2025 VON Grand Rounds Date: 02/19/2025

Planners: Roger Soll MD; Denise Zayack RN, MPH

Speaker(s): Roger Soll MD, Danielle Ehret MD, Elizabeth Rogers, MD

Purpose Statement/Goal of this Activity: The 2025 VON Grand Rounds webinar series will provide evidence reviews, a summary of the current practice guidelines, a synthesis of the application of evidence in real work practice settings and will be supported by discussion and question and answer opportunities with expert faculty

The following have relevant financial relationships with ineligible companies (all have been mitigated):
All other speakers/planners/CMIE reviewers do not have ay relevant financial relationships.

This activity did not receive any support for ineligible companies (grants or in-kind).

All recommendations involving clinical medicine made during this talk were based on evidence that is accepted within the profession of medicine as adequate justification for their indication and contradictions in the care of patients.

In support of improving patient care, this activity ahs been planned and implemented by The Robert Larner College of Medicine at the University of Vermont and Vermont Oxford Network. The University of Vermont is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialling Center (ANCC), to provide continuing education for the healthcare team.

The University of Vermont designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extend of their participation in the activity.

This program has been reviewed and is acceptable for up to 1.0 Nursing Contact Hours.

This activity was planned by and for the healthcare team, and learners will receive 1 Interprofessional Continuing Education (IPCE) credit for learning and change.

1

VON Grand Rounds

Evidence to Practice: Therapeutic Hypothermia

February 19th, 2025

VON Vermont Oxford NETWORK

2

VON Vermont Oxford NETWORK

Moderators

Roger F. Soll, MD
H. Wallace Professor of Neonatology, University of Vermont
Coordinating Editor, Cochrane Neonatal
Director, VON Institute for Evidence Based Practice, Vermont Oxford Network

Danielle Ehret, MD, MPH
Asfaw Yemiru Green and Gold Professor, University of Vermont
Chief Medical Officer, Director, Global Health, Vermont Oxford Network

3

VON Vermont Oxford NETWORK

Discussant

Elizabeth Rogers, MD
Professor of Pediatrics
UCSF School of Medicine
Director of the ROOTS Small Baby Programs in the Intensive Care Nursery at UCSF Mission Bay

4

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Evidence to Practice: Therapeutic Hypothermia

Disclosures

Danielle Ehret MD, MPH is the Director of Global Health and Chief Medical Officer at Vermont Oxford Network (VON) and receives salary support to UVM for non-clinical time dedicated to her leadership roles.

Roger F. Soll, MD is the H. Wallace Professor of Neonatology at the Larner College of Medicine at the University of Vermont, Vice President of the Vermont Oxford Network, Director of the VON Institute for Evidence Based Practice, and Coordinating Editor of Cochrane Neonatal. He is a consultant with the International Liaison Committee on Resuscitation (ILCOR).

Elizabeth Rogers MD has no commercial interests to disclose.

No other relevant financial issues to disclose

6

How to Participate in Today's Webinar

- Chat questions and comments to "Everyone" at any time.
- Respond to poll questions posed during the session.

Three Ways to Respond to Polls:

Go to PollEv.com/vtoxford:

Text "vtoxford" to 22333
Then send A, B, or C

Poll Everywhere app:
Enter username
"vtoxford"

VON Vermont Oxford NETWORK

7

Poll Question Guidelines

Join by Web PollEv.com/vtoxford Join by Text Send vtoxford to 22333

Do you have written guidelines that address the use of therapeutic hypothermia in infants with hypoxic ischemic encephalopathy? 157

(A) Yes 93%
(B) No 6%
(C) Uncertain 1%

8

VON Vermont Oxford NETWORK

Evidence to Practice: Therapeutic Hypothermia

Roger F. Soll, MD
H. Wallace Professor of Neonatology, University of Vermont
Coordinating Editor, Cochrane Neonatal
Director, VON Institute for Evidence Based Practice, Vermont Oxford Network

9

10

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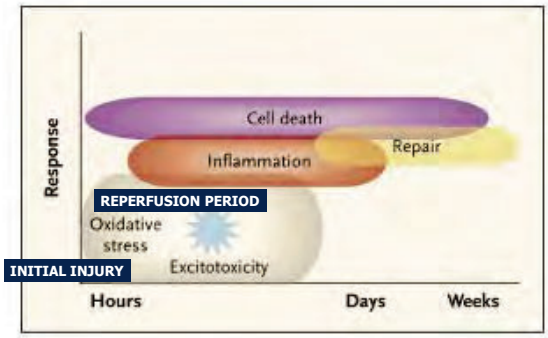
Hypoxic ischemic encephalopathy

Major predictor of neurodevelopmental disability

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

11

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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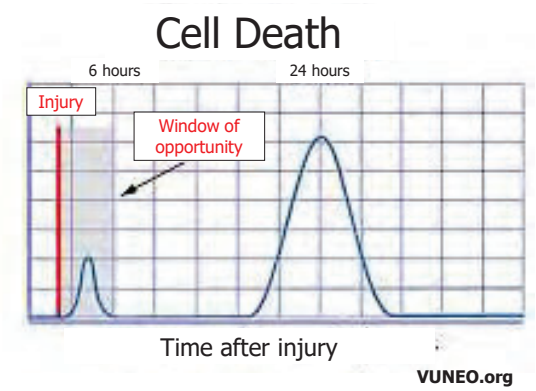

13

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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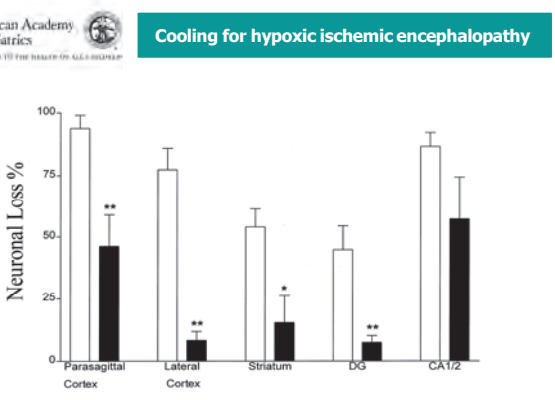

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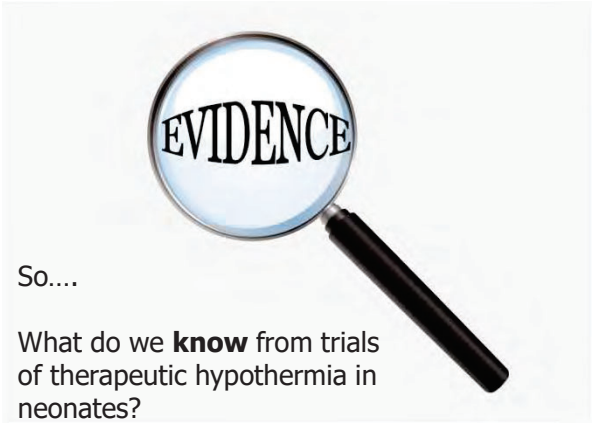


16

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.

17

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

18

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

19

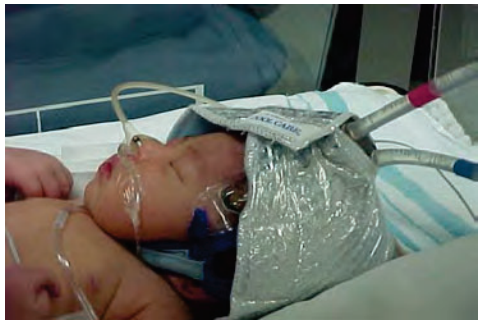
Cooling for hypoxic ischemic encephalopathy

Types of interventions

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

20

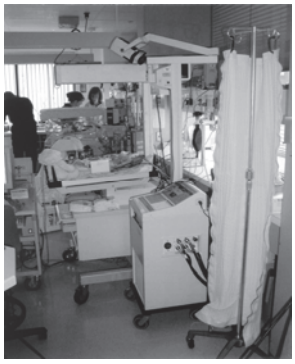
Head Cooling (with temperature servocontrol)



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

21

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

22

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

23

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.

24

Cooling for newborns with hypoxic ischemic encephalopathy.

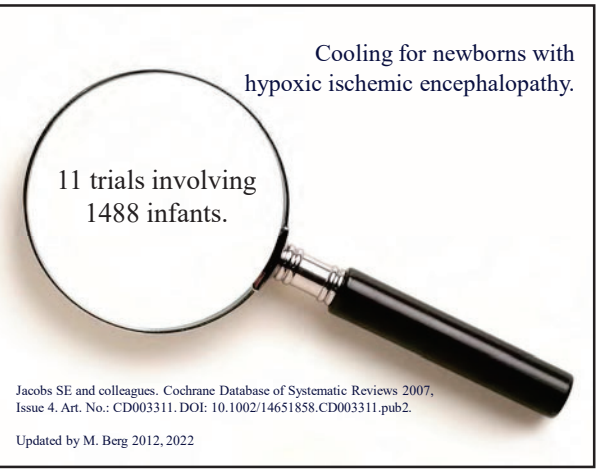
Jacobs SE, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG.
Cochrane Database of Systematic Reviews 2007, Issue 4.
Art. No.: CD003311.
DOI: 10.1002/14651858.CD003311.pub2.

Updated by M. Berg 2012, 2022

THE COCHRANE COLLABORATION®

25

Cooling for newborns with hypoxic ischemic encephalopathy.

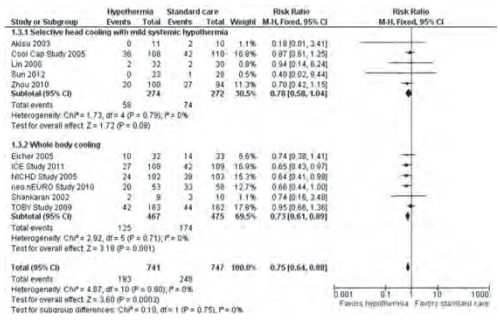


Jacobs SE and colleagues. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003311. DOI: 10.1002/14651858.CD003311.pub2.

Updated by M. Berg 2012, 2022

26

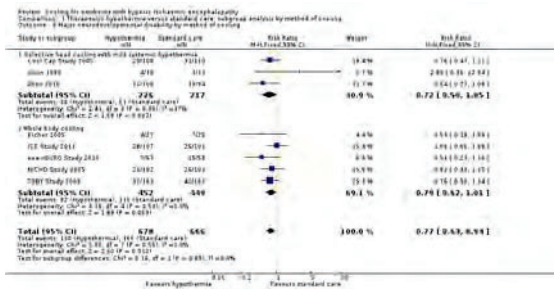
Cooling for newborns with hypoxic ischemic encephalopathy: effect on death



RR 0.75, 95% CI 0.64 to 0.88; RD -0.09, 95% CI -0.13 to -0.04; NNTB 11, 95% CI 8 to 25 (11 studies, 1468 infants)

27

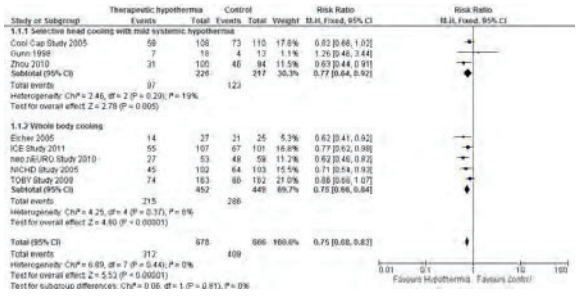
Cooling for newborns with hypoxic ischemic encephalopathy: effect on major disability in survivors



RR 0.77, 95% CI 0.63 to 0.94; RD -0.13, 95% CI -0.19 to -0.07; NNTB 8, 95% CI 5 to 14 (8 studies, 917 infants)

28

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



RR 0.75, 95% CI 0.68 to 0.83; RD -15, 95% CI -0.20 to -0.10;
number needed to treat for an additional beneficial outcome (NNTB) 7, 95% CI 5 to 10 (8 studies, 1344 infants)

29

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.

30

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.

31

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.

32

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?

33

Cooling for hypoxic ischemic encephalopathy

What are we supposed to do?

34

Later?

35

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.

36

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.

37

In LMICs?

38

Therapeutic hypothermia is now standard care in high-income countries for the treatment of moderate or severe hypoxic ischemic encephalopathy in term and near-term infants.

However, uncertainty persists about the efficacy of therapeutic hypothermia in low-resource settings or in low- and middle-income countries.

39

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

40

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

41

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.

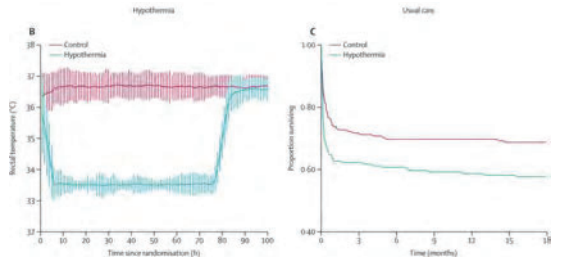
Therapeutic hypothermia should not be offered as treatment for neonatal encephalopathy in low-income and middle income countries, even when tertiary neonatal intensive care facilities are available

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

42

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

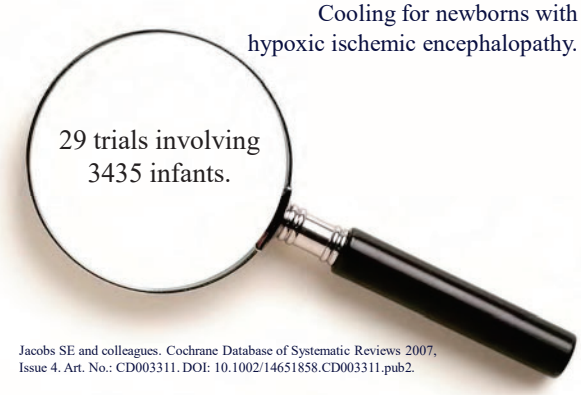


Sudhin Thayyil for the Helix Consortium. Lancet Glob Health 2021; 9: e1273–85 DOI: https://doi.org/10.1016/S2214-109X(21)00264-3

43

Cooling for newborns with hypoxic ischemic encephalopathy.

29 trials involving 3435 infants.

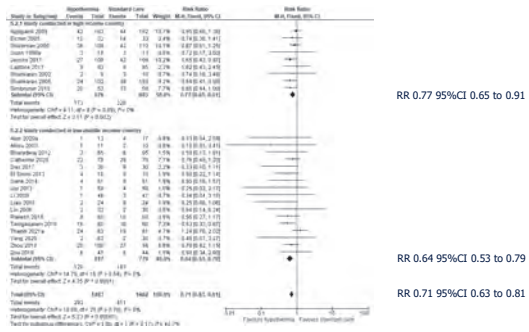


Jacobs SE and colleagues. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003311. DOI: 10.1002/14651858.CD003311.pub2.

Updated by M. Berg 2012, 2022

44

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

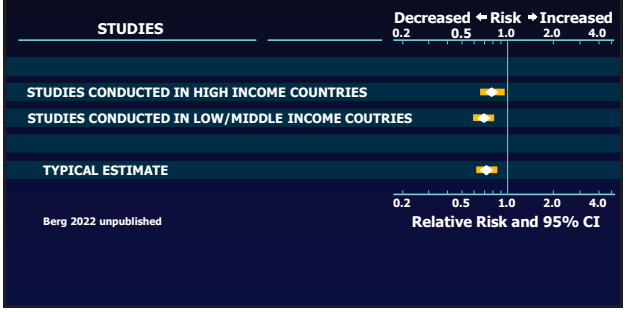
RR 0.71 95%CI 0.63 to 0.81

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

45

HYPOTHERMIA FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY

Effect on death



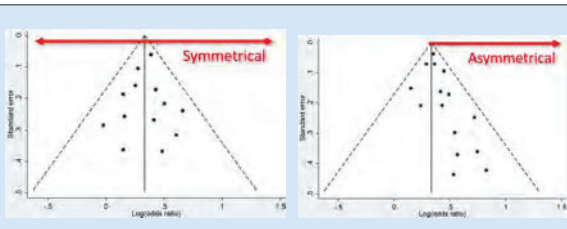
Berg 2022 unpublished

46

What is a "funnel plot"

An ideal funnel plot is one where the included studies have scattered on either side of the overall effect line in a symmetrical manner.

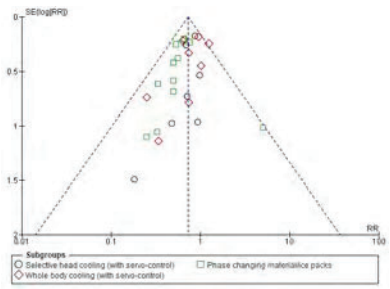
Severe asymmetry to either side, however, is an indication that publication bias may be present.



47

Cooling for newborns with hypoxic ischemic encephalopathy: effect on death

Berg 2022 unpublished



48

Longer and deeper?

49

The chicken soup theory

"If a little is good…more is better"

50

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

51

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

52

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)

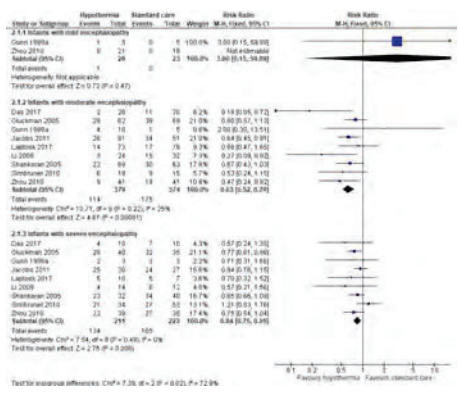
Shankaran and colleagues. Effect of Depth and Duration of Cooling on Deaths in the NICU Among Neonates With Hypoxic Ischemic Encephalopathy: A Randomized Clinical Trial. JAMA. 2014;312(24):2629–2639. doi:10.1001/jama.2014.16058

53

Severity

54

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



55

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.

56

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.

57

Early Human Development
Volume 120, May 2018, Pages 80-87

Mild hypoxic ischaemic encephalopathy and long-term neurodevelopmental outcome - A systematic review.

Conway JM, Walsh BH, Boylan GB, Murray DM

Early Hum Dev. 2018;120:80-87.
doi:10.1016/j.earlhumdev.2018.02.007

58

Early Human Development
Volume 120, May 2018, Pages 80-87

Mild hypoxic ischaemic encephalopathy and long term neurodevelopmental outcome - A systematic review

Aims: Hypoxic ischaemic encephalopathy (HIE) remains a significant cause of long term neurodisability despite therapeutic hypothermia (TH). Infants with mild HIE, representing 50% of those with HIE, are perceived as low risk and are currently not eligible for TH [1]. This review examines the available evidence of outcome in term infants with mild HIE.

Methods: Medline, Embase and Cochrane Clinical Trials databases were searched in March 2017. Studies with well-defined HIE grading at birth and standardised neurodevelopmental assessment at ≥18 months were included. Abnormal outcome was defined as death, cerebral palsy or standardised neurodevelopmental test score more than 1 standard deviation below the mean.

Result: Twenty studies were included. Abnormal outcome was reported in 86/341 (25%) of infants. There was insufficient evidence to examine the effect of TH on outcome.

Conclusion: A significant proportion of infants with mild HIE have abnormal outcome at follow up.

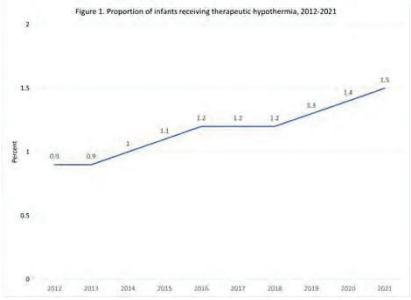
Conway and colleagues. Mild hypoxic ischaemic encephalopathy and long term neurodevelopmental outcome - A systematic review. Early Hum Dev. 2018;120:80-87. doi:10.1016/j.earlhumdev.2018.02.007

59

Current practice?

60

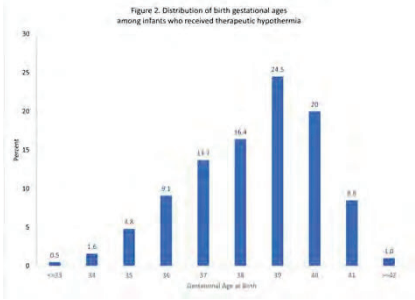
Vermont Oxford NETWORK



Overall, 23,047 of 1,932,346 (1.2%) infants reported to the Vermont Oxford Network expanded database of all neonatal intensive care unit admissions received therapeutic hypothermia. The rate of cooling increased linearly from 0.9% in 2012 to 1.5% in 2021

61

Vermont Oxford NETWORK



Of those who received therapeutic hypothermia, 6.8% were less than 36 weeks gestational age at birth

62

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.

63

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.

64

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.

65

American Academy of Pediatrics

Trends in HIE and Use of Hypothermia in California: Opportunities for Improvement.

Sonia Lomeli Bonifacio, Jessica Liu, Henry C. Lee, Susan R. Hintz, Jochen Profit;

Pediatrics September 2024; 154 (3): e2023063032. 10.1542/peds.2023-063032

66

American Academy of Pediatrics

Trends in HIE and Use of Hypothermia in California: Opportunities for Improvement

BACKGROUND AND OBJECTIVES : Hypoxic-ischemic encephalopathy (HIE) is a leading cause of neonatal morbidity and mortality. Therapeutic hypothermia (TH), a proven treatment of moderate–severe HIE, was first used clinically after 2006. We describe trends in HIE diagnosis and use of TH over a 10-year period in California.

METHODS: We identified 62 888 infants ≥ 36 weeks gestation, who were cared for in California Perinatal Quality Care Collaborative-participating NICUs between 2010 and 2019, and linked them to birth certificate data.

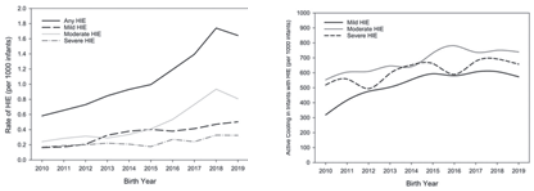
We evaluated trends in HIE diagnosis and use of TH.

Bonifacio and colleagues. Trends in HIE and Use of Hypothermia in California: Opportunities for Improvement. Pediatrics September 2024; 154 (3): e2023063032. 10.1542/peds.2023-063032

67

American Academy of Pediatrics

Trends in HIE and Use of Hypothermia in California: Opportunities for Improvement



Bonifacio and colleagues. Trends in HIE and Use of Hypothermia in California: Opportunities for Improvement. Pediatrics September 2024; 154 (3): e2023063032. 10.1542/peds.2023-063032

68

Journal of Perinatology

Prospective research on infants with mild encephalopathy: the PRIME study.

Prempunpong C, Chalak LF, Garfinkle J, Shah B, Kalra V, Rollins N, Boyle R, Nguyen KA, Mir I, Pappas A, Montaldo P, Thayyil S, Sánchez PJ, Shankaran S, Laptook AR, Sant'Anna G.

J Perinatol. 2018 Jan;38(1):80-85. doi: 10.1038/jp.2017.164.

69

Journal of Perinatology

Prospective research on infants with mild encephalopathy: the PRIME study

Objective: To determine short-term outcomes of infants with evidence of hypoxia-ischemia at birth and classified as mild neonatal encephalopathy (NE) at <6 h of age.

Study design: Prospective multicenter study. Mild NE was defined as ⩾1 abnormal category in modified Sarnat score. Primary outcome was any abnormality on early amplitude integrated electroencephalogram (aEEG) or seizures, abnormal brain magnetic resonance imaging (MRI) or neurological exam at discharge.

Results: A total of 54/63 (86%) of enrolled infants had data on components of the primary outcome, which was abnormal in 28/54 (52%): discontinuous aEEG (n=4), MRI (n=9) and discharge exam (n=22). Abnormal tone and/or incomplete Moro were the most common findings. MRI abnormalities were confined to cerebral cortex but two infants had basal ganglia and/or thalamus involvement. The 18 to 24 months follow-up is ongoing.

Conclusions: A larger than expected proportion of mild NE infants with abnormal outcomes was observed. Future research should evaluate safety and efficacy of neuroprotection for mild NE.

Trial registration: ClinicalTrials.gov NCT01747863.

Prempunpong and colleagues. Prospective research on infants with mild encephalopathy: the PRIME study. J Perinatol. 2018 Jan;38(1):80-85. doi: 10.1038/jp.2017.164.

70

COOL PRIME

COOL Prime (Comparative Effectiveness for Cooling Prospectively Infants with Mild Encephalopathy) is an observational study that will look at the effects of therapeutic hypothermia (TH) vs normothermia (NT) in infants with mild hypoxic ischemic encephalopathy (HIE). The choice of therapy will be based on each clinical site's existing practice.

430 infants with mild HIE will be enrolled across 15 pediatric hospitals. Seven of the site routinely practice TH, and 8 practice NT.

Infants will be followed for two years to assess cognitive and language outcomes using the Bayley Scales of Infant and Toddler Development and parental questionnaires. Early evaluations of sensory modulation along with standardized questionnaires of mother-infant bonding, parenting structure and attachment, mood and stress, allow a meaningful evaluation.

https://www.coolprime.org/about/

71

Seminars in FETAL & NEONATAL

Cooling in mild encephalopathy:
Costs and perils of therapeutic creep.

Kumar V, Singla M, Thayyil S.

Seminars in Fetal and Neonatal Medicine.
2021;26(3):101244. doi:10.1016/j.siny.2021.101244

72

Seminars in FETAL & NEONATAL

Cooling in mild encephalopathy:
Costs and perils of therapeutic creep

Increasing confidence in therapeutic hypothermia and ambiguity of cooling guidelines has led to many clinicians extending its use to untested populations like mild encephalopathy, or even no encephalopathy.

Poor quality clinical neurological examination for encephalopathy staging coupled with a fear of litigation if a baby with mild encephalopathy progress to moderate or severe encephalopathy appears to be the primary driver for this therapeutic creep.

Recent data suggesting increased apoptosis with cooling uninjured brains, and lack of hypothermic neuroprotection in partial prolonged hypoxia, implies that such therapeutic creeps may cause more harm than benefit. Currently available preclinical and clinical data do not support the clinical use of therapeutic hypothermia for mild encephalopathy, although phase II clinical trials are ongoing.

We recommend that until further evidence from adequately powered randomised controlled trials are available, cooling in mild encephalopathy need to be considered experimental and parental consent should be obtained before providing this therapy.

Kumar and colleagues. Cooling in mild encephalopathy: Costs and perils of therapeutic creep. Seminars in Fetal and Neonatal Medicine. 2021;26(3):101244. doi:10.1016/j.siny.2021.101244

73

JAMA Network Open

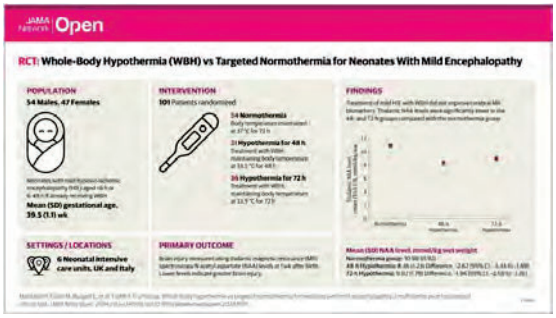
Whole-Body Hypothermia vs Targeted Normothermia
for Neonates With Mild Encephalopathy:
A Multicenter Pilot Randomized Clinical Trial.

Montaldo P, Cirillo M, Burgod C, Caredda E, Ascione S, Carpentieri M, Puzone S, D'Amico A, Garegrat R, Lanza M, Moreno Morales M, Atreja G, Shivamurthappa V, Kariholu U, Aladangady N, Fleming P, Mathews A, Palanisami B, Windrow J, Harvey K, Soe A, Pattnayak S, Sashikumar P, Harigopal S, Pressler R, Wilson M, De Vita E, Shankaran S, Thayyil S; COMET Trial Group.

JAMA Netw Open. 2024 May 1;7(5):e249119. doi: 10.1001/jamanetworkopen.2024.9119.

74

JAMA Network Open



75

76

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?

77

VON Vermont Oxford NETWORK

Discussant

Elizabeth Rogers, MD
Professor of Pediatrics
UCSF School of Medicine
Director of the ROOTS Small Baby
Programs in the Intensive Care Nursery
at UCSF Mission Bay

78

Therapeutic hypothermia

Whom to cool?

79

Case presentation 1

You are called to see a 4-hour old 35-week gestational age newborn with a history of cord prolapse, severe acidosis on an umbilical blood sample (pH < 7.00), an Apgar score of 3 at 5 minutes and 5 at ten minutes who has lethargy, decreased spontaneous activity and hypotonia (moderate encephalopathy based on Sarnat staging).

Join by Web PollEv.com/vtoxford Join by Text Send vtoxford to 22333

Case Presentation 1: Do you recommend starting therapeutic hypothermia? 233

(A) Yes 79%

(B) No 21%

80

Case presentation 2

You are called by a referring physician regarding an 8-hour old 40-week gestational age newborn with a history of shoulder dystocia, severe acidosis on an umbilical blood sample (pH < 7.00), Apgar score of 3 at 5 minutes and 5 at ten minutes who has lethargy, decreased spontaneous activity and hypotonia (moderate encephalopathy based on Sarnat staging).

Join by Web PollEv.com/vtoxford Join by Text Send vtoxford to 22333

Case Presentation 2: Do you recommend starting therapeutic hypothermia? 240

(A) Yes 34%

(B) No 66%

81

Case presentation 3

You are called to see a 5-hour old 40-week gestational age newborn with a history of severe acidosis on an umbilical blood sample (pH < 7.00), an Apgar score of 3 at 5 minutes and 5 at ten minutes who is noted to be hyperalert, jittery, inconsolable and an exaggerated response to minimal stimuli (mild encephalopathy based on Sarnat staging).

Join by Web PollEv.com/vtoxford Join by Text Send vtoxford to 22333

Case Presentation 3: Do you recommend starting therapeutic hypothermia? 235

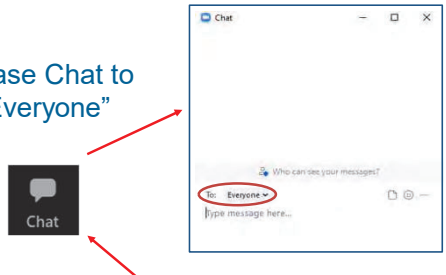
(A) Yes 53%

(B) No 47%

82

Questions? Comments? Ideas to Share?

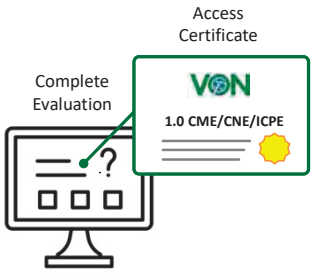
Please Chat to "Everyone"



VON Vermont Oxford NETWORK

83

Continuing Education Credit



VON Vermont Oxford NETWORK

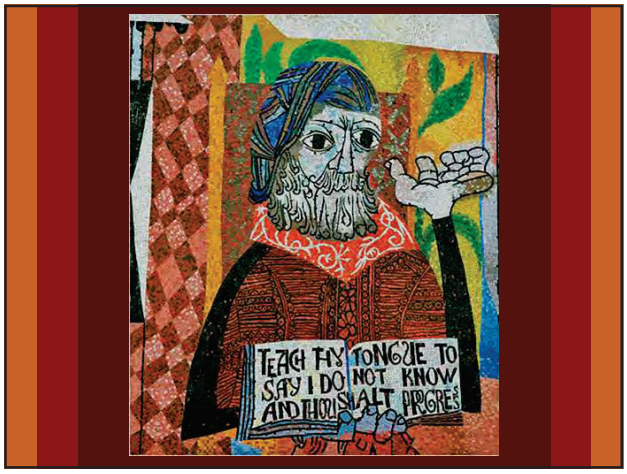
84

Future sessions

May 14th 2025 – Evidence to Practice: Eat Sleep Console

85

86



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