Neuroprotection for Hypoxic Ischemic Encephalopathy

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UCSD Professor of Pediatrics
Objectives

1. Understand the relationship between the stage of encephalopathy and early childhood outcome for infants who have hypoxic-ischemic encephalopathy (HIE).

2. Understand the impact of therapeutic hypothermia on the outcome of infants who have HIE.

3. Understand that the provision of therapeutic hypothermia for infants who have HIE does not guarantee a normal neurodevelopmental outcome.

4. Discuss adjunctive therapies used with hypothermia.
Incidence and outcome of HIE

- Incidence ranges from 1 to 8 per 1,000 births depending on definition used
- Moderate encephalopathy is associated with 10% risk of death and 30% risk of disability
- Severe encephalopathy is associated with 60% risk of death and most survivors will be disabled
- In the U.S. with 4 million births annually, HIE accounts for approximately 1,200 deaths and 1,800 disabled infants

Causes of neonatal mortality

- Sepsis/Pneumonia: 26%
- Tetanus: 7%
- Diarrhea: 3%
- Preterm: 27%
- Asphyxia: 23%
- Congenital: 7%
- Other: 7%

Risk factors for Encephalopathy

- Preconceptual (69%)
- Antepartum-Intrapartum (25%)
- Intrapartum (5%)
- (2%) Unknown

Definition of Hypoxic Ischemic Encephalopathy (HIE)

- Synonyms: Post-asphyxial encephalopathy, birth asphyxia, and perinatal asphyxia

- Clinical syndrome consisting of abnormal neurologic findings in the first week of life in term infants believed to have experienced asphyxia during labor and delivery

- The primary processes are hypoxia and ischemia due to systemic hypoxemia, reduced cerebral blood flow, or both.
I. DEFINITIONS:

ESSENTIAL CHARACTERISTICS:

1. Umbilical cord arterial blood metabolic or mixed acidemia (pH < 7.0)

2. Apgar score 0-3 for > 5 minutes

3. Clinical neurologic sequelae in immediate neonatal period

4. Evidence of multi-organ dysfunction
Relation of Apgar Score to Mortality and Cerebral Palsy

<table>
<thead>
<tr>
<th>Apgar score ≤3</th>
<th>Mortality (%)</th>
<th>CP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>5 min</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>10 min</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>15 min</td>
<td>48</td>
<td>9</td>
</tr>
<tr>
<td>20 min</td>
<td>59</td>
<td>57</td>
</tr>
</tbody>
</table>

Nelson KB et al., *Pediatrics* (1981)
Clinical findings in HIE

- **Abnormal neurologic exam:**
  - Level of consciousness
  - Tone
  - Tendon reflexes
  - Primitive reflexes
  - Respiratory function
  - Autonomic function

- **Other clinical findings:**
  - Need for resuscitation
  - Seizures
  - EEG abnormalities
  - Other organ injury
    - heart
    - lung
    - liver
    - kidney
  - Hematologic
MRI: Patterns of Injury

- Parasagittal cerebral injury
  - Cerebral cortex; watershed
- Basal ganglia and thalamus
  - Selective neuronal necrosis of deep nuclear structures
- Periventricular leukomalacia (40-50% of term asphyxiated infants)
- Selective cerebral cortical neuronal injury
  - Loss of cerebral gray-white matter differentiation
MRI Patterns of Injury
Parasagittal (Watershed)
MRI Patterns of Injury
Basal Ganglia-Thalamus (BGT)
### MRI and Outcome

173 term infants with neonatal encephalopathy MRI at a median age of 6 days (1-24 days)

<table>
<thead>
<tr>
<th></th>
<th>Normal 51 (29%)</th>
<th>Watershed 78 (45%)</th>
<th>BGT 44 (25%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>38%</td>
<td>44%</td>
<td>72%</td>
</tr>
<tr>
<td>Encephalopathy Score</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Seizure Score</td>
<td>0</td>
<td>0</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Miller et al. J Pediatr 146: 453, 2005
35 yr old mom presents to the ED, 38wks pregnant
Severe abdominal pain
Bleeding in the waiting room
No fetal HR
To the OR stat for C-section
NICU called stat to delivery
Baby born blue, floppy, no respiratory effort
Resuscitated and taken to NICU
Case report

• Apgars 1, 3, 5
• Lines placed, pressors started for hypotension
• O negative blood ordered – hypovolemia
• 45min – UAC 6.9/40/82/-18
• Pale, limp, improved respiratory effort
• ? Now what
Hypoxic-Ischemic Encephalopathy

• A decade ago – although research active, care was supportive, stabilization of physiologic parameters

• Our patient 10 years ago –
  – IVF
  – Pressors
  – Ventilation
  – LFTs, Cr
  – Seizures
Pathophysiology

- Current therapeutic approach is based on understanding the evolution of neuronal damage after HI
- Main problem with treating HIE
  - pathway of injury is complex and not always clear
- Factors
  - etiology
  - extent of hypoxia or ischemia
  - maturational age of the brain
  - general health before the injury
  - all impact the pattern and extent of brain injury
  - ->outcome after injury
HIE stages and cell death

Primary phase
Latent phase
2° Energy Failure
Secondary phase

Cell Death

Time
Hypothermia has its day

- Adult stroke
- Cardiac arrest
- Near Drowning
- Cardiac surgery
- Liver failure
- Neonatal asphyxia
“Well, I guess we’re the control group.”
Animal Studies

Bar graph showing neuronal loss (%) in different brain regions.

- Parasagittal Cortex
- Lateral Cortex
- Striatum
- Dentate Gyrus
- CA 1/2
- Thalamus

Comparison between Control and Cooled conditions.
## NICHD Neonatal Network

**Eligibility criteria for therapeutic hypothermia**

### Two step process for infants ≥36 weeks and ≤6 hours of age

<table>
<thead>
<tr>
<th>If blood gas is available</th>
<th>If blood gas is not available,</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>or</strong> pH 7.01 - 7.15</td>
</tr>
<tr>
<td></td>
<td><strong>or</strong> Base deficit 10 - 15.9mEq/L</td>
</tr>
</tbody>
</table>

Infant should have:

- Cord or first postnatal blood gas within 1 hour with pH ≤ 7.0
  - **or**
- Base deficit on cord gas or first postnatal blood gas within 1 hour at ≥ 16 mEq/L

Infant should have history of acute perinatal event *and*

- Apgar score ≤ 5 at 10 minutes
  - **or**
- Continued need for ventilation at 10 minutes

NICHD Inclusion/Exclusion criteria

• Inclusion:  ≥36 weeks gestation
  Historical and lab criteria met
  Modified Sarnat exam with abnormalities
  in 3 of 6 categories
  OR clinical seizures

• Exclusion:  Congenital or chromosomal anomaly
  Birth weight <1800 grams
  Chronologic age >6 hours
  Decision to not provide full intensive care
  Refusal of consent by MD or parent

**NICHD Trial: Primary Outcome**

**Death or Disability**

- **Hypothermia (n = 102)**
  - RR: 0.72
  - 95% CI: 0.54-0.95
  - P value: 0.01
  - 44%

- **Control Group (n = 106)**
  - 62%

Disability defined as:
- Bayley MDI < 70
- GMFCS ≥ level 2
- Hearing impairment
- Seizure disorder
- Blindness

NICHD Trial: Subgroup Analysis in Moderate Encephalopathy Group


NICHD Trial: Subgroup Analysis in Severe Encephalopathy Group

## Cooling trials

<table>
<thead>
<tr>
<th>Trial (Publication date)</th>
<th>N</th>
<th>GA (wks)</th>
<th>Mode</th>
<th>Transport Cooling</th>
<th>Temp goal &amp; site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eicher (2005)</td>
<td>65</td>
<td>≥35</td>
<td>Whole body</td>
<td>Yes</td>
<td>33° ± 0.5 rectal</td>
</tr>
<tr>
<td>CoolCap (2005)</td>
<td>234</td>
<td>≥36</td>
<td>Selective head</td>
<td>No</td>
<td>34-35°C rectal</td>
</tr>
<tr>
<td>Shankaran (2005)</td>
<td>208</td>
<td>≥36</td>
<td>Whole body</td>
<td>No</td>
<td>33.5°C esophageal</td>
</tr>
<tr>
<td>TOBY (2009)</td>
<td>325</td>
<td>≥36</td>
<td>Whole body</td>
<td>Yes</td>
<td>33.5°C rectal</td>
</tr>
<tr>
<td>Neo.nEURO (2010)</td>
<td>125</td>
<td>≥36</td>
<td>Whole body</td>
<td>No</td>
<td>33-34°C rectal</td>
</tr>
<tr>
<td>Zhou (2010)</td>
<td>194</td>
<td>≥37</td>
<td>Selective head</td>
<td>No</td>
<td>34° ± 0.2 nasopharyngeal</td>
</tr>
<tr>
<td>ICE (2011)</td>
<td>221</td>
<td>≥35</td>
<td>Whole body</td>
<td>Yes</td>
<td>33-34°C rectal</td>
</tr>
</tbody>
</table>
## Meta-analysis of hypothermia RCTs

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Risk Ratio M-H, Fixed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight, %</td>
</tr>
<tr>
<td>Azzopardi et al., 2009</td>
<td>74</td>
<td>163</td>
<td>22.6</td>
</tr>
<tr>
<td>Gluckman et al., 2005</td>
<td>59</td>
<td>108</td>
<td>18.9</td>
</tr>
<tr>
<td>Gunn et al., 1998</td>
<td>7</td>
<td>18</td>
<td>1.2</td>
</tr>
<tr>
<td>Jacobs et al., 2011</td>
<td>51</td>
<td>91</td>
<td>16.3</td>
</tr>
<tr>
<td>Shankaran et al., 2005</td>
<td>45</td>
<td>102</td>
<td>16.7</td>
</tr>
<tr>
<td>Simbruner et al., 2010</td>
<td>27</td>
<td>53</td>
<td>12.0</td>
</tr>
<tr>
<td>Zhou et al., 2010</td>
<td>31</td>
<td>79</td>
<td>12.3</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>614</strong></td>
<td><strong>600</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

- **Total events**: 294 (Hypothermia) / 379 (Normothermia)
- **Heterogeneity**: $\chi^2 = 5.79; P = .45; I^2 = 0\%$
- **Test for overall effect**: $z = 5.29; P < .001$

### Conclusion:

Hypothermia improves survival and neurodevelopment in newborns with moderate to severe HIE. Risk ratio is 0.76 with confidence interval 0.69-0.84. Number need to treat =7.

## Meta-analysis: Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies/No. of participants</th>
<th>Relative risk</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>12/1390</td>
<td>0.78 (0.65, 0.92)</td>
<td></td>
</tr>
<tr>
<td>ND disability in survivors</td>
<td>6/687</td>
<td>0.67 (0.54, 0.84)</td>
<td></td>
</tr>
<tr>
<td>Severe cerebral palsy</td>
<td>3/518</td>
<td>0.65 (0.48, 0.88)</td>
<td></td>
</tr>
<tr>
<td>MDI &lt;70</td>
<td>4/522</td>
<td>0.70 (0.54, 0.90)</td>
<td></td>
</tr>
<tr>
<td>PDI &lt;70</td>
<td>4/512</td>
<td>0.70 (0.54, 0.90)</td>
<td></td>
</tr>
<tr>
<td>Severe visual deficit</td>
<td>4/535</td>
<td>0.59 (0.35, 0.98)</td>
<td></td>
</tr>
<tr>
<td>Severe hearing deficit</td>
<td>4/510</td>
<td>0.75 (0.36, 1.55)</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>5/413</td>
<td>0.80 (0.48, 1.31)</td>
<td></td>
</tr>
<tr>
<td>Life support withdrawn</td>
<td>6/746</td>
<td>0.93 (0.73, 1.18)</td>
<td></td>
</tr>
</tbody>
</table>

## Meta-analysis: Safety Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies/No. of participants</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>5/806</td>
<td>4.08 (1.55, 10.74)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>8/1108</td>
<td>1.03 (0.93, 1.13)</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>7/1114</td>
<td>0.96 (0.80, 1.15)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4/638</td>
<td>1.28 (1.07, 1.52)</td>
</tr>
<tr>
<td>Seizure after enrollment</td>
<td>8/1102</td>
<td>0.96 (0.86, 1.06)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5/310</td>
<td>0.95 (0.53, 1.70)</td>
</tr>
<tr>
<td>Hepatic side effects</td>
<td>5/678</td>
<td>0.85 (0.69, 1.04)</td>
</tr>
<tr>
<td>Infection</td>
<td>7/544</td>
<td>0.86 (0.40, 1.88)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>5/636</td>
<td>1.36 (0.95, 1.96)</td>
</tr>
</tbody>
</table>

Maternal and Infant Characteristics from the different RCT’s

<table>
<thead>
<tr>
<th>Patient Variable</th>
<th>Percentage of Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal distress</td>
<td>75–90</td>
</tr>
<tr>
<td>Sentinel events</td>
<td>30–40</td>
</tr>
<tr>
<td>Emergent cesarean section</td>
<td>40–75</td>
</tr>
<tr>
<td>Out-born</td>
<td>40–80&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apgar at 10 min &lt; 6</td>
<td>75–80</td>
</tr>
<tr>
<td>pH &lt;7.0 in cord or blood gas at age ≤1 h</td>
<td>≈75</td>
</tr>
<tr>
<td>Intubation in the delivery room</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>
Recommendations for use of Hypothermia

Newborns with moderate to severe HIE should be offered hypothermia. Treatment should be consistent with trial protocols.


Hypothermia at <6 hours decreases mortality and severe disability with minimal side effects and without increasing disability. Severe HIE less likely benefit.

No difference in outcome between head and body cooling.


Therapeutic hypothermia is an effective therapy, treated infants should meet trial entry criteria, and education of referring hospitals regarding identification of hypothermia candidates is critical.

Committee on Fetus and Newborn. Pediatrics (2014)
Methods of cooling: Definitions

- **Passive cooling**: Turning off all external heat sources such as radiant warmer or transport isolette.

- **Active cooling**: When ice, gel packs, fans, or other cooling devices such as the Cool-Cap, Tecotherm Neo, CritiCool, or the Blanketrol II/III are used.
Will the benefits of Therapeutic hypothermia persist beyond 2 years of age?
Hypothermia for HIE Childhood outcomes:


208 Infants underwent randomization

102 Were assigned to the hypothermia group
5 Were lost to follow-up
27 Died by 6–7 yr of age
70 Were included in the 6–7-yr follow-up
97 Were included in the primary analysis

106 Were assigned to the control group
13 Were lost to follow-up
41 Died by 6–7 yr of age
52 Were included in the 6–7-yr follow-up
93 Were included in the primary analysis

190 Were included in the primary analysis
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypothermia (N=97)</th>
<th>Control (N=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>31 (32)</td>
<td>35 (38)</td>
</tr>
<tr>
<td>White</td>
<td>39 (40)</td>
<td>31 (33)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>27±6</td>
<td>27±6</td>
</tr>
<tr>
<td>Education less than high school — no. (%)‡</td>
<td>20 (21)</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Complications of pregnancy — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>11 (11)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Antepartum hemorrhage§</td>
<td>9 (9)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Intrapartum complications — no. (%)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal heart-rate deceleration¶</td>
<td>69 (71)</td>
<td>68 (74)</td>
</tr>
<tr>
<td>Cord prolapse</td>
<td>22 (23)</td>
<td>13 (14)</td>
</tr>
<tr>
<td>Uterine rupture</td>
<td>16 (16)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>11 (11)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Maternal hemorrhage</td>
<td>6 (6)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Emergency cesarean delivery — no. (%)</td>
<td>68 (70)</td>
<td>72 (77)</td>
</tr>
<tr>
<td><strong>Neonatal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at randomization — hr</td>
<td>4.3±1.3</td>
<td>4.3±1.2</td>
</tr>
<tr>
<td>Transferred from another hospital — no. (%)</td>
<td>45 (46)</td>
<td>42 (45)</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>48 (49)</td>
<td>58 (62)</td>
</tr>
<tr>
<td>Apgar score a5 — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 min</td>
<td>87 (91)</td>
<td>86 (92)</td>
</tr>
<tr>
<td>At 10 min</td>
<td>76 (84)</td>
<td>66 (79)</td>
</tr>
<tr>
<td>Birth weight — g</td>
<td>3391±620</td>
<td>3358±587</td>
</tr>
<tr>
<td>Intubation in the delivery room — no. (%)</td>
<td>93 (96)</td>
<td>86 (92)</td>
</tr>
<tr>
<td>Continued resuscitation at 10 min — no. (%)</td>
<td>90 (93)</td>
<td>88 (95)</td>
</tr>
<tr>
<td>Cord-blood pH</td>
<td>6.9±0.2</td>
<td>6.8±0.2</td>
</tr>
<tr>
<td>Base deficit — mmol/liter</td>
<td>18.5±6.8</td>
<td>20.5±8.6</td>
</tr>
<tr>
<td>Seizure — no. (%)</td>
<td>41 (42)</td>
<td>48 (52)</td>
</tr>
<tr>
<td>Encephalopathy — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>67 (69)</td>
<td>53 (57)</td>
</tr>
<tr>
<td>Severe</td>
<td>30 (31)</td>
<td>40 (43)</td>
</tr>
<tr>
<td>Use of anticonvulsant agent — no. (%)**</td>
<td>39 (43)</td>
<td>39 (48)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Percentages are based on the numbers of mothers or children for whom data were available. Baseline characteristics did not differ significantly between the groups, except as noted. Maternal race was self-reported.

† Data were missing for 24 mothers in the hypothermia group and 27 in the control group.

‡ P=0.04.

§ Data were missing for 1 infant in the control group.

¶ Data were missing for 1 infant in the hypothermia group and 1 in the control group.

** Data were missing for 7 infants in the hypothermia group and 8 in the control group.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothermia (N = 97)</th>
<th>Control (N = 93)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or IQ score &lt;70 (primary outcome)</td>
<td>46/97 (47)</td>
<td>58/93 (62)</td>
<td>0.78 (0.61–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>Among children with moderate hypoxic–ischemic encephalopathy†</td>
<td>22/67 (33)</td>
<td>25/53 (47)</td>
<td>0.70 (0.45–1.09)</td>
<td>0.11</td>
</tr>
<tr>
<td>Among children with severe hypoxic–ischemic encephalopathy†</td>
<td>24/30 (80)</td>
<td>33/40 (82)</td>
<td>0.97 (0.77–1.22)</td>
<td>0.79</td>
</tr>
<tr>
<td>Death‡</td>
<td>27/97 (28)</td>
<td>41/93 (44)</td>
<td>0.66 (0.45–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Death or moderate or severe disability</td>
<td>51/97 (53)</td>
<td>60/93 (65)</td>
<td>0.84 (0.66–1.06)</td>
<td>0.14</td>
</tr>
<tr>
<td>Death or severe disability</td>
<td>38/93 (41)</td>
<td>53/89 (60)</td>
<td>0.72 (0.54–0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death or IQ score &lt;55</td>
<td>38/93 (41)</td>
<td>53/89 (60)</td>
<td>0.72 (0.54–0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death or cerebral palsy</td>
<td>39/96 (41)</td>
<td>56/93 (60)</td>
<td>0.71 (0.54–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Survival</td>
<td>70/97 (72)</td>
<td>52/93 (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQ score &lt;70 among survivors†</td>
<td>19/70 (27)</td>
<td>17/52 (33)</td>
<td>0.83 (0.48–1.44)</td>
<td>0.51</td>
</tr>
<tr>
<td>Attention and executive function score &lt;70 among survivors†</td>
<td>2/48 (4)</td>
<td>4/32 (13)</td>
<td>0.33 (0.06–1.71)</td>
<td>0.19</td>
</tr>
<tr>
<td>Visuospatial score &lt;70†</td>
<td>2/53 (4)</td>
<td>1/36 (3)</td>
<td>1.36 (0.13–14.4)</td>
<td>0.80</td>
</tr>
<tr>
<td>Level of disability among survivors</td>
<td></td>
<td></td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Moderate or severe disability</td>
<td>24/69 (35)</td>
<td>19/50 (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild disability</td>
<td>17/69 (25)</td>
<td>10/50 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28/69 (41)</td>
<td>21/50 (42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy†</td>
<td>12/69 (17)</td>
<td>15/52 (29)</td>
<td>0.60 (0.31–1.18)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hearing impairment†</td>
<td>3/63 (5)</td>
<td>1/50 (2)</td>
<td>2.38 (0.26–22.2)</td>
<td>0.45</td>
</tr>
<tr>
<td>Bilateral blindness†</td>
<td>1/67 (1)</td>
<td>2/50 (4)</td>
<td>0.37 (0.03–4.00)</td>
<td>0.42</td>
</tr>
<tr>
<td>Seizures†</td>
<td>7/67 (10)</td>
<td>8/50 (16)</td>
<td>0.65 (0.25–1.68)</td>
<td>0.38</td>
</tr>
<tr>
<td>Motor-skill abnormalities among nondisabled survivors</td>
<td></td>
<td></td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Every day</td>
<td>0/27</td>
<td>1/21 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex</td>
<td>3/27 (11)</td>
<td>2/21 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine</td>
<td>3/27 (11)</td>
<td>2/21 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>21/27 (78)</td>
<td>16/21 (76)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* For IQ scores, the Spanish version of the Wechsler Intelligence Scale for Children IV was administered to 3 of the 18 children assessed by means of this tool. The P value for level of disability among survivors was calculated with the use of multinomial cumulative logistic regression with adjustment for center. The P value for motor-skill abnormalities was calculated with the use of Fisher’s exact test.
† Results for relative risk were not adjusted for center.
‡ In the hypothermia group, there were 24 deaths before and 3 after 15 months, and in the control group, 38 deaths before and 3 after 18 months.
Childhood outcomes after therapeutic hypothermia for neonatal HIE

Eligibility: Children age 6-7 enrolled in NICHD cooling trial

1° outcome: Death or IQ less than 70

Results:

<table>
<thead>
<tr>
<th></th>
<th>HT group (%)</th>
<th>Control (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or IQ &lt;70</td>
<td>47%</td>
<td>62%</td>
<td>.06</td>
</tr>
<tr>
<td>Death</td>
<td>28%</td>
<td>44%</td>
<td>.04</td>
</tr>
<tr>
<td>IQ &lt;70</td>
<td>27%</td>
<td>33%</td>
<td>.51</td>
</tr>
</tbody>
</table>

Conclusion: The outcome of death or IQ<70 was lower in the hypothermia group but not significantly. Hypothermia resulted in fewer deaths and did not increase the rate of severe disability.
Effects of Hypothermia for the treatment of HIE: Childhood outcomes


July 10, 2014
DOI: 10.1056/NEJMoa1315788
Effects of Hypothermia for the treatment of HIE: Childhood outcomes

- 325 Neonates with HIE
- > 36 weeks EGA
- Control vs Hypothermia 33.5 C for 72 hrs, started during the first 6
- Neurocognitive evaluation at 6-7 years of age
- **Primary Outcomes:** Frequency of survival with a IQ > 85
Primary Outcome

- Survival with a IQ > 85

75/145 (52%) hypothermia group
52/132 (39%) control group
Secondary Outcome

- Death: 29% vs 30%

- Survival without neurological abnormalities
  65/145 (45%) hypothermia group
  37/132 (28%) control group

- Cerebral Palsy
  21% vs 36%

- Risk of moderate to severe disability
  22% vs 37%
Unanswered Questions Regarding Hypothermia

- What is the most effective technique, selective head or whole body cooling?
- What is the most effective temperature and duration of cooling?
- What is the safest timing and method of rewarming?
- What is the long term outcome at school age and beyond?
- Which subgroups are most likely to benefit?
- What is the optimal age to institute hypothermia and when is it too late?
- Is cooling on transport appropriate and safe?

Conclusions: Both head and body cooling decrease the outcome of death or major disability. However, body cooling significantly decreases mortality, neuromotor disability, and developmental delay but head cooling does not. This finding may be due to small sample size.

It is not possible to determine if one method is preferable to another.

Optimizing (longer, deeper) cooling for neonatal HIE

Study design: Multi-center, randomized, non-masked with factorial design

Eligibility: Same NICHD criteria

Intervention: 33.5 C x 72 hours, 33.5 C x 120 hour, 32 C x 72 hours, 32 C x 120 hours

1° outcome: Death or moderate/severe disability at 18-22 months of age

Sample size: 726 (stopped after enrollment of 364 patients)

PI Dr. Seetha Shankaran
ClinicalTrials.gov NCT01192776
Optimizing cooling for neonatal HIE: NICHD trial results

In-hospital mortality rates for the four treatment groups were:
- 33.5°C for 72 h: 7%
- 32.0°C for 72 h: 14%
- 33.5°C for 120 h: 16%
- 32.0°C for 120 h: 17%

The in-hospital mortality rate for the control arm was unexpectedly low and the reason was not identified.

The mortality rates for all arms of the trial were lower than the cooled arm of our original hypothermia trial.

Cooling for 120 hours or 32°C may be harmful.

Study Design: Multi-center, unmasked, Bayesian analysis

Eligibility: 33 0/7 – 35 6/7 weeks and ≥1500 g + usual NICHD criteria

Intervention: Whole body cooling to esophageal T 33.5 C x 72 hours or control

1° outcome: Death or moderate/severe disability at 18-22 months of age

Sample size: Data are insufficient to predict enrollment, a Bayesian approach is planned. Enrollment for at least 2 years

PI Dr. Roger Faix
ClinicalTrials.gov NCT01793129
Should a baby be cooled after 6 hours?

How this happens:

– Arrive at a cooling center after 6 hrs of age
– Progress from stage I to II/III encephalopathy after 6hrs of age
– Are not recognized to qualify until after 6hrs of age
– Cooling cannot be initiated within 6 hrs of age (equipment or personnel not available)
Effects in delaying Cooling for the treatment of HIE

Parasagittal Neuronal Loss (%)

Time Delay in Initiation of Cooling

- Control
- 1.5 h
- 5.5 h
- 8.5 h

Study design: Multi-center, randomized, non-masked, Bayesian analysis

Eligibility: 6-24 hours of age with evidence of moderate or severe encephalopathy

Intervention: Whole body cooling to esophageal temperature 33.5 C x 96 hours or control

1° outcome: Death or moderate/severe disability at 18-22 months of age

Sample size: 168 (current enrollment is 161)

PI Dr. Abbot Laptook
ClinicalTrials.gov NCT00614744
California Cooling Centers: Challenges to cool by 6 hours of age
NICU admit temperatures for newborns cooled in transport

- 43% above target
- 44% at target
- 13% below target

Akula VP et al., *J Perinatol* 2012
RCT of therapeutic hypothermia during transport for HIE: Device regulated cooling versus standard practice

Arm 1: Passive/active hypothermia per usual center practice

Arm 2: Device-regulated hypothermia using Tecotherm Neo

Hypothesis: Device regulated cooling will result in improved temperature profiles during neonatal transport for HIE when compared to standard practice.

Trajectory of temperatures every 15 minutes during transport
## Results: Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Device (n=51)</th>
<th>Standard (n=49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome:</strong> Temperature in target range during transport (%) median (IQR)</td>
<td>71 (17-89)</td>
<td>0 (0-52)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Secondary Outcome:</strong> Subjects in target range at 1 hour (%)</td>
<td>72</td>
<td>20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Subjects in target temperature range anytime during transport n (%)</td>
<td>41 (80)</td>
<td>24 (49)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Time to target temperature (minutes)</td>
<td>44 ± 31</td>
<td>63± 37</td>
<td>0.038</td>
</tr>
</tbody>
</table>
Cellular mechanisms of cellular injury induced by HIE

Muller A J, and Marks J D Neoreviews 2014;15:e177-e186
Adjunctive Therapies

- Data from animal models suggest that neurologic outcome after HIE can be improved by adding adjuvant therapies to hypothermia

- Promising agents
  - Antiepileptic drugs
  - *Erythropoietin
  - *Xenon
  - Melatonin
  - Anesthesia (cerebral metabolism, suppression seizures, sympathetic discharge, inhibiting glutamine release, activating inhibitory GABA, minimizing intracellular Ca$^{2+}$)
  - * Stem cells
EFFICACY OF INTRAVENOUS LEVETIRACETAM IN NEONATAL SEIZURES

- *phase 2 blinded controlled* study of the efficacy of intravenous LEV as *first line* treatment for neonatal seizures in patients with HIE. Our further aim is to obtain dose escalation safety and efficacy information in order to optimize the dose used in this emergent setting.

Richard Hass M.D., Jose Honold M.D., Brian Lane M.D., Mark Nespecac M.D., Jonathan Bui M.D., Mary Harbert M.D.
History of Erythropoietin.

1906 Hemopoiandin Hypothesized (Carnot)
1977 Epo isolated from urine (Miyake)
1985 Cloned (Lin)
1989 FDA approved Epogen®
1994 – Epo is expressed in brain (Masuda)

Neuroprotection Studies

1987 1st clinical trial chronic kidney disease

2008 FDA hold
2009-2010 Epo Studies Resuming
Multiple dosis of Epo, much better!

Gonzalez et al, Dev Nsci

* : p<0.05 vs. VO
• To date – 2 trials in term infants with HIE
• Zhu, et al, Epo (n=83), conventional (n=84), reduced disability for moderate HIE at 18mo. Significant only in patients with moderate injury
• Combination therapy – hypothermia
OBJECTIVES: The purpose of this study was to evaluate the efficacy and safety of erythropoietin in neonatal hypoxic-ischemic encephalopathy (HIE), by using a randomized, prospective study design.

METHODS: 167 newborns with moderate/severe HIE were assigned randomly to receive either erythropoietin (N = 83) or conventional treatment (N = 84). rEPO, at either 300 U/kg (N = 52) or 500 U/kg (N = 31), administered every other day for 2 weeks, starting <48 hours after birth.

The primary outcome was death or disability. Neurodevelopmental outcomes were assessed at 18 months of age.
(EPO) trial profile.

Erythropoietin (EPO) concentrations in serum (A) and CSF (B) after subcutaneous administration
### Outcomes at 18 Months of Age for Erythropoietin and Control Groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Erythropoietin (N = 73)</th>
<th>Control (N = 80)</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3/73 (4.1)</td>
<td>4/80 (5.0)</td>
<td>0.89 (0.37–2.13)</td>
<td>&gt;.999</td>
</tr>
<tr>
<td>Disability</td>
<td>15/70 (21.4)</td>
<td>31/76 (40.8)</td>
<td>0.59 (0.38–0.93)</td>
<td>.013</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or disability</td>
<td>18/73 (24.6)</td>
<td>35/80 (43.8)</td>
<td>0.62 (0.41–0.94)</td>
<td>.017</td>
</tr>
<tr>
<td>Moderate HIE</td>
<td>3/47 (6.4)</td>
<td>19/59 (32.2)</td>
<td>0.26 (0.09–0.76)</td>
<td>.001</td>
</tr>
<tr>
<td>Severe HIE</td>
<td>15/26 (57.7)</td>
<td>16/21 (76.2)</td>
<td>0.70 (0.43–1.15)</td>
<td>.227</td>
</tr>
<tr>
<td>Male</td>
<td>17/57 (29.8)</td>
<td>25/55 (45.5)</td>
<td>0.71 (0.47–1.08)</td>
<td>.118</td>
</tr>
<tr>
<td>Female</td>
<td>1/16 (6.3)</td>
<td>10/25 (40.0)</td>
<td>0.18 (0.03–1.22)</td>
<td>.029</td>
</tr>
<tr>
<td>MDI of &lt;70</td>
<td>7/70 (10.0)</td>
<td>17/76 (22.4)</td>
<td>0.56 (0.30–1.08)</td>
<td>.048</td>
</tr>
<tr>
<td>Moderate HIE</td>
<td>2/47 (4.3)</td>
<td>9/57 (15.8)</td>
<td>0.38 (0.11–1.34)</td>
<td>.106</td>
</tr>
<tr>
<td>Severe HIE</td>
<td>5/23 (21.7)</td>
<td>8/19 (42.1)</td>
<td>0.62 (0.29–1.30)</td>
<td>.193</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>5/70 (6.8)</td>
<td>14/76 (18.4)</td>
<td>0.51 (0.23–1.11)</td>
<td>.051</td>
</tr>
<tr>
<td>Moderate HIE</td>
<td>1/47 (2.1)</td>
<td>8/57 (14.0)</td>
<td>0.23 (0.04–1.47)</td>
<td>.039</td>
</tr>
<tr>
<td>Severe HIE</td>
<td>4/23 (17.4)</td>
<td>6/19 (31.6)</td>
<td>0.67 (0.30–1.52)</td>
<td>.468</td>
</tr>
</tbody>
</table>
Erythropoietin improved neurologic outcomes in newborns with Hypoxic-Ischemic Encephalopathy.

PEDIATRICS Vol. 124 No. 2 August 1, 2009

RESULTS: Complete outcome data were available for 153 infants. Death or moderate/severe disability AT 18 months occurred for;

35 (43.8%) control group
18 (24.6%) erythropoietin group.

CONCLUSION: Repeated, low-dose, recombinant human erythropoietin treatment reduced the risk of disability for infants with moderate HIE, without apparent side effects.
ERYTHROPOIETIN FOR NEUROPROTECTION IN NEONATAL ENCEPHALOPATHY: SAFETY AND PHARMACOKINETICS

- Wu Y W et al. Pediatrics
  October, 2012;130:683-691
Mean plasma Epo concentrations measured in infants who received 250, 500, 1000, or 2500 U/kg Epo in conjunction with hypothermia.

Wu Y W et al. Pediatrics 2012;130:683-691

©2012 by American Academy of Pediatrics
The purpose of this study is to determine the efficacy of high dose Erythropoietin to improve survival and neurologic outcome in asphyxiated term newborn undergoing cooling.

- **Primary Outcome Measures:**
  Survival without neurologic sequelae

- **Secondary Outcome Measures:**
  Mortality rates
  Rate of moderate and severe sequelae
  Aspect of brain lesions on MRI
  Tolerance of treatment
Efficacy of Erythropoietin to Improve Survival and Neurological Outcome in Hypoxic Ischemic Encephalopathy (Neurepo)

- Erythropoietin beta: 1000 to 1500 U/kg/dose X 3 doses every 24 hours with the first dose within 12 hours of delivery

- Placebo: 0.2 ml saline solution X 3 doses given every 24 hours with the first dose within 12 hours of delivery
Xenon (Xe)

- Rare, expensive, anesthetic gas
- Anesthetic properties – 1950’s
- No documented adverse effects
- 1998 – First report of neuronal protection
- NMDA receptor antagonist
- Reducing apoptosis/necrosis
- Other interactions
- Rapidly reversed
- Research in adults – safe for anesthesia
- Expensive and requires a special delivery system
Xenon (Xe)

- Combining Xe_{50\%} and HT in neonatal rat model of HI-stroke
- 71\% neuroprotection and long-lasting functional improvement vs. 52\% protection with HT alone (2009, Thoresen)
Pig model – Xe/HT

- 48% neuroprotection - 24hr HT
- 28% neuroprotection - 18 hr Xe 50%
- 76% neuroprotection - combo

*Thoresen et al, Ann Neurol 2010*
Xenon - future

• Clinical trials
  – Neonatal asphyxia
  – Cardiopulmonary bypass
  – Cardiac arrest
You want to be a brain cell? You have to study! You goof off - you'll end up in the rectum!
Possible biomarkers of neonatal brain injury.

Douglas-Escobar M, and Weiss MD. *NeoReviews* 2013;14:e501-e512

©2013 by American Academy of Pediatrics
Conclusions

• The use of therapeutic hypothermia for term and near term infants with moderate to severe HIE represents one of the major advances in neonatal care of the last two decades.

• Therapeutic hypothermia should be limited to those infants found to benefit in the randomized clinical trials.

• There are a number of unanswered questions that require additional study.

• Work is needed to disseminate this intervention so all eligible infants with HIE can benefit.