Evidence to practice:
cooling for hypoxic ischemic encephalopathy

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Cooling for hypoxic ischemic encephalopathy

To develop an understanding of the strengths and weaknesses of evidence provided by systematic reviews and meta-analyses to inform our practice of neonatal-perinatal medicine.

Today’s focus will be on therapeutic hypothermia for hypoxic ischemic encephalopathy

According to the World Health Organization, Hypoxic Ischemic Encephalopathy is the 5th leading cause of death worldwide for children under the age of five years.


Major predictor of neurodevelopmental disability
- 1-6/1000 live term births
- 15-20% die during newborn period
- 25% permanent neurologic deficits

Mechanisms of brain injury in the term neonate

Cell Death

Injury

Window of opportunity

Time after injury

VUNEO.org

**Cooling for hypoxic ischemic encephalopathy**

**Hypothermia in animal models after experimental hypoxic ischemic insult**

- mild hypothermia (cooling to 32 to 34°C) is neuroprotective
- brain cooling should be initiated as early as feasible (preferably within 2 hours) and not later than 6 hours
- cooling should be continued for 48 to 72 hours

**Cochrane Neonatal**

**Cooling for hypoxic ischemic encephalopathy**

Who might benefit from cooling?

Types of participants

Newborn infants

Evidence of peripartum asphyxia, with each enrolled infant satisfying at least one of the following criteria:

a. Apgar score of 5 or less at 10 minutes;

b. mechanical ventilation or resuscitation at 10 minutes

c. cord pH < 7.1, or an arterial pH < 7.1 or base deficit of 12 or more within 60 minutes of birth

d. evidence of encephalopathy according to Sarnat staging

No major congenital abnormalities recognizable at birth.
Cooling for hypoxic ischemic encephalopathy

Study entry criteria: Evidence of moderate or severe encephalopathy
Criteria modified from Sarnat and Sarnat including lethargy, stupor or coma, with one or more of hypotonia, abnormal reflexes including oculomotor or pupillary abnormalities, an absent or weak suck or clinical evidence of seizures.

Infants were then assessed for abnormal aEEg

Gluckman on behalf of the CoolCap Study Group. Selective Head Cooling with Mild Systemic Hypothermia to Improve Neurodevelopmental Outcome Following Neonatal Encephalopathy

Types of interventions
• Head Cooling (with temperature servocontrol)
• Whole Body Cooling (with temperature servocontrol)
• Phase changing materials (without temperature servocontrol)

Whole-Body Hypothermia (with servo-control)


Whole-Body Hypothermia (with servo-control)


Head Cooling (with temperature servocontrol)


TOBY

Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial.

Treatment of hypoxic ischemic encephalopathy in infants from a wide geographic region, using simplified protocols.

Hypothermia is achieved by turning off the ambient heating systems and by applying “Hot-Cold” gel packs (at 10°C) around the infant’s head and over the chest, so that the rectal temperature is reduced to 33°–34°C.

Enrollment: 221 infants from 28 participating centers in Australia, New Zealand, Canada and US


Cooling for newborns with hypoxic ischemic encephalopathy.


Updated by M. Berg 2012, 2022
**Cochrane Neonatal**

**Cooling for hypoxic ischemic encephalopathy**

**ILCOR recommendations**

"Intensive care nurseries should now consider adopting one of the validated protocols for the selection of term infants with HIE, be appropriately equipped and train staff to offer hypothermia according to the protocol of the currently published large hypothermia trials."

"Because HIE is a relatively uncommon condition, it would be highly desirable where possible to centralize this treatment to larger intensive care units."

"With the data presently available, there is no longer any reasonable justification to deny this apparently efficacious treatment for those who most urgently need it."


**Difficulty of translating evidence to practice**

**Efficacy:**

Mild hypothermia is a promising therapy in a highly selected population of infants with moderate to severe hypoxic ischemic encephalopathy when treated before 6 hours of age.

**Effectiveness and Efficiency:**

- Does in work in the most affected infants? Does it provide a benefit to less severely affected infant?
- Does it work outside the restricted time window predicted by animal models and tested in clinical trials?
- Does selective or whole body hypothermia work best?
- What is the relationship of hypothermia to other therapeutic interventions?
Cooling for hypoxic ischemic encephalopathy

What are we supposed to do?

- Promising therapy in a highly selected population with moderate to severe hypoxic ischemic encephalopathy when treated before 6 hours of age
- Unknown if worthwhile in the most affected infants or in cases where injury is less severe
- Unknown whether clinically effective outside of restricted time window
- Unknown if selective or whole body hypothermia conveys greatest advantage
- Unknown relationship to other therapeutic interventions
- Unknown school age follow up

Current practice?

Therapeutic hypothermia in mild neonatal encephalopathy: a national survey of practice in the UK

Although major cooling trials (and subsequent guidelines) excluded babies with mild encephalopathy, anecdotal evidence suggests that cooling is often offered to these infants.

We report a national survey on current cooling practices for babies with mild encephalopathy in the UK. From 74 neonatal units contacted, 68 were cooling centres.

We received 54 responses (79%) and included 48 (five excluded due to incomplete data and one found later not to offer cooling).

Of these, 36 centres (75%) offered cooling to infants with mild encephalopathy.

Therapeutic hypothermia in mild neonatal encephalopathy: a national survey of practice in the UK


Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial.


Objectives: To estimate the probability that hypothermia initiated at 6 to 24 hours after birth reduces the risk of death or disability at 18 months among infants with hypoxic-ischemic encephalopathy.

Design, setting, and participants: A randomized clinical trial was conducted between April 2008 and June 2016 among infants at 36 weeks or later gestation with moderate or severe hypoxic-ischemic encephalopathy enrolled at 6 to 24 hours after birth. Twenty-one US Neonatal Research Network centers participated. Bayesian analyses were prespecified given the anticipated limited sample size.

Interventions: Targeted esophageal temperature was used in 168 infants. Eighty-three hypothermic infants were maintained at 33.5°C (acceptable range, 33°C-34°C) for 96 hours and then rewarmed. Eighty-five noncooled infants were maintained at 37.0°C (acceptable range, 36.5°C-37.3°C).

Main outcomes and measures: The composite of death or disability (moderate or severe) at 18 to 22 months adjusted for level of encephalopathy and age at randomization.

Results: Randomized at a mean (SD) of 16 (5) and 15 (5) hours for hypothermic and noncooled groups, respectively. The primary outcome occurred in 19 of 78 hypothermic infants (24.4%) and 22 of 79 noncooled infants (27.9%) (absolute difference, 3.5%; 95% CI, -1% to 17%).

Conclusions and relevance: Among term infants with hypoxic-ischemic encephalopathy, hypothermia initiated at 6 to 24 hours after birth compared with noncooled infants resulted in a 76% probability of any reduction in death or disability, and a 64% probability of at least 2% less death or disability at 18 to 22 months. Hypothermia initiated at 6 to 24 hours after birth may have beneficial effects beyond 24 hours, but this study is insufficient to make a determination.


Hypothermia for moderate or severe neonatal encephalopathy in low-income and middle-income countries (HELIX): a randomised controlled trial in India, Sri Lanka, and Bangladesh

Sudhin Thayyil for the Helix Consortium

Lancet Glob Health 2021; 9: e1273–85

DOI: https://doi.org/10.1016/S2214-109X(21)00264-3
Methods: We did a multicountry, open-label, randomised controlled trial in seven tertiary neonatal intensive care units in India, Sri Lanka, and Bangladesh. We enrolled infants born at or after 36 weeks of gestation with moderate or severe neonatal encephalopathy and a need for continued resuscitation at 5 min of age or an Apgar score of less than 6 at 5 min of age (for babies born in a hospital), or both, or an absence of crying by 5 min of age (for babies born at home). We allocated infants into a group receiving whole body hypothermia (33.5°C) for 72 h using a servo-controlled cooling device, or to usual care (control group), within 6 h of birth.

The primary outcome was a combined endpoint of death or moderate or severe disability at 18–22 months, assessed by the Bayley Scales of Infant and Toddler Development (third edition) and a detailed neurological examination. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, NCT02387385.

Findings: We recruited 408 eligible infants and we assigned 202 to the hypothermia group and 206 to the control group. 50% infants in the hypothermia group and 47% infants in the control group died or had a moderate or severe disability (risk ratio 1.06; 95% CI 0.87–1.30; p=0.55). 84 infants (42%) in the hypothermia group and 63 (31%; p=0.022) infants in the control group died, of whom 72 (36%) and 49 (24%; p=0.0087) died during neonatal hospitalisation.

Interpretation: Therapeutic hypothermia did not reduce the combined outcome of death or disability at 18 months after neonatal encephalopathy in low-income and middle-income countries, but significantly increased death alone. Therapeutic hypothermia should not be offered as treatment for neonatal encephalopathy in low-income and middle income countries, even when tertiary neonatal intensive care facilities are available.
Effect of Depth and Duration of Cooling on Deaths in the NICU Among Neonates With Hypoxic Ischemic Encephalopathy: A Randomized Clinical Trial

Importance: Hypothermia at 33.5°C for 72 hours for neonatal hypoxic ischemic encephalopathy reduces death or disability to 44% to 55%; longer cooling and deeper cooling are neuroprotective in animal models.

Objective: To determine if longer duration cooling (120 hours) or deeper cooling (32.0°C) or both are superior to cooling at 33.5°C for 72 hours in neonates who are full-term with moderate or severe hypoxic ischemic encephalopathy.

Design, Setting, and Participants: A randomized, 2 × 2 factorial design clinical trial performed in 18 US centers in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)/NIH/NIH Research Network between October 2010 and November 2013.

Interventions: Neonates were assigned to 4 hypothermia groups; 33.5°C for 72 hours, 32.0°C for 72 hours, 33.5°C for 120 hours, and 32.0°C for 120 hours.

Main Outcomes and Measures: The primary outcome of death or disability at 18 to 22 months is ongoing. The independent data and safety monitoring committee paused the trial to evaluate safety (cardiac arrhythmia, persistent acidosis, major vessel thrombosis and bleeding, and death in the neonatal intensive care unit [NICU]) after the first 50 neonates were enrolled, then after every subsequent 25 neonates. The trial was closed for emerging safety profile and futility analysis after the eighth review with 364 neonates enrolled (of 726 planned).

This report focuses on safety and NICU deaths by marginal comparisons of 72 hours’ vs 120 hours’ duration and 33.5°C depth vs 32.0°C depth (predefined secondary outcomes).

Trial Registration: clinicaltrials.gov Identifier: NCT01192776


Effect of inborn vs. outborn delivery on neurodevelopmental outcomes in infants with hypoxic–ischemic encephalopathy: secondary analyses of the NICHD whole-body cooling trial.


Effect of inborn vs. outborn delivery on neurodevelopmental outcomes in infants with hypoxic–ischemic encephalopathy: secondary analyses of the NICHD whole-body cooling trial.


Background: The effect of birth location on hypothermia-related outcomes has not been rigorously examined in the literature. In this study, we determined whether birth location had an impact on the benefits of whole-body cooling to 33.5 °C for 72 h in term infants (n = 208) with hypoxic–ischemic encephalopathy (HIE), who participated in the Neonatal Research Network (NRN) randomized controlled trial.

Methods: Heterogeneity by birth location was examined with respect to cooling treatment for the 18-mo primary outcomes (death, moderate disability, severe disability) and secondary outcomes (death, components of disability), and in-hospital organ dysfunction. Logistic regression models were used to generate adjusted odds ratios.

Results: Infants born at a location other than an NRN center (outborn) (n = 93) experienced significant delays in initiation of therapy (mean (SD): 5.5 (1.1) vs. 4.4 (1.2) h), lower baseline temperatures (36.6 (1.2) vs. 37.1 (0.9) °C), and more severe HIE (45 vs. 29%) than infants born in an NRN center (inborn) (n = 115).

When adjusted for NRN center and HIE severity, there were no significant differences in 18-mo outcomes or in-hospital organ dysfunction between inborn and outborn infants.

Conclusion: Although limited by sample size and some differences in baseline characteristics, the study showed that birth location does not appear to modify the treatment effect of hypothermia after HIE.

Severity

Should therapeutic hypothermia be offered to babies with mild neonatal encephalopathy in the first 6 h after birth?

El-Dib M, Inder TE, Chalak LF, Massaro AN, Thoresen M, Gunn AJ.


Cooling for newborns with hypoxic ischemic encephalopathy: effect on death or major disability based on intial disease severity

Should therapeutic hypothermia be offered to babies with mild neonatal encephalopathy in the first 6 h after birth

Infants with moderate to severe neonatal encephalopathy (NE) benefit significantly from therapeutic hypothermia, with reduced risk of death or disability. However, the need for therapeutic hypothermia for infants with milder NE remains unclear.

It has been suggested that these infants should not be offered therapeutic hypothermia as they may not be at risk for adverse neurodevelopmental outcome and thus the balance of risk against potential benefit is unknown.

Several key questions need to be answered including first, whether one can define NE in the first 6 h after birth so as to accurately distinguish infants with brain injury who may be at risk for adverse neurodevelopmental consequences.

Second, will treatment of infants with mild NE with therapeutic hypothermia improve or even worsen neurological outcomes?

Although alternate treatment protocols for mild NE may be feasible, the use of the current approach combined with rigorous avoidance of hypothermia and initiation of hypothermia as early as possible after birth may promote optimal outcomes. Animal experimental data support the potential for greater benefit for mild HIE compared with moderate to severe HIE.
Questions regarding cooling….
Where does the evidence take us?
Who needs to be cooled?
What are best “practices” regarding optimizing cooling?
What future research is urgently needed?

Guest Discussants

Deirdre O'Reilly, MD, MPH
Associate Professor, University of Vermont
Director, NPM Fellowship, University of Vermont

Marie T. Berg, MD
Johns Hopkins All Children's Maternal, Fetal & Neonatal Institute

Cochrane Neonatal

As Cochrane Neonatal’s host organization, VON provides financial support and resources for the creation and dissemination of systematic reviews of the evidence in newborn care.

These resources help our community of practice provide the best possible evidence-based care for infants and families around the world.

https://public.vtoxford.org/cochrane-at-von/
Cooling for hypoxic ischemic encephalopathy

Disclosure

Roger F. Soll, M.D. is the Vice President of the Vermont Oxford Network and the Coordinating Editor of Cochrane Neonatal

No other relevant financial issues to disclose

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How to Participate in Today’s Webinar

• Type questions you have into the chat box at anytime during the presentation.

• Use Poll Everywhere to answer questions posed during the session.

Three ways to use Poll Everywhere

• Open your web browser and type in pollev.com/vtoxford

• Download the app Poll Everywhere on your phone. After it is installed open and select Join Presentation and type in vtoxford

• Text vtoxford to 22333
Have you ever participated in a Cochrane Neonatal web seminar?

- Yes
- No
- I can't remember

What to actually do?

What do we know about...

Benefits and Harms

- **Desirable Effects:** How substantial are the desirable anticipated effects?
- **Undesirable Effects:** How substantial are the undesirable anticipated effects?

Overview of therapeutic hypothermia

Trials of therapeutic hypothermia in infants with moderate to severe encephalopathy have been shown to decrease the risk of:

- Mortality
- Moderate to severe developmental disability
- Mortality or moderate to severe developmental disability
- All of the above

HYPOTHERMIA FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY

**IMPACT OF COOLING ON DEATH AND DISABILITY**

<table>
<thead>
<tr>
<th>OUTCOMES (N STUDIES)</th>
<th>Risk Difference (95% CI)</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEATH OR MAJOR DISABILITY (13)</td>
<td>-0.14 (-0.19 to -0.09)</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>DEATH (26)</td>
<td>-0.08 (-0.11 to -0.05)</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>MAJOR DISABILITY (12)</td>
<td>-0.08 (-0.11 to -0.04)</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Modified from Jacobs 2007; updated M. Beng 2022

Cooling for newborns with hypoxic ischemic encephalopathy.

29 trials involving 3435 infants.
Harms

Trials of therapeutic hypothermia in infants with moderate to severe encephalopathy have been shown to increase the risk of:

- Arrythmia requiring treatment
- Hypotension requiring treatment
- PPHN
- Thrombocytopenia

COAGULOPATHY /DIC (10) 0.02 (-0.00, 0.04)
THROMBOCYTOPENIA (13) 0.05 (0.02, 0.09)
HYPOGLYCEMIA (12) -0.03 (-0.06, 0.00)
INHALED NITRIC OXIDE (5) 0.01 (-0.04, 0.07)
PPHN (7) 0.04 (-0.01, 0.09)
HYPOGLYCERIA (12) -0.03 (-0.06, 0.00)
THROMBOCYTOPENIA (13) 0.03 (0.02, 0.09)

Method of therapeutic hypothermia

Total body cooling (with temperature servocontrol) has been shown to be superior to all other methods of therapeutic hypothermia in infants with moderate to severe encephalopathy.

Yes
No
Uncertain

Cooling for hypoxic ischemic encephalopathy

ILCOR recommendations

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"Because HIE is a relatively uncommon condition, it would be highly desirable where possible to centralize this treatment to larger intensive care units."

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Does your center have formal guidelines addressing the indications and methods for therapeutic hypothermia in infants with hypoxic ischemic encephalopathy?

- Yes
- No
- Uncertain

Does your center have formal guidelines addressing the gestational age of infants with hypoxic ischemic encephalopathy eligible for therapeutic hypothermia?

- Yes
- No
- Uncertain

Does your center have formal guidelines addressing the severity of illness of infants with hypoxic ischemic encephalopathy eligible for therapeutic hypothermia?

- Yes
- No
- Uncertain

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Upcoming VON Grand Rounds

Variants of Uncertain Significance  
(Presented in partnership with Rady Children’s Institute for Genomic Medicine)  
Wednesday, September 21, 2022 | 3:00 – 4:00 p.m.  
(Eastern)  
Faculty: Nathaly Sweeney and others

AAP/VON Scholar Presentations
Wednesday, October 26, 2022 | 3:00 – 4:00 p.m.  
(Eastern)

Topic: CPAP  
November 16, 2022 | 3:00 – 4:00 p.m. (Eastern)

Topic: Pain  
(A Cochrane at VON presentation)  
December 2022 | 3:00 – 4:00 p.m. (Eastern)