Neonatal Hypoxic Ischemic Encephalopathy: Current Practices and Emerging Therapies

Sara V. Bates, MD
MGHfC Division of Newborn Medicine
Child Neurology Conference
September 8, 2017
I have no financial interests or relationships to disclose
Overview/Learning Objectives

• Criteria that mandate the use of therapeutic hypothermia (TH) for HIE

• Imaging initiatives – potential to improve injury detection

• Emerging therapies for HIE - autologous cord blood cells
Hypoxic Ischemic Encephalopathy (HIE)

• HIE continues to occur at a rate of 2.5/1,000 term U.S. births
  • Much higher in developing countries (5-7/1000)

• Inadequate blood flow and oxygen delivery

• Low Apgar scores, abnl neuro exams, metabolic acidosis, +/- seizures, & may need respiratory support
Neonatal Encephalopathy May be caused by:

- HIE
- Cerebrovascular events/Stroke
- Infection
- Metabolic disorders
- Medication exposures
- CNS malformations

*Neonatal encephalopathy is the preferred term to document until more information is gathered
*Never presume a baby with encephalopathy has HIE
Etiologies and potential mechanisms of HIE are complex and usually multifactorial.
Mechanisms of Brain Injury in the Term Neonate

Primary energy failure

Secondary energy failure/reprogramming of brain cell lifespan

Acute cell death

Apoptosis

Inflammation

Altered growth factor and protein synthesis

Treatment

ORIGINAL ARTICLE

Whole-Body Hypothermia for Neonates with Hypoxic–Ischemic Encephalopathy


CONCLUSIONS

Whole-body hypothermia reduces the risk of death or disability in infants with moderate or severe hypoxic–ischemic encephalopathy.
Primary Outcomes
4 Pivotal Whole Body Hypothermia Trials

• 44 – 51% of infants died or survived with disabilities
• 24 - 38% of babies with HIE and were cooled died
• 13 – 28% of the survivors were later diagnosed with cerebral palsy.

% of kids in control groups w/ primary outcomes in red bars, cooled kids are blue bars
Cerebral Palsy
4 Pivotal Whole Body Hypothermia Trials

% of kids in control groups w/ cerebral palsy outcome in red bars, cooled kids are blue bars
To cool or not to cool???
Therapeutic Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy (MGHfC)

Criteria Which MANDATE Therapeutic Hypothermia for Hypoxic Ischemic Encephalopathy

If all four of the following criteria are met, then therapeutic hypothermia MUST be provided:

- Age ≤ 6 hours
  - DO NOT delay initiation of therapy – the earlier the initiation, the greater the likely benefit

2. Unavailable or moderately abnormal blood gas, with clinical history consistent with HIE
   - ANY blood gas during first hour after birth with pH 7.0 – 7.15 or no blood gas available
   - Acute perinatal event (e.g., late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest)
   - Postnatal depression (10-minute Apgar score ≤ 5 or assisted ventilation after birth ≥ 10 minutes)

Reminder
- An abnormal blood gas, even if markedly abnormal, without any evidence of encephalopathy is not, on its own, an indication for therapeutic hypothermia

Exceptions, for which therapeutic hypothermia may be withheld
- Moribund infants for whom no further aggressive treatment is planned
- Major congenital abnormality
- Refusal by a parent – however, standard of care may not easily permit parental refusal
Therapeutic Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy (MGHfC)

Other situations when therapeutic hypothermia might be considered

At the discretion of the attending neonatologist, therapeutic hypothermia may still be considered even if the above four criteria are not met. Input from pediatric neurology may be beneficial.

Examples when therapeutic hypothermia might be considered include:
- Late-preterm birth at 34 or 35 weeks
- Arrival at NICU shortly after 6 hours
- Initial encephalopathy, but with rapid improvement, in setting of likely hypoxic-ischemic insult
- Milder degree of encephalopathy
- Acute cardiorespiratory collapse, outside the newborn period, immediately after successful resuscitation

• Lot’s of “other” situations which are left up to attending’s discretion
• Clear collaboration and discussion with neurology team, OB, and family
Therapeutic Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy (MGHfC)

Moderate and severe encephalopathy, defined by clinical signs in at least 3 of the following 6 categories.

<table>
<thead>
<tr>
<th>Category</th>
<th>Moderate encephalopathy</th>
<th>Severe encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>□ Lethargic</td>
<td>□ Stupor or coma</td>
</tr>
<tr>
<td>Spontaneous activity</td>
<td></td>
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<tr>
<td>Posture</td>
<td></td>
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<tr>
<td>Tone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primitive reflexes</td>
<td>□ Weak suck</td>
<td>□ Absent suck</td>
</tr>
<tr>
<td></td>
<td>□ Incomplete Moro</td>
<td>□ Absent Moro</td>
</tr>
<tr>
<td>Autonomic system</td>
<td>□ Constricted pupils</td>
<td>□ Deviated, dilated, or non-reactive</td>
</tr>
<tr>
<td></td>
<td>□ Bradycardia</td>
<td>□ Variable heart rate</td>
</tr>
<tr>
<td></td>
<td>□ Periodic breathing</td>
<td>□ Apnea</td>
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- Sarnat scoring system - late 1970’s
- Exams are often difficult due to medications
- Many of our infants are out born
- Some terms are confusing
CRICO Taskforce: 2016

More consistent clinical practices for infants with moderate to severe HIE – educational initiatives
Should mild HIE infants be cooled?

- Transient/continuum
- Scoring systems
- Trial data
- MRI interpretations
Should mild HIE infants be cooled?


Research efforts
REDCap: Research Electronic Data Capture

- >15 years of data – electronic healthcare records (EHR)
- Cohorts of perinatal brain injury
- Maternal history
- Labor & delivery course
- Infant’s clinical course
- Blood work
- Imaging - pending
- Placenta pathology
- Diagnoses
- Outcomes (short and long-term)
MRI – The Basics

• Most sensitive, noninvasive imaging modality for the documentation of neonatal brain injury with T1- and T2- weighted images combined with Apparent Diffusion Coefficient (ADC) maps (created from DWI acquisitions)

• Injuries may be overcalled as the appearance of the neonatal brain on MRI changes rapidly with normal development in ways that can easily be confused with injury

• Injuries can be missed due to the often diffuse and symmetric patterns of injury

• Uncommon disorders presenting with encephalopathy, some of which require immediate intervention, may be misdiagnosed as hypoxic ischemic injury

  SOD case example
Normal MRI: 3 day-old FT infant

**Axial T1**
- Hypointense appearance of the white matter
- Relative hyperintense signal in the cortical gray matter & deep gray nuclei

**Axial T2**
- Normal hyperintense signal of the unmyelinated white matter
- Low SI in areas with early myelination

High signal intensity in the PLIC & VL thalamus – early myelination
MRI interpretation

• Current clinical practice for analyzing the ADC maps - visual assessment

• Scroll though slices of the image looking for regions where intensity is visibly lower than expected, and makes a non-quantitative report based on an impression of the volume, severity and pattern of the injuries

• On-screen tool to identify a 2D region of interest (e.g. an ellipse) and obtain a measurement (e.g. average ADC value) - manually laborious; limited to a few small areas

• Scoring systems have been suggested and used in research studies - based on visual assessment

• Lack of quantifiable, precise, reproducible measurements
• What are the normal regional ranges of ADC variation and how low is too low? (regional brain variation)

• The lack of an answer to this question has caused 20-50% uncertainty/errors in radiologists’ interpretation of ADC maps in neonates with HIE


Pediatric Brain Atlases

• Creating whole brain, age-specific atlases with ADC statistics (means and standard deviation) at every voxel in the brain

• Structural and diffusion images

• Normal development birth → 6 years (earlier time points more richly sampled)

• Brain injury - potential
Imaging information:

- Studies performed on a Siemens TIM Trio 3T scanner

- Clinical diffusion protocol:
  TR=7500-9500ms, TE=80-115ms, max b value = 1000s/mm², matrix=128x128x60, voxel size= 2x2x2mm

- ADC maps generated by diffusion sequence
How do we obtain images?

Research Patient Data Registry (RPDR) used to query EHR → Medical Imaging Informatics Bench to Bedside (mi2b2) software → access identified pts from PACS at MGH

N = ~100,000
- Brain MRI in MGH

N = 2,871
- Scanned 2006-2013 with ADC maps in Siemens 3T scanner
- 0-6 years old at the time of scan
- Radiological reports suggesting free of abnormality

N = 1,648
- ADC maps found and not corrupted

N = 705
- ADC maps re-examined & confirmed to be normal by a neuro-radiologist (EG) and a neonatologist (SB)

N = 201
- Duplicates removed
- Still normal 3 years after the initial visit

Mi2b2 engine:
https://www.nmr.mgh.harvard.edu/lab/mi2b2
Lead: Profs. Shawn Murphy, Randy Gollub (MGH) [Murphy et al, 2015]
Atlas Construction (The Basics)

• 201 subjects divided into 10 age groups
• ADC maps were skull stripped
• Pair-wise registration
• Age-specific ADC values

• Image analysis algorithms
• Segmentation and processing

Mi2b2 engine: https://www.nmr.mgh.harvard.edu/lab/mi2b2
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Lilla Zollei, PhD & Yangming Ou, PhD - Computational Neuroimaging
Using Clinically-acquired MRI to Construct Age-Specific ADC Atlases: Quantifying Spatiotemporal ADC Changes from Birth to 6 Years Old
Yangming Ou1,2,3,9*, Lilla Zöllei2, Kallirroi Retzepi1,2, Victor Castro4,5, Sara V. Bates6, Steve Pieper7, Katherine P. Andriole8, Shawn N. Murphy4,5, Randy L. Gollub1,2, P. Ellen Grant9

Figure 3. Representative coronal, sagittal and axial views of the constructed age-specific ADC atlases.
• Abnormality detected as outliers to the characterized normal ranges of ADC values

• Quantitative comparison of patient’s ADC values to the population mean and stdev, at the voxel level

Ou et al, in preparation

Mi2b2 engine: [https://www.nmr.mgh.harvard.edu/lab/mi2b2](https://www.nmr.mgh.harvard.edu/lab/mi2b2)
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Examples of emerging therapies & trials

• Length, timing of TH
• Antiepileptic drugs
• Erythropoietin
• Melatonin
• Umbilical cord blood
Cord Blood

- Allogenic CB is a clinically effective stem cell source to prevent deterioration in some childhood conditions: Krabbe’s, Hurler’s, CP
  - Allogenic, unrelated CB transplantation demonstrate hematopoietic and non-hematopoietic cells engraft in the CNS

https://sites.duke.edu/ccbb/
Cord Blood

- Rich source of progenitor cells
- Mesenchymal (MSCs) and hematopoietic stems cells (HSCs)
- Monocytes (5-10%)
  - Angiogenic and anti-inflammatory effects
Phase I trial: May 2014

Feasibility of Autologous Cord Blood Cells for Infants with Hypoxic-Ischemic Encephalopathy

C. Michael Cotten, MD¹, Amy P. Murtha, MD², Ronald N. Goldberg, MD¹, Chad A. Grotegut, MD², P. Brian Smith, MD¹, Ricki F. Goldstein, MD¹, Kimberley A. Fisher, PhD¹, Kathryn E. Gustafson, PhD³, Barbara Waters-Pick, BS, MT(ASCP)⁴, Geeta K. Swamy, MD², Benjamin Rattray, MD¹, Siddhartha Tan, MD⁵, and Joanne Kurtzberg, MD⁶
Phase I trial

• Population: ≥35 weeks; met NICHD cooling criteria
• UCB available
• 2 families did not consent (>90% consent rate)
• 23 infants were cooled and received CB; 82 infants cooled without CB
• No safety concerns
Phase I trial

<table>
<thead>
<tr>
<th>Table V. Survival with Bayley III scores ≥85 in 3 domains</th>
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<tbody>
<tr>
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<tr>
<td>Survived to 15 mo</td>
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<tr>
<td>Survival with all 3 Bayley domain scores ≥85</td>
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</table>
A Phase II Multi-site Study of Autologous Cord Blood Cells for Hypoxic Ischemic Encephalopathy (HIE)  IND 14753

MGH & BWH – Summer 2017
Participating Sites/locations

- DUKE
- Boston
  - MGH/BWH
- Florida Neonatal Neuro Network
  - U Fla, Fla Hospital, Winnie Palmer
- CHOP/PENN
- UAB
- Indiana U
- UT Houston
- Wayne State
Target Population:

- Near term and term infants with evidence of hypoxic-ischemic injury and moderate/severe encephalopathy
Screening

- $\geq$ 36 weeks
- Post-natal age $< 24$ hours
- Admitted to a NICU
- Potential diagnoses
  - Neonatal depression
  - Birth asphyxia
  - Hypoxia-Ischemia
  - Slow to start
  - Encephalopathy/seizures
- Cord Blood Collected
  - In Phase I, approximately 6 units collected for every one qualified
  - If collected and not enrolled, and not public bank donor, unit to be discarded as medical waste
Exclusion Criteria:

- Major congenital or chromosomal abnormalities
- Severe growth restriction (birth weight <1800 g)
- Opinion by attending neonatologist that the study may interfere with treatment or safety of subject
- Moribund neonates for whom no further treatment is planned
- Infants born to mothers are known to be HIV, Hepatitis B, Hepatitis C or who have active syphilis or CMV infection in pregnancy
- Infants suspected of overwhelming sepsis
- ECMO initiated or likely in the first 48 hours of life
- ALL blood gases (cord and postnatal) done within the first 60 minutes had a pH >7.15 AND a base deficit < 10 mEq/L (source can be arterial, venous or capillary)
CD14+ monocytes are likely responsible for paracrine signaling that promotes repair. Secretion of IL-6, IL-10 (anti-inflammatory).

Fig. 1. Left diagram pathophysiological effects of ischemic brain injury or perinatal hypoxia-ischemia in the brain, resulting in an impaired functional outcome. Right diagram - possible mechanisms of modulation in ischemia-associated pathophysiological events upon transplantation of human umbilical cord blood (hUCB) cells.
OB Cord Blood Collection Workflow

- Pediatrics team is paged to a delivery
- OB nurse puts labeled bag in cooler and notifies OA
- Collection kits stocked in all rooms
- OB nurse puts labeled bag in cooler and notifies OA
- Collection kits stocked in all rooms

OA e-mails MGHBABYBAC@partners.org to notify the study team of collection
MGH labor & delivery
Cord blood collected & stored. Consent obtained if infant is undergoing TH and eligible

Transport product to DFCI: randomization & cell processing

Product/placebo transported from DFCI directly to NICU

quality/safety checks

Infusion administered
Randomization

- After informed consent, randomization to placebo or study product.
  - Web-based
  - 24/7 availability by DCC
  - Only unblinded laboratory personnel will be trained on randomization and have knowledge of study arm.

- Randomization stratified by severity of encephalopathy

- Randomized to:
  - Study product: $2 - 5 \times 10^7$ cells/kg/dose
  - Placebo group
Processed cellular product vs. placebo (samples used for teaching*)
Infusions

- Up to two infusions allowed within first 48 postnatal hours
  - First infusion as soon as possible
  - Second at least 8 hours after first

- Pre-treatment with hydrocortisone
  - 1 mg/kg 30 – 60 minutes prior to dose(s) if baby is not receiving hydrocortisone for clinical reasons.
  - Rationale: to minimize risk of infusion-related and/or allergic reaction to manipulated cells.

- Study product/placebo over 15 – 20 minutes followed by saline flush (≤5mL) to clear the line.
Follow-Up

- 12 month + 2 months post-infusion
- History and physical
- Bayley III
- Neuro-exam
- Adverse event data collection
- Concomitant medications data collection
Other Treatments and Tests

- Anti-seizure medications and sedation ideally not administered prior to decision to start hypothermia
- EEG practice at discretion of sites
- MRI practice at discretion of sites
- Echocardiogram at discretion of sites

Multi-site secondary MRI study
Short Term Outcomes

• Secondary short term outcomes:
  • In hospital mortality
  • Seizures (any)
  • Need for iNO
  • Need for ECMO
  • Need for g-tube at discharge
  • Need for anti-seizure medication at discharge
# RISKS

<table>
<thead>
<tr>
<th>Cells or placebo</th>
<th>Hydrocortisone</th>
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<tbody>
<tr>
<td>• Infection</td>
<td>• Increase blood sugar</td>
</tr>
<tr>
<td>• Volume overload</td>
<td>• Increase blood pressure</td>
</tr>
<tr>
<td>• Hypertension</td>
<td>• Fluid retention</td>
</tr>
<tr>
<td>• Allergic or anaphylactic reactions</td>
<td></td>
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<tr>
<td>• Hyperviscosity or pulmonary edema</td>
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Benefits

• Infusion of a neonate’s own cord blood cells during routine cooling is hoped to improve survival and neurological outcome as compared to infants that are only cooled.

• Autologous cells should eliminate any risk of graft vs host reaction.

• If cord blood is collected and not infused, it will be cryopreserved for later use by the family.
Infant Brain Center at MGH

WEBSITE LAUNCH PENDING
Special thanks to:

- Research mentors & lab: Ellen Grant, Randy Gollub, Joe Chou, Camilo Jaimes Cobos, Yangming Ou, Lilla Zollei, Steve Piper, Susan Sotardi, Rudolph Pieanaar, Eva Ratai, Rebecca Weiss
- MGH Division of Pediatric Neurology: Kevin Staley, Kalpathy Krishnamoorthy, Catherine Chu, Patricia Musolino
- MGH Pediatric Neuroradiology: Paul Caruso
- MGH Placental Pathology: Drucilla Roberts
- MGH Division of Newborn Medicine: Paul Lerou, Sergei Roumiantsiev, Melissa Woythaler, Mayya Geha
- MGH OBGYN: Jeff Ecker, Anjali Kaimal, Bill Barth, Marie Henderson
- MGH OBGYN and newborn medicine nursing: Beth West, Michele O’Hara, Peggy Settle
- BWH collaborators: Terrie Inder, Mohamed El-Dib, Brian Walsh
- DUKE collaborates: Joanne Kurtzberg, Mike Cotten, Becky Durham & many others