Screening and Identification of Newborns Eligible for Therapeutic Hypothermia

Krisa Van Meurs, M.D.
Rosemarie Hess Professor of Neonatal and Developmental Medicine
Medical Director, Neuro NICU

Sonia Bonifacio, M.D.
Associate Professor Neonatal and Developmental Medicine
Associate Medical Director, Neuro NICU

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Causes of neonatal mortality

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

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

The therapeutic window is ~6 hours, the duration of the latent phase between primary and secondary energy failure.
Phases of Cerebral Injury

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

**Latent**
- 6 to 15 h
- Recovery of oxidative metabolism vs residual mitochondrial injury
- Apoptotic cascade
- 2nd Inflammation
- Receptor hyperactivity

**Secondary**
- From 6 h to >3 days
- Deteriorating mitochondrial function
- Seizures
- Cytotoxic edema
- Excitotoxins
- Final cell death

**Reperfusion**

Hypothermia probably impacts many of these pathways

<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>
**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.
Recommendations for use of Hypothermia

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.

AAP Committee on Fetus and Newborn. *Pediatrics* (2014)

Newborns with moderate to severe HIE should be offered hypothermia

- Treatment should be consistent with trial protocols.

CPQCC Tool Kit Screening Criteria

Birth

≥36 weeks
≤6 hours

0 - 10 mins

Apgar ≤6 at 10 min
History of acute perinatal event
Continued PPV at 10 min or CPR
Cord blood gas pH ≤7.15 or BE ≤-10

10 - 60 mins

- Request cord blood gas
- Obtain blood gas at ≤1 hour of age
- Perform targeted neurologic exam using chart below
- Observe for seizures

60 - 120 mins

Call LPCH Attending Neonatologist at (650) 723-7342 to discuss the need for transfer and cooling

Download Toolkit @ www.cpqcc.org
### 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>Infant should have:</td>
<td>or pH 7.01 - 7.15,</td>
</tr>
<tr>
<td>▪ Cord or first postnatal</td>
<td>▪ Base deficit 10 - 15.9mEq/L</td>
</tr>
<tr>
<td>blood gas within 1 hour</td>
<td>or</td>
</tr>
<tr>
<td>with pH ≤ 7.0</td>
<td>▪ Apgar score ≤ 5 at 10 minutes</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>▪ Base deficit on cord gas</td>
<td>▪ Continued need for ventilation at</td>
</tr>
<tr>
<td>or first postnatal blood</td>
<td>10 minutes</td>
</tr>
<tr>
<td>gas within 1 hour at ≥16</td>
<td></td>
</tr>
<tr>
<td>mEq/L</td>
<td></td>
</tr>
</tbody>
</table>


The modified Sarnat exam

• Six categories (level of consciousness, spontaneous activity, posture, tone, primitive reflexes, and autonomic system)

• To be eligible for hypothermia:
  – 3 of 6 categories have to be coded as either moderate or severe encephalopathy
# MODIFIED SARNAT EXAM

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>MODERATE HIE</th>
<th>SEVERE HIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Level of consciousness</td>
<td>2 = Lethargic</td>
<td>3 = Stupor/coma</td>
</tr>
<tr>
<td>2. Spontaneous Activity</td>
<td>2 = Decreased activity</td>
<td>3 = No activity</td>
</tr>
<tr>
<td>3. Posture</td>
<td>2 = Distal flexion, complete extension</td>
<td>3 = Decerebrate</td>
</tr>
<tr>
<td>4. Tone</td>
<td>2a = Hypotonia (focal or general)</td>
<td>3a = Flaccid</td>
</tr>
<tr>
<td>5. Primitive Reflexes</td>
<td>2 = Weak or has bite</td>
<td>3 = Absent</td>
</tr>
<tr>
<td>Suck</td>
<td>2 = Incomplete</td>
<td>3 = Absent</td>
</tr>
<tr>
<td>Moro</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Autonomic System</td>
<td>2 = Constricted</td>
<td>3 = Deviation/dilated/ or nonreactive to light</td>
</tr>
<tr>
<td>Pupils</td>
<td>2 = Bradycardia</td>
<td>3 = Variable HR</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>2 = Periodic breathing</td>
<td>3a = on vent with spontaneous respirations</td>
</tr>
<tr>
<td>Respiration</td>
<td></td>
<td>3b = on vent without spontaneous breathes</td>
</tr>
</tbody>
</table>
Sarnat & Sarnat - 1976

- 21 patients evaluated every 12-24 hours daily for 6 days, then every other day till discharge
- Follow-up at 3, 6, 9, 12 months (only 2 seen at 1 year of age)
- Stage of encephalopathy is NOT static
- Evolution over first hours to days
- Stage 1 → 2 → 3
- Serial exams are important if on the fence
- Once you meet criteria you do not reassess with thought of recovery and not cooling the patient
Neurologic exams after birth

Challenging assessments

- Transient effects of delivery, anesthesia, analgesia
- Examination findings may improve or get worse
  - Severity and timing of hypoxia-ischemia
  - Compensatory hemodynamic changes
  - Endogenous CNS protective mechanisms
- Associated conditions: Respiratory distress
- Simultaneous mix of neurological findings
  - Components of none/mild, moderate or severe encephalopathy
Spontaneous activity

- Evaluate Spontaneous activity
  - Code 1 if infant is active
  - Code 2 if activity is decreased
  - Code 3 if no activity

If infant is sedated clinical judgment has to be used to decide whether the examination is reliable.

Paralysis will preclude a meaningful exam.

The transport team and clinical team should be aware of need for this exam without sedation.
Posture

• Observe infant in awake state; **assess lower extremity**
  – Code 1 if infant is moving around and does not maintain one posture, should have flexion of lower extremity at hip and/or knees
  – Code 2 if strong **distal** flexion, complete extension or “frog-legged” position
  – Code 3 if decerebrate with or without stimulation
Level of consciousness

– Code 1 if infant arouses to wakefulness, responds appropriately and promptly to external stimuli, or appears hyperalert or inconsolable/irritable

– Code 2 if lethargic: delayed but complete response to external stimuli (start with mild stimuli first then proceed to more noxious stimuli)

– Code 3 if stupor/coma: infant is not arousable and is non-responsive to external stimuli; may have a delayed but incomplete response to stimuli

LOC: may be the deciding factor to assign HIE stage
Tone

• Response to passive movement: **assess lower extremity**
  
  – Code 1 if there is normal resistance
  – Code 2:
    – 2a if hypotonic or floppy either focal or generalized
  – Code 3:
    – 3a if flaccid (like a rag doll)

Evaluate extremities, trunk and neck tone and make clinical judgment of tone based on tone in these areas. If responses differ in multiple areas, base code on the lower extremity

If varying tone, code the predominant state
Primitive Reflexes
Suck and Moro
Suck

- Code 1 if the infant vigorously sucks the examiners finger or the endotracheal tube
  –Code 2 if suck is weak or if infant bites
  –Code 3 if suck is absent
Moro

– Code 1 if Moro is normal with extension of limbs followed by flexion with stimulus (gently raising and lowering the head)
– Code 2 if incomplete
– Code 3 if absent

If neonate has fracture of clavicle or brachial plexus injury, evaluate other extremity
Moro has to be done by gently raising and lowering the head when infant is intubated
Autonomic System

Pupils, Heart Rate and Respiration
ANS – Pupils

– Code 1 if normal in size and reactive to light
– Code 2 if constricted and reacting to light
– Code 3 if skew deviation of eyes, pupils are dilated or non-reactive to light
  • If pupils asymmetric, assign 3

Pupils are difficult to assess in the newborn infant with edema of eyelids---you will need to gently separate the eyelids while a second person shines light
ANS – Heart rate

- **HR**
  - Code 1 if >100 per min consistently or tachycardia
  - Code 2 if bradycardia (< 100/min) with only occasional increases to >120/min
  - Code 3 if heart rate is not constant and varies widely between <100 and > 120

Heart rate should be evaluated based on documented rate over the previous min/hrs

Do not code heart rate if cooling has been initiated
ANS - Respiration

– Code 1 if breathing spontaneously
– Code 2 if periodic breathing
– Code 3 if apnea or requiring ventilator support:
  3a, if spontaneous breaths above the ventilator
  3b, if no spontaneous breaths above the vent

An intubated infant with spontaneous breaths would still be coded as 3 as it cannot be ascertained if the spontaneous breaths can sustain respiration without ventilator support
Oxygen concentration should be weaned as soon as the heart rate recovers. In addition, aggressive recognition and management of seizures, which can occur in 50% of these infants, is recommended. aEEG is useful for continuous monitoring and detection of subclinical seizures during hypothermia and rewarming. (13)

**HYPOTHERMIA IN RESOURCE-LIMITED AREAS**

Induced hypothermia in term infants with moderate to severe HIE in resource-limited countries was reviewed by the NRP committee in 2015. For death or disability, low-quality evidence showed the use of therapeutic hypothermia to be beneficial (odds ratio [OR], 0.43; 95% confidence interval [CI], 0.26 – 0.7). For death and developmental follow-up, low-quality evidence showed no benefit of therapeutic hypothermia (OR, 0.72; 95% CI, 0.44 – 1.16).

The NRP 2015 recommendations were that use of therapeutic hypothermia in resource-limited settings may be considered and offered, but only under clearly defined protocols similar to those used in published clinical trials and in facilities with the capabilities for multidisciplinary care and longitudinal follow-up. Knowledge gaps were recognized with lack of adequately powered randomized controlled trials.

**MILD NEONATAL ENCEPHALOPATHY**

Current published protocols from randomized trials do not describe cooling for newborns with mild encephalopathy. However, it has been recognized that the level of encephalopathy may change over time. Preliminary observations from the current author’s group indicate that 20% of infants with mild encephalopathy can have neurologic abnormalities at discharge or evidence of brain injury on magnetic resonance imaging (MRI) performed during the neonatal period. (14) Unfortunately, precise data on the outcomes of this specific population are not available because of the retrospective nature of these studies and the absence of randomized trials. An ongoing multicenter observational prospective study is underway to determine the natural history of infants with early diagnosis (< 6 hours of age) of mild neonatal encephalopathy, who are not candidates for therapeutic hypothermia. The intervention includes the

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**TABLE 2. Classification of the Neurologic Examination Findings**

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>NORMAL</th>
<th>STAGE 1 (MILD)</th>
<th>STAGE 2 (MODERATE)</th>
<th>STAGE 3 (SEVERE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>0 = Alert, responsive to external stimuli (state-dependent, eg, postfeeds)</td>
<td>1 = Hyper-alert, apparent awareness, responds to minimal stimuli</td>
<td>2 = Lethargic</td>
<td>3 = Stupor/coma</td>
</tr>
<tr>
<td>Spontaneous activity</td>
<td>0 = Changes position when quiet</td>
<td>1 = Normal or decreased</td>
<td>2 = Decreased</td>
<td>3 = None</td>
</tr>
<tr>
<td>Posture</td>
<td>0 = Predominately flexed when quiet</td>
<td>1 = Mild flexion of distal joints (fingers, wrist usually)</td>
<td>2 = Distal flexion, complete extension</td>
<td>3 = Decerebrate</td>
</tr>
<tr>
<td>Tone</td>
<td>0 = Strong flexor tone in all extremities</td>
<td>1 = Normal or slightly (†)</td>
<td>2a = Hypotonia (focal or general)</td>
<td>3a = Flaccid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2b = Hypertonia</td>
<td>3b = Rigid</td>
</tr>
<tr>
<td>Primitive reflexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suck</td>
<td>0 = Strong, easily elicited</td>
<td>1 = Weak or Incomplete</td>
<td>2 = Weak or incomplete and/or bite</td>
<td>3 = Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>0 = Complete</td>
<td>1 = Intact, low threshold to elicit</td>
<td>2 = Incomplete</td>
<td>3 = Absent</td>
</tr>
<tr>
<td>Automatic system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupils</td>
<td>0 = Normal, reactive</td>
<td>1 = Mydriasis</td>
<td>2 = Myosis</td>
<td>3 = Variable/ nonreactive to light</td>
</tr>
<tr>
<td>HR</td>
<td>0 = 100–160 bpm</td>
<td>1 = Tachycardia</td>
<td>2 = Bradycardia</td>
<td>3 = Variable HR</td>
</tr>
<tr>
<td>Respirations</td>
<td>0 = Regular respirations</td>
<td>1 = Hyperventilation</td>
<td>2 = Periodic breathing</td>
<td>3 = Apnea or requires ventilation</td>
</tr>
</tbody>
</table>
The Neurologic Exam for Neonates with Suspected Encephalopathy

Encephalopathy is defined by the presence of one or more signs in at least three of the following six categories:

- level of consciousness
- spontaneous activity
- posture
- tone
- primitive reflexes
- autonomic nervous system

When findings are mixed, the extent of encephalopathy is determined by which category describes the majority of signs. If signs were equally distributed, categorize based on the level of consciousness.
Important pointers

- If after DR resuscitation, the Sarnat exam shows evidence of moderate or severe encephalopathy (abnormalities in ≥3 categories), the newborn should be cooled as long as there are no exclusions and the other laboratory/historical criteria are met.

- Improvement or changes in the Sarnat exam over time are the norm and should not be interpreted as negating the overall risk of HIE and adverse neurodevelopmental outcome.

- Newborns with laboratory or historical data making them potentially eligible with an initial Sarnat exam that is normal or mild must be examined hourly for changes in the Sarnat exam.