EXCLUSION**
- Severe chromosomal or other anomalies
- Extremis / nonintervention

**PHYSIOLOGIC CRITERIA**

- Cord or arterial blood gas < 1 hr?
  - No blood gas < 1 hr
    - pH 7.01-7.15
    - OR
    - Base deficit 10-15.9
  - Combined with
    - A MAJOR PERINATAL EVENT:
      - variable/late FHR decels,
      - cord prolapse/rupture,
      - uterine rupture,
      - Mom trauma,
      - Mom hemorrhage/abruption,
      - Mom CPR
    - AND
    - Apgar < 5 at 10 min, OR PPV@ > 10 min
    - + moderate or severe encephalopathy

**NEUROLOGIC EXAM CRITERIA**

- Moderate or Severe Encephalopathy is demonstrated by the following.
  - Moderate encephalopathy has three of six findings below:
    1. Lethargic
    2. Inactive, decreased activity
    3. Flexion/extension posture
    4. Hypotonia focal or general
    5. Weak suck/incomplete Moro
    6. Pupils constricted, bradycardia, periodic breathing
  - Severe encephalopathy has three of six findings below:
    1. Stupor/coma
    2. No activity
    3. Decerebrate
    4. Flaccid tone
    5. Absent suck/Moro
    6. Pupils dilated/unreactive/skew, variable HR, apnea

**COOLING**

*Shankaran et al NEJM 2005
How Does One Cool?

- Early identification of neonates at high risk of moderate to severe brain injury
- Cooling must be initiated within 6 hrs from birth
- Selective head versus whole body cooling
- Prolonged cooling for 72 hrs with gradual rewarming
- Monitoring for adverse events
- Evaluate for extent of brain injury
Hypothermia
Selective head cooling* vs Whole body cooling**

- Easy of use
- Both cooling to rectal temperatures of 33.5-34°C
  - Selective head cooling uses radiant warmer to warm the body while cooling the head
- Rapidity of cooling (20-30 min versus 2.5 hrs)
- Differential cooling of the brain
- Developmental outcome

*Gluckman et al Lancet 2005
**Shanakaran et al NEJM 2005

7 degree difference

< 2 degree difference
Laptook et al 2001
Selective Head Cooling Criteria*

- Amplitude-integrated EEG (aEEG) was used to stratify moderate versus severe NE
  - Al Naqeeb et al 1999 Pediatrics
    - 56 patients performed 0-21 days of life
    - Sensitivity 1.0, Specificity 0.82
    - PPV 0.85, NPV 1.0
  - Shalak et al 2003 Pediatrics
    - 50 patients
    - Sensitivity 0.79, Specificity 0.89
    - PPV 0.73, NPV 0.9

*Gluckman et al Lancet 2005
Complications During Cooling

- **Cardiac**
  - Bradycardic
  - Hypotension (MAP)

- **Renal**
  - Renal insufficiency

- **Hematology**
  - Coagulopathy (PT/PTT, platelets)

- **Immunologic**
  - Poor WBC function
  - Sepsis

- **Electrolytes**
  - Hypo & hyper glycemia
  - Hyponatremia
  - Hypokalemia
  - Acidosis

- **Skin edema/necrosis**

- **Rebound hyperthermia**
Therapeutic Hypothermia
Outcomes

Shah et al 2010
Seminars in Fetal & Neonatal Medicine

Number needed to treat = 9

Edwards et al 2010
British Medical Journal
Call to Arms

- Perlman 2006 Pediatrics
  “Summary proceedings from the Neurology group on HIE”
  - Early identification of the infant at highest risk for evolving to the syndrome of HIE

  - Supportive care to facilitate adequate perfusion and nutrients to the brain

  - Consideration of interventions to ameliorate the processes of ongoing brain injury
New 2010 Neonatal Resuscitation Guidelines

- Adopt a protocol from a published clinical trial - ILCOR 2010 Guidelines for Neonatal Resuscitation
- Identify neonates in potential need for resuscitation
- Hyperthermia should be avoided
- Oximetry should be used when resuscitation is anticipated
- Resuscitation of term newborns should be started on room air
- Hypoglycemia should be avoided
- Cooling must be initiated within 6 hrs from birth
- Selective head versus whole body cooling
- Prolonged cooling for 72 hrs
- Gradual rewarming for at least 4 hrs
- Monitor for adverse events
- Performed in facilities with capabilities for multi-disciplinary care and longitudinal follow-up
WHAT IS BRAIN-ORIENTED NEONATAL CARE?
EEG monitoring to detect sentinel neurologic events.
39 week old infant born via SVD delivery at home. Thick meconium reported. Apgar scores of 4 and 5. Infant was transferred for therapeutic whole body cooling. V-A ECMO was started shortly after arrival for severe PPHN. Serial head ultrasounds were normal. Continuous video EEG captured focal electrographic seizures on DOL#4. A head ultrasound at DOL#8 showed evidence of a focal left temporal hemorrhage not seen on DOL#6. ECMO was stopped. A MRI of the brain at DOL#9 confirmed a left temporal hemorrhage as well as smaller hemorrhages.
A 5 day old term female infant presented acutely with a large left thalamic hemorrhage with diffuse cerebral edema & hydrocephalus was noted to have a discontinuous background and electrographic & electroclinical seizures on continuous video EEG. By 24hrs after admission, the EEG was increasingly discontinuous. At 48hrs after admission, the EEG tracing progresses from discontinuous with prolonged interburst intervals, to burst suppression and then flat and non-reactive over 90 minutes. Serial head CT scans overlapping this interval of time demonstrate tonsillar herniation.
Neonatal neurointensivist evaluation leading to diagnosis of a non-sentinel case of neonatal encephalopathy.

A newborn with refractory status epilepticus leading to a new neurocritical care protocol for NICU seizure management.
43wk infant born via emergent CS for NRFHR & meconium to a 19y G1P0 with uncontrolled IDDM & lack of recent prenatal care. Seizure like activity noted shortly after birth. Phenobarbital loaded. Transferred for therapeutic hypothermia. Continuous video EEG confirmed multifocal subclinical status epilepticus. SE refractory to phenobarbital boluses & IV keppra. Midazolam drip initiated to stop seizures and induce burst suppression. Portable head CT scan shows diffuse cerebral edema concerning for tonsillar herniation, right MCA infarction and left PCA infarction. Placenta pathology had severe chorioamnionitis & funisitis. MRI of brain at DOL#10 had diffuse cortical laminar necrosis with relative sparing of anterior temporal pole, perisylvian cortex and deep gray structures. EEG on DOL# 14 had a continuous background. At 11 mos of age, he is alert & social, fixates & tracks, decreased axial tone, and increased appendicular tone.
Neonatal neurointensivist evaluation leading to identification of cause of a perinatal arterial stroke.
41wk infant born via NSVD to a 20y G1P0 mom without complications. Agpar scores were 6\(^1\) and 9\(^5\). Right sided seizures noted on DOL#0. Phenobarbital loaded. Acute stroke of the entire left MCA territory seen on MRI. Infant transferred for stroke evaluation. Placental pathology showed acute chorioamnionitis, funisitis, chorionic plate vasculitis and a fresh clot in the cord.
The Neonatal Brain

Figure 3-8. Characteristic configuration of fetal brains from 22 to 40 weeks' gestation at two-week intervals. All brains have been brought to the same size. (From Dovvini-Z Flor, K., and Dolman, C. L.: Gestational development of the brain. Arch. Pathol. Lab. Med., 101:192-195, 1977.)
Neonatal Cortical Excitability: Compounding Complexity

- Peak density in synapses and dendritic spines (Rakic et al. Science 1989)

- Overexpression of glutamate receptors
  - Developmentally regulated NMDA subunits → less Mg sensitivity → more excitable (Choi. Prog Brain Res 1994)
  - AMPA receptors lack GluR2: Ca++ permeable (Sanchez et al. J Neurosci 2001)

- Ontogeny of GABA receptors

Show Me the Brain
From Insult to Injury

Ferriero 2004 NEJM
Is there a Single Marker?
Is there a Single Time Point?

- Multiple markers needed to increase sensitivity & NPV
  - CBG
  - Apgars scores
  - aEEG may not be as sensitive as initially suspected (Sarkar et al, Tharp)

- Earlier markers & markers of injury severity needed
  - Multiple methodologies – cord blood, serum markers, EEG, neuroimaging, placental pathology
  - Interdisciplinary – OB, NICU, neurology, neuroradiology

- Serial measurements needed to improve accuracy as our patients and their injuries are not static
  - EEG (Holmes, Tharp), S100B (Nagdayman, Thorgen), MRI
Traditional Markers of Neonatal Brain Injury

- **Clinical Markers**
  - BPP, Apgar scores, acidosis, encephalopathy, clinical seizures

- **Neurophysiological markers**
  - EEG, VEP, SSEP, BAER, NIRS

- **Neuroimaging**
  - Ultrasound, CT, MR imaging

- **Neurodevelopmental Outcome**
  - encephalopathy, irritability, habituation, state changes, sleep cycling, temperature stability, ventilatory needs, visual development, feeding, tone
Defining Severity of Encephalopathy in a Newborn

- Can it be based on immediate markers of Apgar score, acidosis, encephalopathy or seizure?

- Can physicians reliably assess & grade encephalopathy in the newborn?

- Should more quantifiable measures like EEG or MRI be used to grade severity of injury?
EEG Background and Prognosis

- EEG features predictive of poor outcome
  - Low voltage, Burst suppression, Inactive\(^1\)
  - Absence of sleep / state change(s)\(^2\)
    - immature sleep- later abnormal cognitive\(^3\)
  - Seizures on EEG\(^4\)

- Abnormal EEG predict outcome better than neurologic exam\(^5\)

- Timing of EEG important in predicting outcome
  - After first 24 hr\(^6\)
  - Serial studies\(^1,7\)

Discontinuous

Low amplitude

Burst suppression

Inactive
aEEG as a Marker of Injury Severity

- Sarkar et al 2008 J Perinatology
  - “Should aEEG be used to identify infants suitable for hypothermic neuroprotection?”
  - aEEG compared to short term adverse outcome of early death or MRI evidence of injury
  - 46 patients
  - Sensitivity 54.8%
  - NPV 44%

- al Naqeeb et al 1999 Pediatrics
  - 56 patients performed 0-21 days of life
  - Sensitivity 1.0, Specificity 0.82
  - PPV 0.85, NPV 1.0

- Shalak et al 2003 Pediatrics
  - 50 patients
  - Sensitivity 0.79, Specificity 0.89
  - PPV 0.73, NPV 0.9
What is a seizure?

- Clinical Definition
  - A paroxysmal alteration in neurologic function

- Electrographic Definition
  - Abnormal hypersynchronous and excessive excitation of a population of cortical neurons
# Neonatal Seizures & Classification

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Rhythmic EEG Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uncopling</td>
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<tr>
<td>+</td>
<td>+</td>
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<td></td>
<td>-</td>
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**Electroclinical Dissociation**
EEG and Seizures

- **Seizure prediction**
  - Less likely with normal EEG\(^1\)
  - More likely with excess sharp waves\(^2\)

- **Seizure detection**
  - Clinically silent in up to 11-13% of neonates at risk for seizures\(^3,4\)
  - Of infants with clinical seizures, only 15-28% of the seizures have associated clinical changes\(^5\)

- **Seizure treatment**
  - Electroclinical dissociation with seizure medications
    - Ongoing clinically silent seizures in up to 58% of neonates\(^6\)

- **Avoid unnecessary treatment**
  - Isolated lip smacking, bicycling, or swimming less likely to be seizure\(^4\)
  - Isolated apnea, paroxysmal changes of blood pressure or heart rate unlikely seizures\(^7\)

EEG during Hypothermia

- Continuous video EEG monitoring during whole body cooling and rewarming
- Serial background evaluations
- Seizures
- Final aEEG background
- Sleep cycling as seen on aEEG
- Correlation with clinical markers, MRI & NICU Outcome
aEEG compared to EEG

- **Prognosis**
  - Similar to EEG in predicting outcomes after HIE\(^1\)
  - Direct comparison to EEG
    - Comparable for low voltage and flat records\(^2\)
    - Comparable when looking at continuous, burst suppression or inactive\(^3\)

- **Seizure**
  - Best seizure detection using 2 channel (C3-P3,C4-P4) aEEG with EEG tracing\(^4-8\)
    - detects 6/7 patients and 76% of seizures\(^4\)
  - Worst seizure detection using single channel frontal electrodes
    - 1 channel (Fp3-Fp4) EEG detects 46% of seizures\(^9\)
  - Low false positive rate
    - 2/7 patients with no seizures\(^4\)

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MR Imaging Limitations

- Not all centers capable
  - No MRI
  - Adult versus pediatric neuroradiologists

- Medically unsafe even with MR compatible incubators
  - Severe PPHN, oscillators, nitric oxide, ECMO

- Effects of hypothermia on ADC changes

- Unknown effects of hypothermia on DTI changes

- More practical for short term outcome evaluation & pattern of injury

- Identified injury does not necessarily equate to complete loss of function
Show Me the Brain!

- Perform a neurologic exam. REPEATEDLY.
  - Apgar score, Sarnat score, neurologic exam

- Examine the activity of the brain by bedside monitoring
  - Continuous video EEG monitoring
  - Amplitude-integrated EEG (aEEG)
  - NIRS

- Ask for a picture of the brain
  - Head US, CT, MRI
How Can We Minimize Brain Injury?

- Prevent intrauterine asphyxia
- Provide supportive care for the brain
  - Ventilation, perfusion, metabolic support
- Minimize cerebral edema & cell death with hypothermia
- Treat EEG-confirmed seizures
- Consider neuroprotective agents & therapies

From Insult to Injury & Recovery

Ferriero 2004 NEJM
Goldilocks Method of Care

- Not too hot, not too cold
- Not too hypoxemic, not too hyperoxemic
- Not too hypotensive, not too hypertensive
- Not too hypoglycemic, not too hyperglycemic
Neuro-supportive Care after Acute Brain Injury

- **Ventilation**
  - Adequate oxygen delivery, minimize apnea & hypercapnia
  - Monitoring continuously via pulse oximetry (NIRS?)

- **Cerebral perfusion**
  - Recognize pressure passive cerebral circulation
  - Narrow range of cerebral autoregulation in the newborn
  - Prevent hypotension or hypertension (MAP ≥ 45)
  - Avoid hyperviscosity

- **Maintain adequate glucose**
  - About 55-110 mg/dl
  - Hypoglycemia which may cause neuronal injury
  - Hyperglycemia which may provoke hemorrhage or worsen cerebral lactic acidosis
## Current Therapies in Neonatal Seizure Treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>20 mg/kg</td>
<td>2-3 mg/kg/dose q12h</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>0.1 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>20 mg/kg PE</td>
<td>2.5-4 mg/kg/dose q8h</td>
</tr>
<tr>
<td>Midazolam (Versed)</td>
<td>None or 0.1 mg/kg</td>
<td>0.05 – 0.3 mg/kg/hr</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2 mg/kg over 20 min</td>
<td>4-6 mg/kg/hr</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td>3 mg/kg</td>
<td>1.5-9 mg/kg/dose q12h</td>
</tr>
<tr>
<td>Levetiracetam (Keppra)</td>
<td>30-40 mg/kg</td>
<td>10-30 mg/kg/dose q8h</td>
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</table>
There is a lot of placental pathology in NE, more in no SE than SE.
Total of Placental Pathology and/or Aberrant Weight

<table>
<thead>
<tr>
<th></th>
<th>Sentinel Event</th>
<th>No Sentinel Event</th>
<th>Total</th>
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<tbody>
<tr>
<td>Abnormal Pathology or Weight</td>
<td>31.4%</td>
<td>12.2%</td>
<td>22.0%</td>
</tr>
<tr>
<td>No Abnormal Findings</td>
<td>68.6%</td>
<td>87.8%</td>
<td>78.0%</td>
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WHAT IS THE FUTURE OF NEONATAL NEUROPROTECTION?
History of Neurocritical Care

- 1960s  First neurologic ICUs established as multidisciplinary services
- 1970s  Appearance of NCC training programs
- 2003   Formation of Neurocritical Care Society and scientific journal Neurocritical Care
- 2005   Acceptance by the United Council for Neurologic Subspecialities (UCNS) as a formal subspecialty
- 2008   First 9 programs accredited by the UCNS
- 2010   25 accredited NCC fellowship programs
          Over 50 dedicated neurologic ICUs
- 2010   Neurocritical Care Society is conducting a workforce evaluation for pediatric NCC
Lessons from Adult Neurocritical Care

- **Specialized teams in dedicated units**
  - Reduce mortality & improve resource utilization, especially in hospitals with high patient volumes

- **Protocol-driven approach**
  - Adherence to guidelines results in lower mortality and higher rates of favorable outcomes

- **Attention to basic physiology**
  - Temperature, glucose, oxygenation, and blood pressure
  - Prevent secondary injury

- **Training and education**
  - Medical *and* nursing staff
Neonatal Neurocritical Care

- Neonatologists remains the primary service

- Multi-interdisciplinary service requiring specialists with experience in newborns
  - Neonatal neurologist, pediatric neurophysiologist, pediatric neuroradiologist, & pediatric neurosurgeon
  - Perinatal pathology, obstetrics, perinatology

- Restricted to regional centers due to the limited number of pediatric subspecialists with neonatal experience, most specifically neonatal neurologists

- Developmental of neonatal-specific protocols
Children’s National Neonatal Neurocritical Care

Three neonatal neurointensivists

- Supported by 8 neurophysiologists, 6 EEG technologists & a biomedical engineer
- Interacting with 7 neonatologists, 4 neuroradiologists, 4 neurosurgeons and a perinatal pathologist
- Using 4 NICU-designated video EEG monitors with aEEG & bedside remote access, 6 NIRS, 1 portable CT, 1 MRI compatible incubator, and 2 MRI scanners
- Attending a separate neonatal neurointensive care service with minimum twice daily bedside rounds
- Independently reviewing studies to intervene as necessary in an acute manner
- Daily bedside family & NICU updates & interdisciplinary family meetings after evaluation or prior to discharge
- Follow up in neonatal neurology clinic or interdisciplinary clinics (perinatal brain injury clinic, cooling clinic)
Children’s National NICU Neurology Consults

History
- July 2004: Neonatal neurology program
- July 2005: Neonatal neurointensive care service
- May 2006: Cooled first newborn
- May 2009: Moved into new 54 bed NICU

- Average 650 NICU admissions per year

* Calendar year  ** Fiscal year
Children’s National Neonatal Protocols

- Neurodiagnostic Protocols
  - Neuromonitoring protocols using bedside video EEG monitoring and/or NIRS
  - Neuroimaging protocols
    - Cooling
    - Stroke
  - Placental pathology

- Neurotherapeutic Protocols
  - Therapeutic hypothermia for neonatal encephalopathy
  - Neonatal seizures - refractory & status epilepticus
Children’s National Protocol for Neonatal EEG Monitoring

- Features video EEG monitoring with remote bedside access and bedside aEEG display

- Standard duration of 24 hours of video EEG monitoring is recommended
  - Infants at high-risk of seizures
  - Infants with spells, events, behaviors or movements concerning for seizures
  - Infants with known seizures until seizure free for 24 hours

- Monitoring response to neuroprotective therapies

- Encourage the use of trend algorithms such as aEEG by NICU staff
Children’s National Protocol for Neonatal Neuroimaging

- Head ultrasounds
  - Serial studies in early premature infants
  - Serial studies in known cases of IVH
  - Serial studies to monitor hydrocephalus
  - Serial studies during ECMO or other high-risk infants

- CT scans of head
  - Routine or at bedside in patients suspected of acute diffuse brain injury consistent with poor prognosis
  - Status post surgery i.e. shunt placement, brain surgery

- MRI of brain
  - Protocols for imaging without sedation
  - Near term in premature infants
  - Near discharge after ECMO
  - 8-10 days after supposed hypoxic ischemic insult
  - Stroke
  - Suspect cerebral malformation and/or dysgenesis
Children’s National Protocols for Refractory & Status Epilepticus

Refractory Seizures
- Refractory seizures defined as recurrent EEG-confirmed seizures refractory to Phenobarbital
- Requires continuous EEG monitoring, preferably with video and remote access
- Second anti-seizure medication choice dependent on underlying etiology (fosphenytoin, keppra, topiramate)
- Rapid titration of all anti-seizure medications guided by EEG-confirmed seizure control/reduction and drug levels
- Goal of seizure control (acute symptomatic) within 12 hrs of EEG identification or seizure reduction (epilepsy) within 3 days

Status Epilepticus
- Status epilepticus defined as EEG-confirmed seizures occupying more than 50% of a 1 hr recording
- Requires continuous EEG monitoring, preferably with video & remote access
- Phenobarbital used as the first anti-seizure medication of choice
- Midazolam infusion initiated if failure to stop status epilepticus after repeat bolus of phenobarbital
- Titration of midazolam infusion every 30 minutes until seizure free on EEG or maximum of 0.3mg/kg/hr
- Status epilepticus is now stopped within 3-4 hrs of EEG identification
Children’s National Protocol for Therapeutic Hypothermia

**ABSOLUTE CRITERIA**
- > 36 Weeks gestation
- > 1,800 Grams at birth
- ≤ 6 Hours of age
- Presence of acidosis ± SE
- NE on exam or seizures

**EXCLUSION**
- Severe chromosomal or other anomalies
- Extremis / nonintervention

- Continuous video EEG monitoring during cooling and rewarming
- Treatment of EEG-confirmed seizures
- Neuroimaging with MR imaging at 7-10 days of life
- Infant development, neurology and/or PM&R follow up clinics

`Shankaran et al NEJM 2005`
Our Response to Hypothermia Case

Our response and management to neonatal encephalopathy presenting for hypothermia:

- Neurointensive care service notified of planned transfer to initiate any treatments prior to transport and to arrange EEG service. Placental pathology requested of birth hospital.

- Initial neurologic assessment upon NICU arrival if in-house or as soon as possible.

- Continuous video EEG started as soon as possible (typically 11 hours of life). Initial background assessed for risk of seizures. If infant considered high risk then EEG reviewed in 2-3 hrs & neurophysiology service made aware.

- Seizures treated with phenobarbital and protocol initiated for monitoring & treatment of status epilepticus.

- Daily neurologic assessments, EEG review and bedside rounds made with NICU team & family.

- Major issues and plan signed out at end of day to NICU, on-call neurology resident & neurophysiologist. Neurointensivist available by page by all team members.

- MRI imaging performed at DOL#8-10 using neonatal specific hypothermia protocols.

- Joint NICU family meeting to review findings, studies, antecedent diagnosis and prognosis.
Children’s National Protocol for Targeted Temperature Management

Steps for initiating therapeutic hypothermia:
1. Call your referral center immediately if patient meets any of the following criteria:
   - Cord/1st hour pH<7.0
   - Base Deficit ≥16
   - Apgar ≤5 at 10 minutes AND
   - Any Sentinel Event:
     - Variable/late FHR decels
     - Cord prolapse/rupture
     - Uterine Rupture
     - Maternal trauma
     - Maternal hemorrhage/abruption
     - Maternal CPR
2. After consultation with cooling center, initiate targeted temperature management:
   - Turn off warmer, remove blankets
   - Monitor temperature every 15 minutes
   - Intervene if T<33°C or >37°C
3. Prepare patient for transfer
4. Request placental pathology

- Document initial axillary temperature
- Turn off radiant warmer
- Monitor and document axillary temperature every 15 minutes
- Baby’s temp <33°C
  - Turn on radiant warmer with servo control set min 33°C and max 35°C
  - Or: Add 1 blanket
- Baby’s temp >34°C
  - Consider tepid bath. Discuss with cooling center prior to initiating active cooling measures.
What Have We Learned?

- Need to have neonatal EEG standards
  - Standard Terminologies, Interpretations, Guidelines, Protocols
  - ACNS Critical Care Committee

- Need to have standard and objective measures for neonatal EEG interpretation
  - Interpretation varies depending on experience of EEG reader
  - Quantitative features of EEG background which can be analyzed in real-time using computer generated algorithms
  - Background assessment more useful indicator than identification of seizures, though seizure most likely need to be treated

- Need earlier biomarkers
  - Maternal, cord and immediate neonatal blood
  - S100B, NSE, CK-BB
  - Proteomics, Genomics?
American Clinical Neurophysiology Society

- Consensus statement on methods and indications for continuous EEG monitoring of high-risk neonates
  - RA Shellhaas, T Chang, T Tsuchida, MS Scher, JJ Rivello, NS Abend, S Nguyen, CJ Wusthoff, RR Clancy

- Standardized EEG research terminology and categorization for description in neonates
  - T Tsuchida, RA Shellhaas, T Chang, MS Scher, JJ Rivello, NS Abend, S Nguyen, CJ Wusthoff, RR Clancy
Future Directions in Neonatal EEG Monitoring in the NICU

- Neonatal EEG Working Group
  - Nick Abend, Taeun Chang, Hannah Glass, Joseph Sullivan, Tammy Tsuchida, Courtney Wusthoff

- Feasibility of EEG monitoring in multi-center neonatal seizure drug trials

- Evaluating neonatal seizure detection algorithms
Future Directions in Neonatal Neuroimaging in the NICU

- MR imaging is likely to substitute as a immediate outcome measure after newborn brain injury.

- Serial imaging may be used to evaluate acute brain injury, monitor during neuroprotective therapies, and correlate with neurodevelopmental outcome.

- Clinical trials for future neonatal neurotherapeutic agents will require some form of neuroimaging.

- Standardized imaging protocols specific to newborns.
Regionalization of Cooling

- Other countries have well established guidelines for therapeutic hypothermia

- NIH NICHD executive summary is forthcoming

- Regionalized efforts are needed to improve implementation of neuroprotective therapy (Carr, Edwards, Martinez 2010)
Future Strategies for Neuroprotection

- Multiple windows for intervention
  - Preventive therapies
  - Acute therapies
  - Subacute therapies
  - Recovery therapies

Degos et al 2008 Anesth Analg

Ferriero 2004 NEJM
## Neonatal Hypothermia Trials

<table>
<thead>
<tr>
<th>Aim</th>
<th>Age</th>
<th>Phase</th>
<th>PI Site</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective head cooling in premature infants</td>
<td>32-35 weeks</td>
<td>Phase I</td>
<td>Vanderbilt</td>
<td>2008</td>
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<tr>
<td>Late Hypothermia</td>
<td>≥ 36 weeks</td>
<td>Phase II/III</td>
<td>NICHD</td>
<td>2008</td>
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<tr>
<td>Using MRI to measure brain temperature</td>
<td>Seizures</td>
<td></td>
<td>Vanderbilt</td>
<td>2009</td>
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<tr>
<td>Cooling to 32°C and/or 120 hrs</td>
<td>≥ 36 weeks</td>
<td>Phase III</td>
<td>NICHD</td>
<td>2010</td>
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# Neonatal Neuroprotection Trials

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Action</th>
<th>Phase</th>
<th>PI Site</th>
<th>Year</th>
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<tbody>
<tr>
<td>EPO for Neonatal Cardiac Surgery</td>
<td>Neuroprotection</td>
<td>Phase I/II</td>
<td>Baylor</td>
<td>2006/2007</td>
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<tr>
<td>Erythropoietin (EPO)</td>
<td>Neuroprotection</td>
<td>Phase I/II</td>
<td>UCSF</td>
<td>2010</td>
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<td>Cerebrolysin in HIE</td>
<td>Neuroprotection</td>
<td>Phase I/II</td>
<td>Egypt</td>
<td>2010</td>
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<tr>
<td>Xenon</td>
<td>Neuroprotection</td>
<td>Phase I/II</td>
<td>Imperial College UK</td>
<td>To Start</td>
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<tr>
<td>NAC for Neonatal Cardiac Surgery</td>
<td>Myocardial Protection</td>
<td>Phase II</td>
<td>Michigan</td>
<td>Completed 2008</td>
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<td>NAC for CA in preterm &amp; term</td>
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<td>Yale</td>
<td>2006</td>
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<tr>
<td>NAC for CA in preterm</td>
<td>Neuroprotection</td>
<td>Phase I/II</td>
<td>MUSC</td>
<td>2008</td>
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# Neonatal Seizure Drug Trials

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<th>Action</th>
<th>Phase</th>
<th>PI Site</th>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>Seizures</td>
<td>Phase I/II</td>
<td>Boston</td>
<td>Ongoing</td>
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<tr>
<td>Levetiracetam / Keppra</td>
<td>Seizures</td>
<td>Phase I/II</td>
<td>UCSD</td>
<td>Ongoing</td>
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<tr>
<td>Topiramate / Topamax</td>
<td>Seizures</td>
<td>Phase I</td>
<td>James Cloyd</td>
<td>2012/2013</td>
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Conclusions

- Hypothermia has become a standard of care for newborns ≥ 36wks gestation presenting with neonatal encephalopathy at birth.

- Brain-oriented neonatal care in the form of neurosupportive care, neuromonitoring & neurotherapies should be incorporated in NICU protocols at levels appropriate for each facility.
Conclusions

- Brain-oriented neonatal care requires specialized multi-disciplinary teams and units implementing protocol-driven therapies.

- Neonatal neurointensivists can contribute greatly to the care of neurologically affected newborns in addition to actively advancing brain-oriented care.

- Additional neonatal neurotherapies are likely to become available in the future.
SHOW ME THE BRAIN
Neonatal Neuroprotection Team

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