PERINATAL ASPHYXIA

NEONATAL THERAPEUTIC HYPOTHERMIA

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Asphyxia

From Greek [ἀσφυξία]: “A stopping of the pulse”

“Loss of consciousness as a result of too little oxygen and too much CO₂ in the blood: suffocation causes asphyxia”

(Webster’s New World Dictionary)
On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum, on the mental and physical condition of the child, especially in relation to deformities.

By W. J. Little, MD (Transactions of the Obstetrical Society of London 1861;3:243-344)

General spastic contraction of the lower extremities. Premature birth. Asphyxia neonatorum of 36 hr duration. Hands unaffected. (Case XLVII)

Perinatal hypoxic-ischemic encephalopathy (HIE)

- Associated with high neonatal mortality and severe long-term neurologic morbidity
- Hypothermia is rapidly becoming standard therapy for full-term neonates with moderate-to-severe HIE
- Occurs at a rate of about 3/1000 live-born infants in developed countries, but the rate is estimated to be higher in the developing world
- Intrapartum-related neonatal deaths (previously called “birth asphyxia”) are the fifth most common cause of deaths among children under 5 years of age, accounting for an estimated 814,000 deaths each year, and also associated with significant morbidity, resulting in a burden of 42 million disability adjusted life years (DALYs).

When is encephalopathy caused by HIE?

If encephalopathy is moderate-severe + . . .

A. Apgar score < 5 at 5 and 10 minutes
B. Acidemia of fetal umbilical artery (pH < 7.0 and BE > -12)
C. Neuroimaging evidence of acute brain injury on brain MRI or MR Spectroscopy consistent with hypoxia–ischemia
D. Multisystem organ failure

→ HIE is the most likely cause of encephalopathy

*2014 Task Force on Neonatal Encephalopathy, American College of Obstetricians and Gynecologists

Courtesy Yvonne Wu, MD, MPH - UCSF
Hypoxic-Ischemic Brain Injury in Full Term Newborn

http://neonatology.ucsf.edu/specialized-care/cerebral-palsy.aspx

Courtesy Yvonne Wu, MD, MPH - UCSF
HIE

- Single largest contributor to perinatal mortality
  - mortality \( \uparrow \) 2-20x in PT infants
  - mortality \( \uparrow \) 200x in Term infants
According to the World Health Organisation, worldwide the three main causes of neo-natal deaths are asphyxia at birth; low birth weight including prematurity; and infections. Access to healthcare can reduce these deaths.
Setting Research Priorities to Reduce Almost One Million Deaths from Birth Asphyxia

814,000
(0.56 – 0.99 million)
neonatal deaths related to intrapartum events

Newborns with neonatal encephalopathy related to acute intrapartum events*

Children and adults long term impairment subsequent to acute intrapartum events*

Inadequate coverage and quality of intrapartum care
60 million births at home each year

Figure 1. The burden of intrapartum-related neonatal deaths, intrapartum stillbirths, maternal deaths, and the unknown associated burden of neonatal morbidity and disability. Data sources: neonatal deaths [13], stillbirths [15,16], maternal deaths [48], place of birth [8]. No systematic estimates are currently available.
doi:10.1371/journal.pmed.1000389.g001
Incidencia y prevalencia de la encefalopatía hipoxico-isquémica en la primera década del siglo XXI

A. García-Alix*, M. Martínez-Biarge, J. Diez, F. Gayá y J. Quero

Grave
Moderada
Leve

Severity of HIE

Decreasing incidence of HIE
Insults e.g. Asphyxia, Impaired perfusion

Mechanisms of perinatal brain injury

Opportunity for neuronal rescue

Primary neuronal death

Cytotoxic mechanisms

Delayed neuronal death
Physiopathological processes of hypoxic-ischemic encephalopathy

Fig 1. Phases of energetic failure

- Primary phase
- Secondary phase
  - Worsening mitochondrial function and excitotoxic damage

Therapeutic window
- Start hypothermia
- Stable temperature 33-34°C

Hours post-event
- 0
- 1
- 2
- 46
- 8
- 10
- 12
- ...
- 72 h.

Oxidative metabolism
- Recovery of oxidative metabolism

PCR/Pi (Phosphocreatinr/inorganic P)

Cell death
Excito-oxidative cascade of events that mediate hypoxic-ischaemic brain injury

Johnston et al. – Lancet 2011 Apr; 10: 372-382
ASSESSMENT TOOLS OF HIE- EEG

A) NORMAL:
- Upper margin >10
- Lower margin >5 µV

B) MODERATELY ABNORMAL:
- Upper margin >10
- Lower margin = 5 µV

C) SUPPRESSED AMPLITUDE:
- Upper margin <10
- Lower margin <5 µV
  (also seen -“Burst suppression”)
RECOMENDACIONES TERAPÉUTICAS DEL VII
CONSENSO CLÍNICO DE SIBEN PARA LA
ENCEFALOPATÍA HIPÓXICO-ISQUÉMICA
NEONATAL

Maria de Lourdes Lemus-Varela, MD, Augusto Sola, MD, Sergio G. Golombek, MD, MPH, Hernando Baquero, MD, Carmen R. Dávila-Aliaga, MD, Diana Fariña, MD, Maria Victoria Lima-Rogel, MD, Ramon Mir Villamayor, MD, Freddy Neira, MD, Ada N. Oviedo-Barrantes, MD, Alfredo García-Alix, MD, PhD, y los participantes del VII Consenso Clínico de SIBEN.

NeoReviews 2016;17;e554-e567
HIE is a clinical syndrome of acute neurologic dysfunction of variable severity that occurs after an episode of asphyxia during birth.

It is a major cause of morbidity and mortality in the newborn and long-term disability, and has a very high socioeconomic cost to families and society.
PROGNOSIS

- **Moderate HIE:**
  - Risk of death close to 10%
  - Disability in 30-40% of the survivors

- **Severe HIE:**
  - Risk of death close to 60%
  - Disability on *most* of the survivors
<table>
<thead>
<tr>
<th>Mecanismos potenciales de acción de la hipotermia moderada</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Reduce gradualmente la depleción de ATP. Por cada grado Celsius de reducción: ↓ 5% el metabolismo cerebral</td>
</tr>
<tr>
<td>- Reduce la acumulación de aminoácidos excitotóxicos</td>
</tr>
<tr>
<td>- Reduce la producción de óxido nítrico y suprime la síntesis explosiva de radicales libres</td>
</tr>
<tr>
<td>- Puede suprimir la reacción inflamatoria</td>
</tr>
<tr>
<td>- Reduce la activación microglial</td>
</tr>
<tr>
<td>- Inhibe el programa de muerte celular o apoptosis</td>
</tr>
<tr>
<td>- Prolonga la ventana terapéutica</td>
</tr>
</tbody>
</table>
TABLA 2. Criterios empleados para incluir a los neonatos con EHI a hipotermia

**Encefalopatía neonatal moderada o grave** en neonatos con edad gestacional ≥35 semanas de gestación y edad postnatal ≤6 horas. Algunos grupos utilizan el EEG de amplitud integrada (aEEG) como un subrogado para establecer la gravedad de la EHI, con base a la gravedad de la alteración del trazado eléctrico.

**Antecedentes de potencial agresión hipóxico-isquémica alrededor del parto;** evento centinela (desprendimiento prematuro de placenta, rotura uterina, exanguinación fetal, plopaso de cordón o nudo verdadero de cordón umbilical) o estado fetal no tranquilizador (registro cardio-tocográfico fetal anormal).

**Alteración del estado al nacimiento:**

a) Apgar ≤ 5 a los 10 minutos de edad postnatal.

b) pH ≤7,0, déficit de base ≥ -16mEq/L en sangre arterial de cordón umbilical o en sangre venosa dentro de la primera hora tras el nacimiento.

c) Necesidad de ventilación mecánica durante por lo menos 10 minutos después del nacimiento.

d) Necesidad de reanimación cardiopulmonar avanzada.
**CLINICAL STAGES OF ENCEPHALOPATHY (SARNAT)**

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>1. Duration &lt; 24 h with hyperalertness</th>
<th>2. Uninhibited Moro and stretch reflexes</th>
<th>3. Sympathetic effects</th>
<th>4. Normal EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>1. Obtundation</td>
<td>2. Hypotonia</td>
<td>3. Decreased spontaneous movements with or without seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5. The EEG may be isopotential or have infrequent periodic discharges</td>
</tr>
</tbody>
</table>
## MODIFIED SARNAT (SEVERITY OF ENCEPHALOPATHY)

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of consciousness (LOC)</strong></td>
<td>Hyperalert or irritable</td>
<td>Lethargic or poorly responsive</td>
<td>Minimal or no responsiveness</td>
</tr>
<tr>
<td><strong>Spontaneous Activity</strong></td>
<td>Slightly decreased</td>
<td>Decreased</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Posture</strong></td>
<td>Mild distal flexion</td>
<td>Distal flexion, complete extension</td>
<td>Decerebrate</td>
</tr>
<tr>
<td><strong>Tone</strong></td>
<td>Hypertonic</td>
<td>Hypotonic</td>
<td>Flaccid</td>
</tr>
<tr>
<td><strong>Primitive Reflexes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suck</td>
<td>N/A</td>
<td>Weak or bites</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>Low threshold to elicit</td>
<td>Weak or incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Autonomic System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupils</td>
<td>N/A</td>
<td>Constricted</td>
<td>Dilated and fixed/sluggish; asymmetric</td>
</tr>
<tr>
<td>Respiration</td>
<td>N/A</td>
<td>Periodic breathing</td>
<td>Intubated and ventilated</td>
</tr>
</tbody>
</table>

*Severity = 3 or more present in a category; LOC breaks ties*
## Clinical hypoxic-ischemic encephalopathy score of the Iberoamerican Society of Neonatology (Slben): A new proposal for diagnosis and management

**Jose Maria Rodriguez Perez, Sergio G. Golombek, Augusto Sola**

### TABLE 1. Slben Neurological Score.

<table>
<thead>
<tr>
<th>HIE</th>
<th>Level of consciousness</th>
<th>Spontaneous activity</th>
<th>Posture</th>
<th>Tonus</th>
<th>Suction</th>
<th>Moro reflex</th>
<th>Pupils</th>
<th>Heart rate</th>
<th>Breathing</th>
<th>Convulsion</th>
<th>Total points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Hyperalert</td>
<td>Normal</td>
<td>Mild distal flexion</td>
<td>Normal</td>
<td>Weak</td>
<td>Strong</td>
<td>Mydriasis</td>
<td>Tachycardia</td>
<td>Spontaneous</td>
<td>Absent</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>Lethargy</td>
<td>Decreased</td>
<td>Marked distal flexion</td>
<td>Hypotonia</td>
<td>Weak or absent</td>
<td>Weak</td>
<td>Miosis</td>
<td>Bradycardia</td>
<td>Periodic</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Stupor/Coma</td>
<td>Not present</td>
<td>Decerebration</td>
<td>Flaccidity</td>
<td>Not present</td>
<td>Not present</td>
<td>Deteriorated/ Non-reactive</td>
<td>Variable</td>
<td>Apnea</td>
<td>Infrequent</td>
<td></td>
</tr>
</tbody>
</table>

HIE: hypoxic ischemic encephalopathy.
**HIE: Diagnosis**

**Table 2** Clinical alterations compatible with HIE.

<table>
<thead>
<tr>
<th>Clinical alteration</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lethargy</td>
<td>18 (69.2%)</td>
</tr>
<tr>
<td>Stupor/Coma</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>Mild distal flexion</td>
<td>9 (34.6%)</td>
</tr>
<tr>
<td>Marked distal flexion</td>
<td>12 (46.15%)</td>
</tr>
<tr>
<td>Decerebration</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>16 (61.5%)</td>
</tr>
<tr>
<td>Flaccidity</td>
<td>10 (38.4%)</td>
</tr>
<tr>
<td>Weak suction</td>
<td>18 (69.2%)</td>
</tr>
<tr>
<td>No suction</td>
<td>8 (30.7%)</td>
</tr>
<tr>
<td>Weak Moro reflex</td>
<td>19 (73.07%)</td>
</tr>
<tr>
<td>No Moro reflex</td>
<td>7 (26.9%)</td>
</tr>
<tr>
<td>Pupils mydriasis/miosis</td>
<td>20 (76.9%)</td>
</tr>
<tr>
<td>Non-reactive pupils</td>
<td>6 (23.07%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>14 (53.8%)</td>
</tr>
<tr>
<td>Bradycardia/Tachycardia</td>
<td>12 (46.15%)</td>
</tr>
<tr>
<td>Periodic respiration</td>
<td>20 (76.9%)</td>
</tr>
<tr>
<td>Apnea</td>
<td>6 (23.07%)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>14 (53.8%)</td>
</tr>
</tbody>
</table>

HIE: hypoxic ischemic encephalopathy.
FIGURE 1 The flowchart summarizes the basic preventive and therapeutic measures of the Siben Neurological Score.

HIE: hypoxic ischemic encephalopathy; CPK: creatine phosphokinase; LDH: lactic dehydrogenase; NICU: neonatal intensive care unit.
The use of this clinical score can improve the objectivity of the assessment and monitoring of newborns and the early start of treatment.

The use of the SIBEN Neurological Score proved to be easy to implement and provided a more objective and early diagnosis of HIE.

It may be of greater value in poor and/or developing countries, or in neonatal units without access to high-cost diagnostic examinations (imaging, laboratory, and others).
COOLING THE NEWBORN AFTER ASPHYXIA
Westin B et al.
Hypothermia and transfusion with oxygenated blood in the treatment of asphyxia neonatorum
Acta Paed Scand 1962;51:1-80

Kopchev SN.
Cranio-cerebral hypothermia in obstetrics.
Moscow: Medicina, 1985;1-112
NEONATFLOW
Predictive Calculations of Efficacy for Hypothermia to Treat Neonatal HIE

- 15-18 babies are born daily in the U.S. with moderate to severe hypoxic-ischemic encephalopathy.
- 10-12, of the above, die or develop moderate to severe disability.
- Hypothermia to all 15-18 babies would prevent 3 from death or moderate to severe disability without any significant adverse effects.

How does Hypothermia work?

- Traditionally, the protective effect of hypothermia has been attributed to a reduction in metabolic rate (Mayer 2005)

- It is estimated that for each 1°C decrease in temperature, the cerebral metabolic rate decreases by 6 to 7% (Shibuya 2004)
Hypothermia

- Anti-excitotoxic
- Anti-inflammatory
- Anti-oxidant
- Mitochondrial failure reduced
- Anti-apoptosis

Courtesy Yvonne Wu, MD, MPH - UCSF
How does Hypothermia work?

- Reduces cellular metabolic demands, delaying depolarization
- Reduces release of excitatory amino acids (e.g. glutamate) and free radicals
- Reduces intracellular reactions of excitatory amino acids.
- Reduces release of pro-inflammatory cytokines, microglial activation, and neutrophil recruitment
- Reduces abnormally upregulated post-hypoxic glutamate receptor hyperactivity
- Suppression of apoptotic biochemical pathways (e.g. caspase activity)
Who Qualifies for Cooling?

- Gestational Age $\geq 36$ weeks and:
  - Apgar $\leq 5$ at 10 minutes after birth
  - Continued need for resuscitation, including endotracheal or mask ventilation at 10 minutes after birth
  - Acidosis—either cord pH or arterial pH within 60 minutes of life less than 7.0
  - Base deficit greater than or equal to 16 mmol/L in cord blood or any blood sample within 60 minutes of birth (venous or arterial)
Who Qualifies for Cooling? (cont.)

- **Moderate to Severe encephalopathy**
  - Altered state of consciousness-lethargy, stupor, or coma; and at least one of:
    - Hypotonia
    - Abnormal reflexes—including oculomotor or pupillary abnormalities
    - Absent or weak suck
    - Clinical seizures

- **aEEG recording of at least 20 minutes that shows either moderately/severely abnormal aEEG background activity or seizures**
SELECTIVE HEAD HYPOTHERMIA
COOL CAP SYSTEM
Selective Head Cooling

- **Technique**
  - Head is fitted with cooling cap
  - Body is warmed with radiant warmer

- **Advantages**
  - Brain is cooler than the rest of the body
  - Fewer side effects
Contraindications (Cool Cap Trial)

- Imperforate anus
- Evidence of head trauma or skull fracture causing major intracranial hemorrhage
- Birth weight < 1,800g
Whole Body Cooling vs. Selective Head Cooling: Which is best?

- Animal studies indicate that WBC was best between 32-34°C, while 34-35°C might be appropriate for SHC.¹
- Porcine model-larger temperature gradient w/ SHC, which resulted in cooler brain periphery and warmer deeper structures; more homogenous in WBC.²
- Cooling to 33°C preserved more neurons in cortex and hippocampus; cooling to 35°C preserved more neurons in the deep nuclear gray matter.³

TRANSFERRING NEWBORNS FOR COOLING

- Educate staff, especially ‘off-hours’ personnel to recognize eligibility for cooling

- Besides providing cardiorespiratory stability:
  - IV glucose, ASAP
  - Avoid Hyperoxia
  - Avoid Hyperthermia-stop warmer, apply cold pack to sides of head, body-goal 34-35°C rectal
  - Use double lumen UV lines if available, low line OK for $D_{10}$ W
  - Initiate transport call ASAP-prenatally if possible-don’t wait for lines/images/labs
  - Discuss cooling but avoid promises for the use of cooling or favorable outcomes-babies still need to qualify based on aEEG; and outcomes for these babies may still be problematic.
TRANSFERRING NEWBORNS FOR COOLING

- Call NICU or MFCH Transfer Center (1-866-468-6962) ASAP to initiate transport, indicating that the infant may be a candidate for Cooling
- Provide Birth weight, gestational age (> 36 weeks), head circumference
- Baby has to initiate selective head cooling within 6 hours of birth (includes a 20 minute aEEG) - *the sooner the better*, since one may not know the length of compromise prior to delivery
- Protect airway during cooling
IN SUMMARY ...
Hypothermia for HIE

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Cooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or mod-severe disability</td>
<td>62-66%</td>
<td>44-55%</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>30-41%</td>
<td>19-28%</td>
</tr>
</tbody>
</table>

3 largest trials: NICHD, CoolCap, TOBY

Optimal intervention strategy

Relative activity

Hypoxia-ischemia

- pH
- FREE-Iron
- Ca²⁺
- glutamate

0 min 3h 6h 12h 24h days

Hypothermia/NOS-inhibitor/2-IB/anti-oxidants/Xenon (<6h reperfusion/reoxygenation)

Anti-inflammation /anti-apoptosis(<9h reperfusion/reoxygenation): NBD, JBD, EPO

Trophic support: EPO, IGF-1

Stem cells

MOST PROMISING PHARMACOLOGICAL INTERVENTION FOR HIE

1. Ion-channels
   - Calcium blockers (nicardipine, flunarizine)
   - Magnesium
   - Xenon-inhalation

2. Anti-oxidants
   - Allopurinol
   - Non-selective NOS-inhibitor (nitro-L-arginine)
   - Selective NOS-inhibitor (7-nitroindazole, aminoguanidine, 2-iminobiotin)
   - Indomethacin

3. Anti-inflammation
   - Erythropoietin
   - Melatonin
   - TNF-α inhibitor (etanercept)

4. Anti-apoptosis
   - TAT-NBD
   - TAT-JBD

5. Trophic factors
   - Erythropoietin
   - Other neurotrophic factors (IGF, FGF, BDNF)
   - Stem cells

Moving Beyond a Single Target

- Cerebral blood flow
- Energy failure
- Calcium-dependent 'excitotoxicity'
- Glutamate release
- Apoptotic cell death
- Necrotic cell death
- Delayed cell death
- Inflammation
- Repair
- Restoration

From Patrick McQuillen & Donna Ferriero - UCSF
Moving Beyond a Single Target

Cerebral blood flow

Energy failure

Antioxidant

Glutamate release

Calcium-dependent ‘excitotoxicity’

Apoptotic cell death

Caspase inhibitors

Anti-inflammatories

NMDA-2nd messenger modulation

Hypothermia

Necrotic cell death

Delayed cell death

Inflammation

Repair

Restoration

Plasticity & Recovery

Stem cells

Growth Factors

From Patrick McQuillen & Donna Ferriero - UCSF
Thank you!