Vermont Oxford Network Grand Rounds 2022

Cochrane Neonatal

Evidence to practice: cooling for hypoxic ischemic encephalopathy

July 11, 2022 3:00 PM EST

VON Vermont Oxford NETWORK

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Evidence to practice: cooling for hypoxic ischemic encephalopathy

Roger F. Soll, MD

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Trusted evidence. Informed decisions. Better health.

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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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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

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Hypoxic ischemic encephalopathy

Major predictor of neurodevelopmental disability

- 1-6/1000 live term births
- 15-20% die during newborn period
- 25% permanent neurologic deficits

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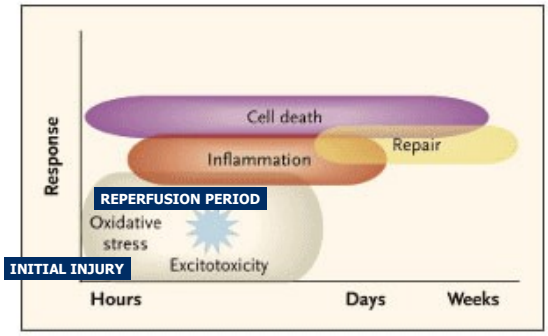
Mechanisms of brain injury in the term neonate



Donna M. Ferriero, M.D. N Engl J Med 2004; 351:1985-1995. DOI: 10.1056/NEJMra041996

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Cell Death

Time after injury

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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

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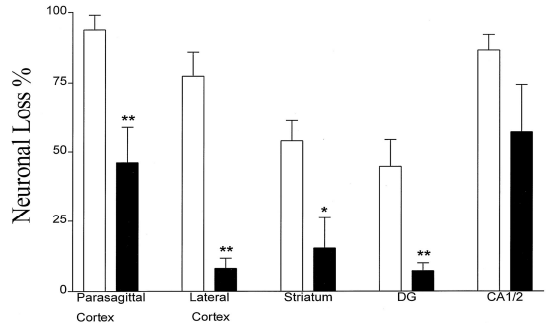
Cooling for hypoxic ischemic encephalopathy



Gunn, A. J. et al. Pediatrics 1998;102:1098-1106

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So….

What do we **know** from trials of therapeutic hypothermia in neonates?

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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.

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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

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Categories	Normal	Mild	Moderate	Severe
1. Level of consciousness	Alert Responsive to stimuli	Hyperalert, stare, jitteriness, high pitched cry, exaggerated response to minimal stimuli, inconsolable	Lethargic	Stupor/coma
2. Spontaneous activity	Normal	Decreased, with or without periods of excessive activity	Decreased	No activity
3. Posture	Predominately flexed when quiet	Mild flexion of distal joints (fingers/wrists)	String distal flexion, complete extension	Intermittent decerebration
4. Tone	Strong flexor tone in all extremities	Slightly increased peripheral tone	Hypotonia or hypertonia	Flaccid, rigid
5. Primitive reflexes				
• Suck	Strong Easy to elicit	Weak, poor	Weak or has bite	Absent
• Moro	Strong Easy to elicit	Low threshold to elicit	Incomplete	Absent
6. Autonomic nervous system				
• Pupils	Normal size	Mydriasis	Constricted Miosis	Skew deviation or dilated, non-reactive to light
• Heart rate			Bradycardia	Variable heart rate
• Respiration			Periodic breathing	Apnea

Modified from Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol.* 1976;33(10):696-705987769

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Cooling for hypoxic ischemic encephalopathy

Types of interventions

- Head Cooling (with temperature servocontrol)
- Whole Body Cooling (with temperature servocontrol)
- Phase changing materials (without temperature servocontrol)

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Head Cooling (with temperature servocontrol)

Gluckman and colleagues. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomized trial. Lancet 2005;365:663-670. doi:10.1016/S0140-6736(05)17946-X

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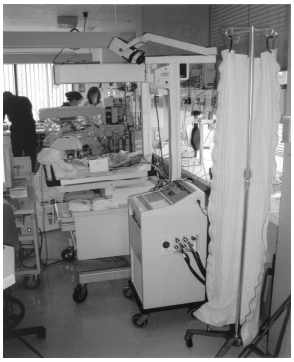
Whole-Body Hypothermia (with servo-control)



"The infant lies supine on the infant-size blanket.

The adult-size blanket is suspended vertically alongside the cooling unit.

Both blankets are attached to the cooling unit with water circulating through them simultaneously."

Shankaran and colleagues. Whole-Body Hypothermia for Neonates with Hypoxic–Ischemic Encephalopathy. N Engl J Med 2005; 353:1574-1584. DOI: 10.1056/NEJMcps050929

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Whole-Body Hypothermia (with servo-control)

Azzopardi and colleagues. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009;361:1349-58. doi:10.1056/NEJMoa0900854

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Phase changing materials (without temperature servocontrol)

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

Jacobs SE for the Infant Cooling Evaluation Collaboration. Arch Pediatr Adolesc Med. 2011 Aug;165(8):692-700. doi: 10.1001/archpediatrics.2011.43. Epub 2011 Apr 4. PMID: 21464374.

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Cooling for newborns with hypoxic ischemic encephalopathy.

Jacobs SE, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003311. DOI: 10.1002/14651858.CD003311.pub2.

Updated by M. Berg 2012, 2022

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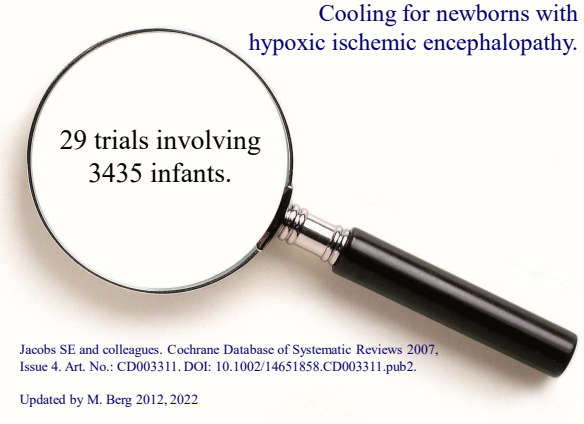
Cooling for newborns with hypoxic ischemic encephalopathy.



Jacobs SE and colleagues. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003311. DOI: 10.1002/14651858.CD003311.pub2.

Updated by M. Berg 2012, 2022

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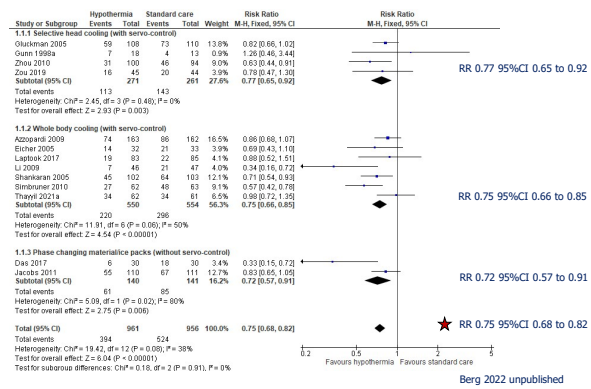
Cooling for newborns with hypoxic ischemic encephalopathy: effect on death or major disability



Berg 2022 unpublished

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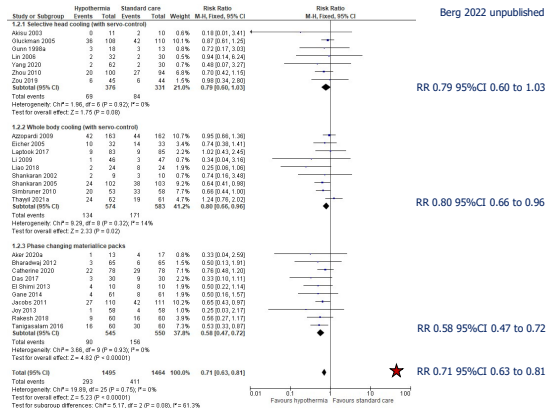
Cooling for newborns with hypoxic ischemic encephalopathy: effect on death



Berg 2022 unpublished

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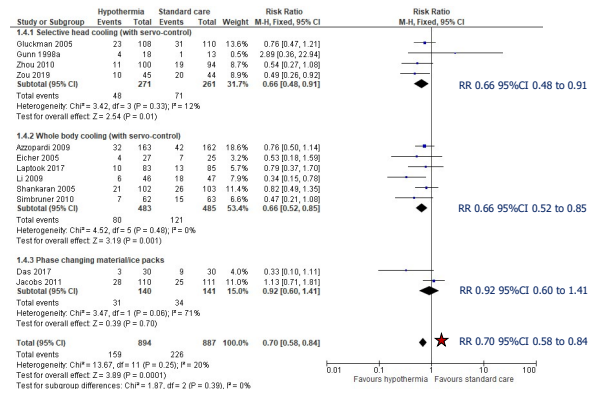
Cooling for newborns with hypoxic ischemic encephalopathy: effect on major disability



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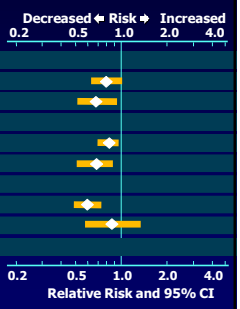
HYPOTHERMIA FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY

Effect on death and effect on disability

OUTCOMES (N STUDIES)	Risk Difference (95% CI)
SELECTIVE HEAD COOLING	
DEATH (7)	-0.05 (-0.11, 0.01)
DISABILITY (4)	-0.09 (-0.16, -0.02)
WHOLE BODY COOLING	
DEATH (9)	-0.06 (-0.11, -0.01)
DISABILITY (6)	-0.08 (-0.13, -0.03)
PHASE CHANGING MATERIAL	
DEATH (10)	-0.12 (-0.17, -0.07)
DISABILITY (2)	-0.02 (-0.12, -0.04)



Modified from Jacobs 2007; updated M. Berg 2022

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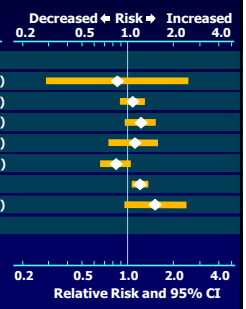
HYPOTHERMIA FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY

COMPLICATIONS OF COOLING

OUTCOMES (N STUDIES)	Risk Difference (95% CI)
ARRTHYMIA REQUIRING RX (13)	-0.00 (-0.01, 0.01)
HYPOTENSION REQUIRING RX (10)	0.04 (-0.02, 0.09)
PPHN (7)	0.04 (-0.01, 0.09)
INHALED NITRIC OXIDE (5)	0.01 (-0.04, 0.07)
HYPOGLYCEMIA (12)	-0.03 (-0.06, 0.00)
THROMBOCYTOPENIA (13)	0.05 (0.02, 0.09)
COAGULOPATHY /DIC (10)	0.02 (-0.00, 0.04)



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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."

Hoehn and colleagues. Therapeutic hypothermia in neonates. Review of current clinical data, ILCOR recommendations and suggestions for implementation in neonatal intensive care units. Resuscitation. 2008 Jul;78(1):7-12. doi: 10.1016/j.resuscitation.2008.04.027. PMID: 18554560.

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Difficulty of translating evidence to practice

Efficacy: The benefit of using an intervention for a particular problem under ideal conditions, for example, in a laboratory setting, within the protocol of a carefully managed randomized controlled trial, or at a "center of excellence."

Effectiveness: The extent to which a specific intervention, procedure, regimen of service … does what it is intended to do for a defined population.

Efficiency: The extent to which objectives are achieved by minimizing the use of resources.

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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

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Difficulty of translating evidence to practice

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?

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Cooling for hypoxic ischemic encephalopathy

What are we supposed to do?

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Cooling for hypoxic ischemic encephalopathy

What answers do we have?

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

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Current practice?

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FETAL& NEONATAL

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

Oliveira V, Singhvi DP, Montaldo P, Lally PJ, Mendoza J, Manerkar S, Shankaran S, Thayyil S.

Arch Dis Child Fetal Neonatal Ed. 2018 Jul;103(4):F388-F390. doi: 10.1136/archdischild-2017-313320. Epub 2017 Sep 23. PMID: 28942433.

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FETAL& NEONATAL

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

Oliveira and colleagues. Arch Dis Child Fetal Neonatal Ed. 2018 Jul;103(4):F388-F390. doi: 10.1136/archdischild-2017-313320.

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Tables & Figures

Table 1: Reasons for offering cooling therapy or not for babies with mild NE

Units offering cooling therapy in mild NE (multiple selections possible)	**36 (75%)**
Risk of long term adverse neurological problems	17 (47%)
It is very difficult to grade NE soon after birth	25 (69%)
Mild NE may progress to moderate NE, missing the window period of cooling	28 (78%)
Litigation risks if baby is not offered cooling, and later develops neurological deficits	8 (22%)
Cooling therapy is extremely safe and easy to provide	12 (33%)
Other(*)	8 (22%)
Units not offering cooling therapy in mild NE (multiple selections possible)	**12 (25%)**
The vast majority of babies with mild NE do well and do not get any neurological deficit	7 (58%)
There is no evidence to support cooling in babies with mild NE	12 (100%)
Cooling therapy is not without side effects	5 (42%)
Avoiding additional interventions (ventilation/sedation) or prolonged hospitalisation	3 (25%)

(*) Other reasons reported were: *those with abnormal aEEG may benefit* (3 responses); *based on clinical experience* (1 response), *colleague/network advice* (1 response). Three units gave unclear answers.

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Table 2: Clinical management practices of cooling in babies with mild NE

Age at initiation of cooling therapy	
< 6 hours	29 (81%)
< 12 hours	7 (19%)
Duration of cooling	
72 hours irrespective of clinical improvement	22 (61%)
Approximately 24h then rewarm if improvement noted	3 (8%)
Less than 24h then rewarm if improvement notes	7 (19%)
Varying duration – can stop any time	3 (8%)
Other(*)	1 (3%)
Sedation used:	
Morphine	32 (89%)
Chloral hydrate	4 (11%)
Other drugs (midazolam/phenobarbital)	2 (6%)
Enteral feeds during cooling:	
Withheld	15 (42%)
Reduced regimen <25% of requirements	8 (22%)
Reduced regimen 25 to 50% of requirements	4 (11%)
Reduced regimen > 50% of requirements	4 (11%)
Other feeding practices – depending on baby's cues/attending consultant	5 (14%)
Magnetic resonance imaging	
Yes – all babies with mild NE	3 (8%)
Yes – if cooled	29 (81%)
No	2 (6%)
Other(**)	2 (6%)
Neurodevelopmental follow-up in mild NE	
Yes – all babies with mild NE	2 (6%)
Yes – if cooled	27 (75%)
Other(***)	3 (8%)
No	4 (11%)

(*) Other cooling duration: one unit (3%) gave unclear answer.
(**) One unit (3%) responded that magnetic resonance imaging *is offered depending on presentation and subsequent course* and 1 (3%) responded that *only babies who received 3 days of cooling therapy will be offered MRI.*
(***) One unit (3%) provides follow-up to all babies in catchment area only; one (3%) only if baby received 3 days of cooling therapy) and one (3%) has no specific criteria.

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Later?

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JAMA The Journal of the American Medical Association

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

Laptook AR, Shankaran S, Tyson JE for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network.

JAMA. 2017 Oct 24;318(16):1550-1560. doi: 10.1001/jama.2017.14972.

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

Objective: 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 noncooling 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 benefit but there is uncertainty in its effectiveness.**

Laptook for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. JAMA. 2017 Oct 24;318(16):1550-1560. doi: 10.1001/jama.2017.14972.

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In LMICs?

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THE LANCET Global Health

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

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THE LANCET Global Health

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

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.

Sudhin Thayyil for the Helix Consortium. Lancet Glob Health 2021; 9: e1273–85 DOI: https://doi.org/10.1016/S2214-109X(21)00264-3

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THE LANCET Global Health

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

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

Sudhin Thayyil for the Helix Consortium. Lancet Glob Health 2021; 9: e1273–85 DOI: https://doi.org/10.1016/S2214-109X(21)00264-3

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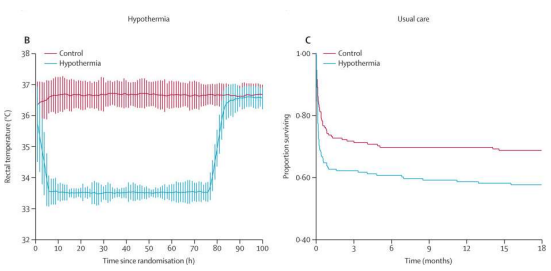
THE LANCET Global Health

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

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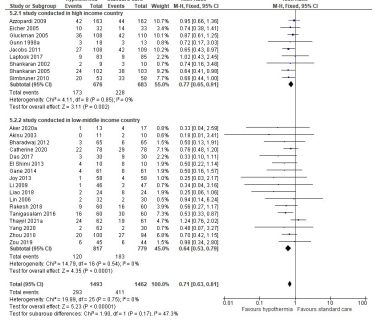
Cooling for newborns with hypoxic ischemic encephalopathy: Analysis based on setting: effect on death



RR 0.77 95%CI 0.65 to 0.91

RR 0.64 95%CI 0.53 to 0.79

RR 0.71 95%CI 0.63 to 0.81

Jacobs SE and colleagues. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003311. DOI: 10.1002/14651858.CD003311.pub2. Updated by M. Berg 2012, 2022

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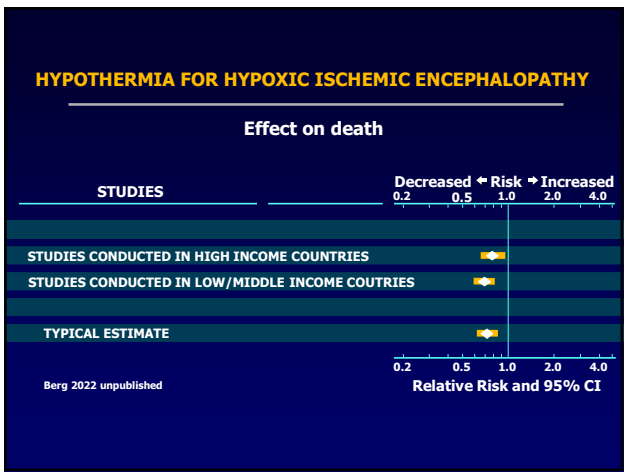
HYPOTHERMIA FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY

Effect on death



Berg 2022 unpublished

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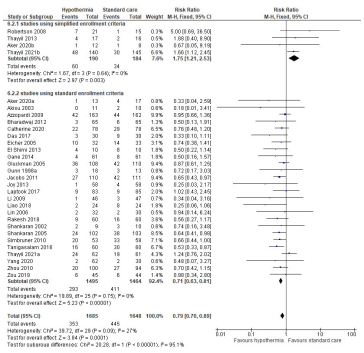
Cooling for newborns with hypoxic ischemic encephalopathy: Sensitivity analysis based on enrollment criteria: effect on death



RR 1.75 95%CI 1.21 to 2.53

RR 0.71 95%CI 0.63 to 0.81

RR 0.79 95%CI 0.70 to 0.89

Jacobs SE and colleagues. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003311. DOI: 10.1002/14651858.CD003311.pub2. Updated by M. Berg 2012, 2022

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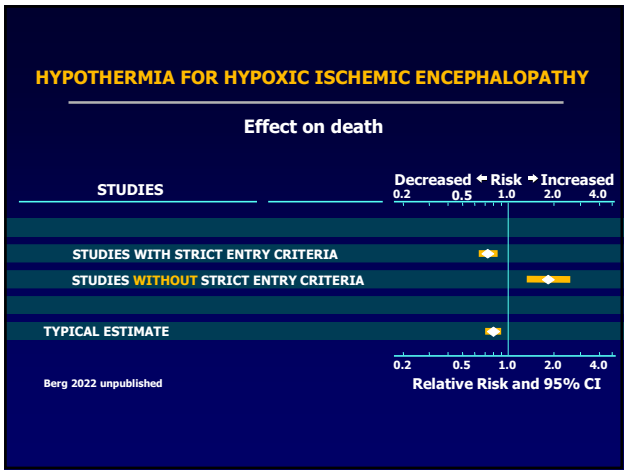

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Longer and deeper?

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JAMA The Journal of the American Medical Association

Effect of Depth and Duration of Cooling on Deaths in the NICU Among Neonates With Hypoxic Ischemic Encephalopathy: A Randomized Clinical Trial.

Shankaran S, Laptook AR, Pappas A, et al.

JAMA. 2014;312(24):2629–2639.
doi:10.1001/jama.2014.16058

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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), 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) Neonatal 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

Shankaran and colleagues. Effect of Depth and Duration of Cooling on Deaths in the NICU Among Neonates With Hypoxic Ischemic Encephalopathy: A Randomized Clinical Trial. JAMA. 2014;312(24):2629–2639. doi:10.1001/jama.2014.16058

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Effect of Depth and Duration of Cooling on Deaths in the NICU Among Neonates With Hypoxic Ischemic Encephalopathy: A Randomized Clinical Trial:
Effect on NICU mortality

Intervention	Intervention	Routine	Risk ratio
Depth of cooling	32.0°C for 72 hours group	33.5°C for 72 hours group	
	13/90 (14%)	7/95 (7%)	
Duration of cooling	32.0°C for 120 hours group	33.5°C for 120 hours group	
	14/83 (17%)	15/96 (16%)	
Duration of cooling			RR 1.37 (95% CI, 0.92 to 2.04)
Depth of cooling			RR 1.24 (95% CI, 0.69 to 2.25)

Shankaran and colleagues. Effect of Depth and Duration of Cooling on Deaths in the NICU Among Neonates With Hypoxic Ischemic Encephalopathy: A Randomized Clinical Trial. JAMA. 2014;312(24):2629–2639. doi:10.1001/jama.2014.16058

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Pediatric RESEARCH

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

Natarajan G, Pappas A, Shankaran S, Laptook AR, Walsh M, McDonald SA, Ehrenkranz RA, Tyson JE, Goldberg RN, Bara R, Higgins RD, Das A, Munoz B.

Pediatr Res. 2012 Oct;72(4):414-9. doi: 10.1038/pr.2012.103. Epub 2012 Jul 25. PMID: 22914450; PMCID: PMC3730811.

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Pediatric RESEARCH

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 (43 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.

Natarajan and colleagues. Effect of inborn vs. outborn delivery on neurodevelopmental outcomes in infants with hypoxic–ischemic encephalopathy: secondary analyses of the NICHD whole-body cooling trial. Pediatr Res 72, 414–419 (2012). https://doi.org/10.1038/pr.2012.103

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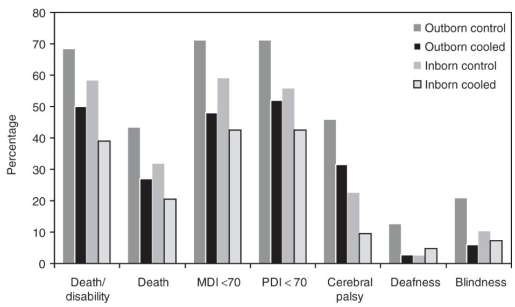
Pediatric RESEARCH

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



Natarajan and colleagues. Effect of inborn vs. outborn delivery on neurodevelopmental outcomes in infants with hypoxic–ischemic encephalopathy: secondary analyses of the NICHD whole-body cooling trial. Pediatr Res 72, 414–419 (2012). https://doi.org/10.1038/pr.2012.103

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Severity

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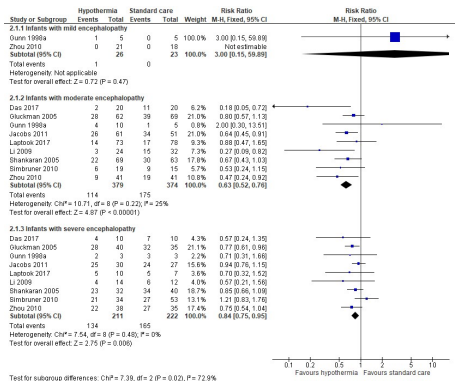
Cooling for newborns with hypoxic ischemic encephalopathy: effect on death or major disability based on intial disease severity



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Pediatric RESEARCH

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.

Pediatr Res. 2019 Mar;85(4):442-448. doi: 10.1038/s41390-019-0291-1. Epub 2019 Jan 16. PMID: 30733613.

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Pediatric RESEARCH

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 that 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 hyperthermia 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.

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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?

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Guest Discussants

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

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

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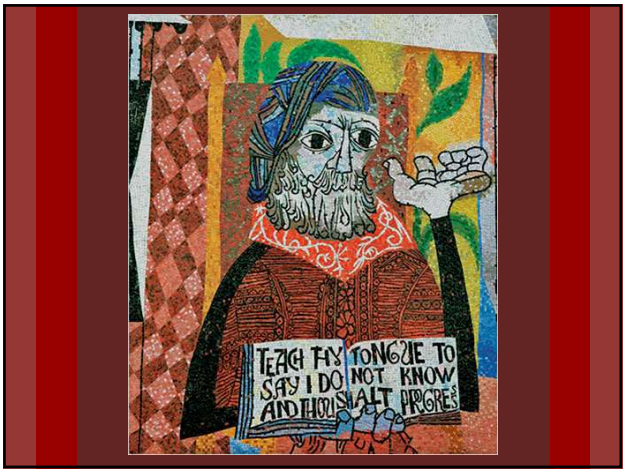

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https://public.vtoxford.org/cochrane-at-von/

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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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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

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Guest Discussants

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

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

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Web voting

- Text vtoxford to 22333

Text voting

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Have you ever participated in a Cochrane Neonatal web seminar?

Yes

No

I can't remember

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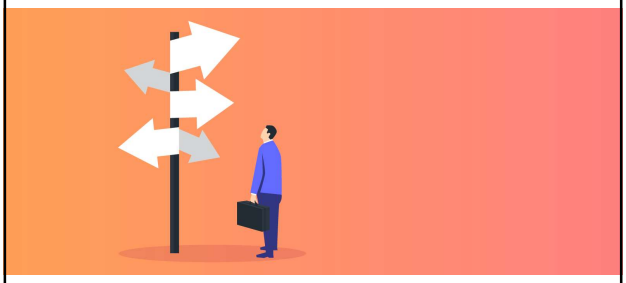
What to actually do?



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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?

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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

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Cooling for newborns with hypoxic ischemic encephalopathy.

Jacobs SE and colleagues. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003311. DOI: 10.1002/14651858.CD003311.pub2.

Updated by M. Berg 2012, 2022

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HYPOTHERMIA FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY

IMPACT OF COOLING ON DEATH AND DISABILITY

OUTCOMES (N STUDIES)	Risk Difference (95% CI)
DEATH OR MAJOR DISABILITY (13)	-0.14 (-0.18 to -0.09)
DEATH (26)	-0.08 (-0.11 to -0.05)
MAJOR DISABILITY (12)	-0.08 (-0.11 to -0.04)

Decreased ⇐ Risk ⇒ Increased

0.2 0.5 1.0 2.0 4.0

Modified from Jacobs 2007; updated M. Berg 2022

0.2 0.5 1.0 2.0 4.0

Relative Risk and 95% CI

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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

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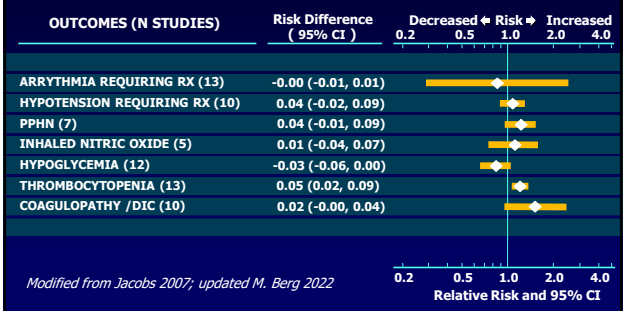
HYPOTHERMIA FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY

COMPLICATIONS OF COOLING

OUTCOMES (N STUDIES)	Risk Difference (95% CI)
ARRYTHMIA REQUIRING RX (13)	-0.00 (-0.01, 0.01)
HYPOTENSION REQUIRING RX (10)	0.04 (-0.02, 0.09)
PPHN (7)	0.04 (-0.01, 0.09)
INHALED NITRIC OXIDE (5)	0.01 (-0.04, 0.07)
HYPOGLYCEMIA (12)	-0.03 (-0.06, 0.00)
THROMBOCYTOPENIA (13)	0.05 (0.02, 0.09)
COAGULOPATHY /DIC (10)	0.02 (-0.00, 0.04)



Modified from Jacobs 2007; updated M. Berg 2022

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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

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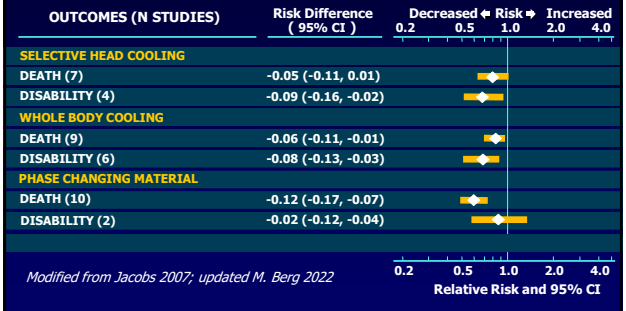
HYPOTHERMIA FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY

Effect on death and effect on disability

OUTCOMES (N STUDIES)	Risk Difference (95% CI)
SELECTIVE HEAD COOLING	
DEATH (7)	-0.05 (-0.11, 0.01)
DISABILITY (4)	-0.09 (-0.16, -0.02)
WHOLE BODY COOLING	
DEATH (9)	-0.06 (-0.11, -0.01)
DISABILITY (6)	-0.08 (-0.13, -0.03)
PHASE CHANGING MATERIAL	
DEATH (10)	-0.12 (-0.17, -0.07)
DISABILITY (2)	-0.02 (-0.12, -0.04)



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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."

Hoehn and colleagues. Therapeutic hypothermia in neonates. Review of current clinical data, ILCOR recommendations and suggestions for implementation in neonatal intensive care units. Resuscitation. 2008 Jul;78(1):7-12. doi: 10.1016/j.resuscitation.2008.04.027. PMID: 18554560.

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Cooling for hypoxic ischemic encephalopathy

What are we supposed to do?

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Hospital Guidelines

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

Yes
No
Uncertain

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Hospital Guidelines Gestational Age

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

Yes
No
Uncertain

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Hospital Guidelines Severity of disease

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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FETAL& NEONATAL

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

Oliveira and colleagues. Arch Dis Child Fetal Neonatal Ed. 2018 Jul;103(4):F388-F390. doi: 10.1136/archdischild-2017-313320.

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Tables & Figures

Table 1: Reasons for offering cooling therapy or not for babies with mild NE

Units offering cooling therapy in mild NE (multiple selections possible)	**36 (75%)**
Risk of long term adverse neurological problems	17 (47%)
It is very difficult to grade NE soon after birth	25 (69%)
Mild NE may progress to moderate NE, missing the window period of cooling	28 (78%)
Litigation risks if baby is not offered cooling, and later develops neurological deficits	8 (22%)
Cooling therapy is extremely safe and easy to provide	12 (33%)
Other(*)	8 (22%)
Units not offering cooling therapy in mild NE (multiple selections possible)	**12 (25%)**
The vast majority of babies with mild NE do well and do not get any neurological deficit	7 (58%)
There is no evidence to support cooling in babies with mild NE	12 (100%)
Cooling therapy is not without side effects	5 (42%)
Avoiding additional interventions (ventilation/sedation) or prolonged hospitalisation	3 (25%)

(*) Other reasons reported were: *those with abnormal aEEG may benefit* (3 responses); *based on clinical experience* (1 response), *colleague/network advice* (1 response). Three units gave unclear answers.

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Hospital Guidelines Age at cooling (chronological age)

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

Yes
No
Uncertain

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Table 2: Clinical management practices of cooling in babies with mild NE

Age at initiation of cooling therapy	
< 6 hours	29 (81%)
< 12 hours	7 (19%)
Duration of cooling	
72 hours irrespective of clinical improvement	22 (61%)
Approximately 24h then rewarm if improvement noted	3 (8%)
Less than 24h then rewarm if improvement notes	7 (19%)
Varying duration – can stop any time	3 (8%)
Other(*)	1 (3%)
Sedation used:	
Morphine	32 (89%)
Chloral hydrate	4 (11%)
Other drugs (midazolam/phenobarbital)	2 (6%)
Enteral feeds during cooling:	
Withheld	15 (42%)
Reduced regimen <25% of requirements	8 (22%)
Reduced regimen 25 to 50% of requirements	4 (11%)
Reduced regimen > 50% of requirements	4 (11%)
Other feeding practices – depending on baby's cues/attending consultant	5 (14%)
Magnetic resonance imaging	
Yes – all babies with mild NE	3 (8%)
Yes – if cooled	29 (81%)
No	2 (6%)
Other(**)	2 (6%)
Neurodevelopmental follow-up in mild NE	
Yes – all babies with mild NE	2 (6%)
Yes – if cooled	27 (75%)
Other(***)	3 (8%)
No	4 (11%)

(*) Other cooling duration: one unit (3%) gave unclear answer.
(**) One unit (3%) responded that magnetic resonance imaging *is offered depending on presentation and subsequent course* and 1 (3%) responded that *only babies who received 3 days of cooling therapy will be offered MRI.*
(***) One unit (3%) provides follow-up to all babies in catchment area only; one (3%) only if baby received 3 days of cooling therapy) and one (3%) has no specific criteria.

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Hospital Guidelines
Setting of care

Centers in low and middle income countries should not consider using therapeutic hypothermia in infants with encephalopathy.

Yes

No

Uncertain

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THE LANCET
Global Health

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

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

Sudhin Thayyil for the Helix Consortium. Lancet Glob Health 2021; 9: e1273–85 DOI: https://doi.org/10.1016/S2214-109X(21)00264-3

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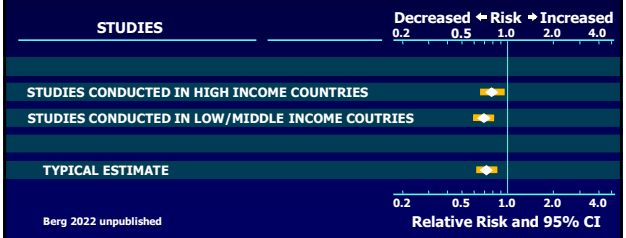
HYPOTHERMIA FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY

Effect on death



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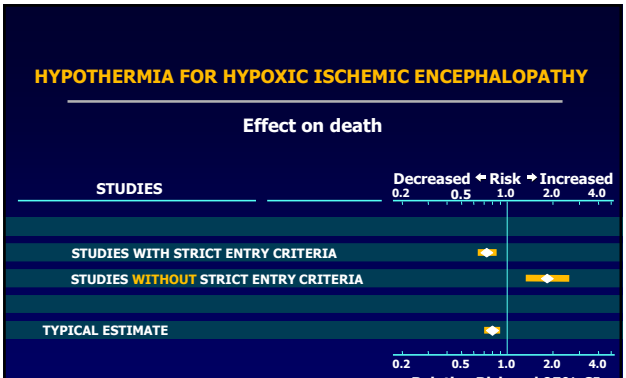
HYPOTHERMIA FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY

Effect on death



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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)

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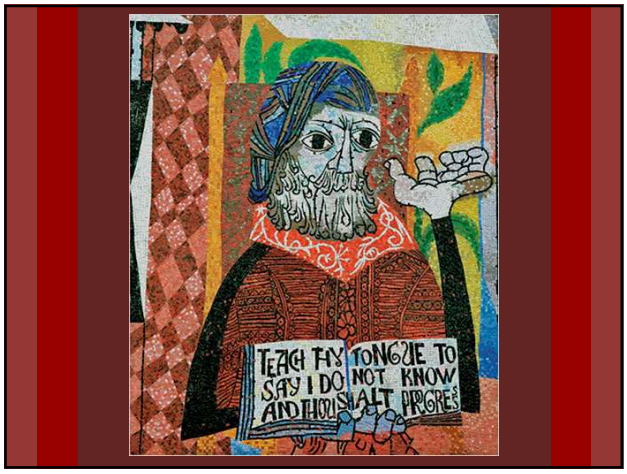

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