Evidenced Based Data on Neuroprotection in Term Infants

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Hypothermia for Moderate/Severe Encephalopathy in HICs
Death or Disability at 18-24m

	Hypothermia	Control	OR (95% CI)
Cool Cap	55%	66%	0.61 (0.34-1.09)
NICHD	44%	62%	0.72 (0.54-0.95)
TOBY	45%	53 %	0.86 (0.68-1.07
Neo.nEURO	51%	83%	0.21 (0.09-0.54)
ICE	51%	66%	0.21 (0.09-0.54)

Hypothermia RCTs IN HICs: CP AT 18-24m

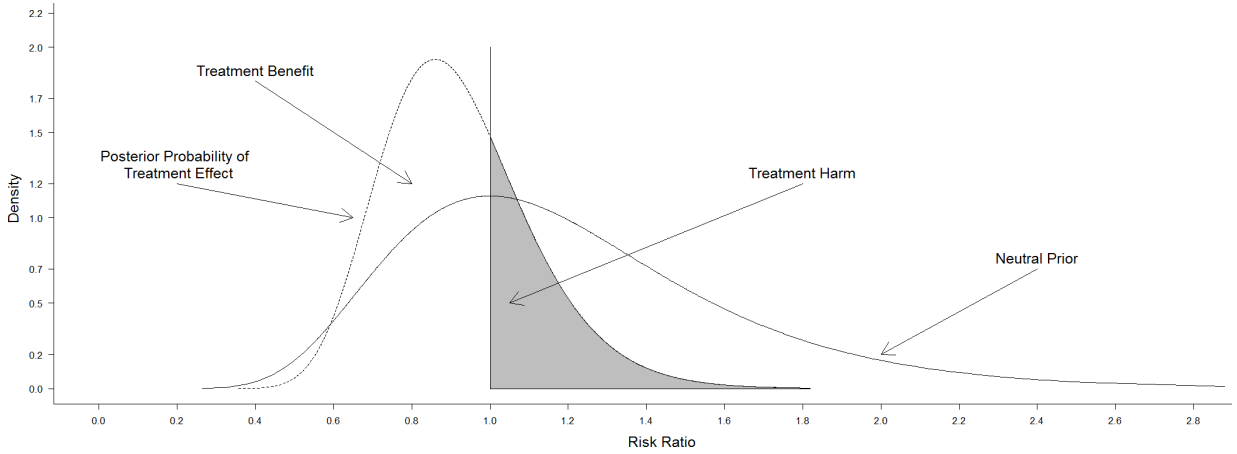
	Hypothermia	Control	OR (95% CI)
Cool Cap	32%	43%	0.75 (0.48-1.16)
NICHD	19%	30%	0.68 (0.38-1.22)
TOBY	28%	41%	0.67 (0.47-0.96)
Neo.nEURO	12%	48%	0.15 (0.04-0.60)
ICE	27%	29%	0.92 (0.54-1.59)

Current Data Shankaran JAMA 2017	Cooled group: First (2005) Hypothermia RCT	Usual Care Cooling: Optimizing Cooling Strategies (2017) RCT
Death or Disability	**44%**	**29%**
Moderate HIE	32%	20%
Severe HIE	72%	62%
Mortality	**24%**	**9%**
MDI (2005) or Bayley III cog >85 (2017)	52%	65%
PDI (2005) or Bayley III motor >85 (2017)	62%	68%
Cerebral palsy	19%	19%

Is Hypothermia effective for moderate or severe HIE if initiated between 6-24 hours ?

Posterior Probability of Reduced Death: Laptook 2017

	Cooled (n=78)		Non-cooled (n=79)		Neutral prior	
	n	%	n	%	aRR, 95% credible intervals	P-TB¥ RR<1.0
Death or mod/sev disability	19	**24.4**	22	**27.9**	**.86 (.58-1.29)**	**.76**



	Cooled (n=69)		Non-cooled (n=70)		*p* value
	n	X±sd or %	n	X±sd, or %	
Bayley III scores					
Cognitive	68	**91.5±16.3**	70	**86.6±16.6**	.08
Language	66	**85.9±19.7**	69	**85.8±21.4**	.96
Motor	67	**89.2±17.9**	70	**86.2±21.0**	.36
CP: Moderate	3	**4**	4	**6**	1.0
Severe	5	**7**	4	**6**	
Blindness	2	**3**	3	**4**	1.0
Hearing impaired	3	**4**	4	**6**	1.0
Seizures + meds	7	**10**	2	**3**	.20

Can greater neuro-protection be achieved with longer cooling or deeper cooling or both?

MR thermometry has shown that BGT temp is higher in severe than moderate HIE and brain temps are lower at the end of TH

WU 2014, Owji 2017

Primary Outcome: 72 vs.120 h:

NICHD NRN Shankaran 2014

	72 h	120 h	Adj RR (95%CI)
Primary Outcome	56/176 (32%)	54/171 (32%)	0.92 0.68-1.25
Death	23/176 (13%)	33/171 (19%)	1.39 1.02-1.89
Moderate/severe disability	33/153 (22%)	21/138 (15%)	0.68 0.41-1.11
CP	28/152 (18%)	18/138 (13%)	0.67 0.37-1.20

Primary Outcome: 33.5°C vs. vs. 32.0°C

Shankaran 2017

	33.5°C	32.0°C	Adj RR (95%CI)
Primary Outcome	59/185 (32%)	51/162 (31%)	0.942 0.68-1.26
Death	26/185 (14%)	30/162 (19%)	1.17 0.67-2.04
Moderate/ severe disability	33/159 (21%)	21/132 (16%)	0.71 0.36-1.39
CP	25/158 (16%)	21/132 (16%)	0.98 0.52-1.82

Evidenced Based Management of Neonates with Moderate/Severe HIE

≥ 36 weeks gestation

< 6 hours of age

2 Steps selection criteria

- ❑ Severe birth acidosis and need for resuscitation
- ❑ Moderate or severe encephalopathy or seizures

The modified Sarnat exam for diagnosing Moderate/Severe HIE

- NICHD: 3 out of the 6 Sarnat exam categories should be moderate or severe to qualify for cooling

- BAPM: TOBY abnormal LOC and any of: hypotonia, abnormal reflexes, clinical seizures plus aEEG criteria (normal with seizures or abnormal background

Elevated Temperature in Control Gp and Odds of Morbidity/Mortality in RCT of Moderate/Severe HIE

Esophageal Temp (°C)	Death or Disability N = 99	Death N = 99	Disability N = 99
Highest quartile	4.0 (1.5 – 11.2)	6.2 (2.1 – 17.9)	1.8 (0.4 – 8.2)
Median	3.3 (0.9 – 11.2)	5.9 (1.5 – 22.7)	1.0 (0.2 – 5.1)

***Adjusted for race, gender, level of encephalopathy, gestational age**
Odds ratio per °C increase (95% confidence interval).
Laptook, 2008

- Similar findings in at 18 mos in CoolCap Trial

- In NICHD 6–7-year outcome analysis, elevated temperature in the control group was associated with increased risk of death or IQ <70

Wyatt 2007, Laptook 2013

Temperature Control

- Before and after Hypothermia therapy elevated temperatures to be treated. These include a tepid bath if temperatures >37.3℃, and cooling device (Blanket) if temperature >37.5℃ after the bath

- Document if infant on radiant warmer, incubator or crib

Temperature monitoring is required hourly to look for elevated temperatures (targeted normothermia)

Hemodynamic Stability and HIE

- Link between cerebral ischemia and cardiac dysfunction unclear
- HIE is associated with myocardial dysfunction or injury
- *Need to monitor blood pressure as the smaller, sicker neonates may require pressor agents*

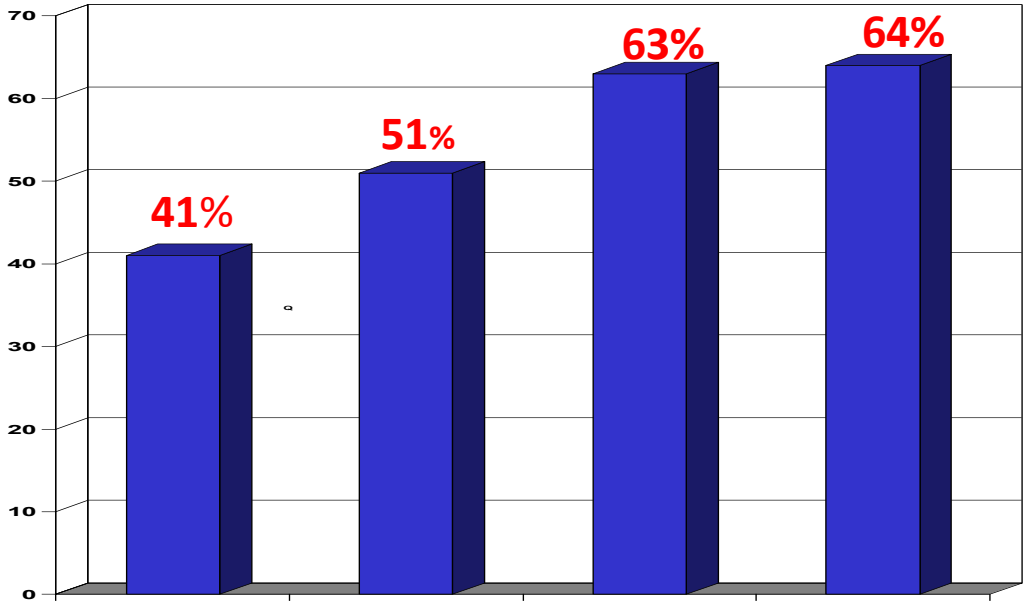
Shankaran 2012
Liu 2011,
Geisinger 2017

Ventilatory Care of Infants with HIE

NICHD Trial: Hypocarbia and 18 mos. outcome in moderate or severe HIE: Pappas 2011

Rate of Death or Disability

(%)



Relationship of PCO_2 and Outcome

Cool Cap Trial data

- Available on 196 of 243 infants enrolled with moderate/severe HIE
- After adjusting for pH, aEEG, birthweight, 5 min Apgar and HIE Stage, PCO_2 during 72 hours of TH was inversely associated with unfavorable outcome
- *Optimize PCO_2 to within normal range among infants on ventilatory support*

Lingappan 2016

Hyperoxemia within first hour of life in HIE

- 120 term infants with birth acidosis
- Infants with hyperoxemia, n=36, (PaO_2 >100 mmHg)
- Those with hyperoxemia had a higher incidence of HIE (58 vs.27%)
- Among all HIE infants, those with hyperoxemia had higher incidence of brain injury on MRI (79 vs.33%)

- *Need to avoid hyperoxemia*

Basu 2016

Hypoglycemia and Hyperglycemia

- 243 infants in the Cool Cap Trial
- Unfavorable outcome was observed in 60% infants
- More common among infants with hypoglycemia (81%), hyperglycemia (67%) and any glycose derangement compared to normoglycemic infants (48%)
- Associations remained after adjustment for birthweight, Apgar score, pH, HIE stage and intervention
- *Need to maintain euglycemia*

Basu 2016

Cerebral function monitoring

- Death or disability is lower among infants with less severe pattern of aEEG or seizures
- Return of background to normal is good predictor of outcome
- Addition of aEEG not better predictor than stage of HIE

Wyatt 2007, Azzopardi 2007, Thoresen 2010, Shankaran 2011

Sedatives, Analgesics?

- Preclinical data has shown that hypothermia was effective only in sedated model
- Pediatric and adult patient are sedated during hypothermia therapy (severe shivering)
- Data in NICHD NRN RCT has demonstrated no efficacy of sedation/analgesia
- Accumulation of morphine
- Parental concerns: morphine use, end-of-life care and addiction

Haaland 1997, Natarajan 2018, Roka 2008, Craig 2018

Time to Initiation of Cooling

- Age at initiation of cooling at <6 hours of age did not impact outcome
- Location of birth did not impact outcome
- *In clinical practice, perform neurological examination only after infant has recovered from resuscitation (>1h of age)*

Shankaran, 2008, Natarajan 2012, Wyatt 2008, Azzopardi 2009

Transport Cooling for Neonates with Moderate or Severe HIE

Use of servo-controlled units vs. passive cooling

- Earlier achievement of target temperature
- Higher percentage of time in target range
- *Confirm stage of encephalopathy; transport with servo-controlled unit; transport team needs to be trained in neuro exams and use of cooling unit*

Johnston 2012, Stafford 2017
Akula 2015, Roberts 2016

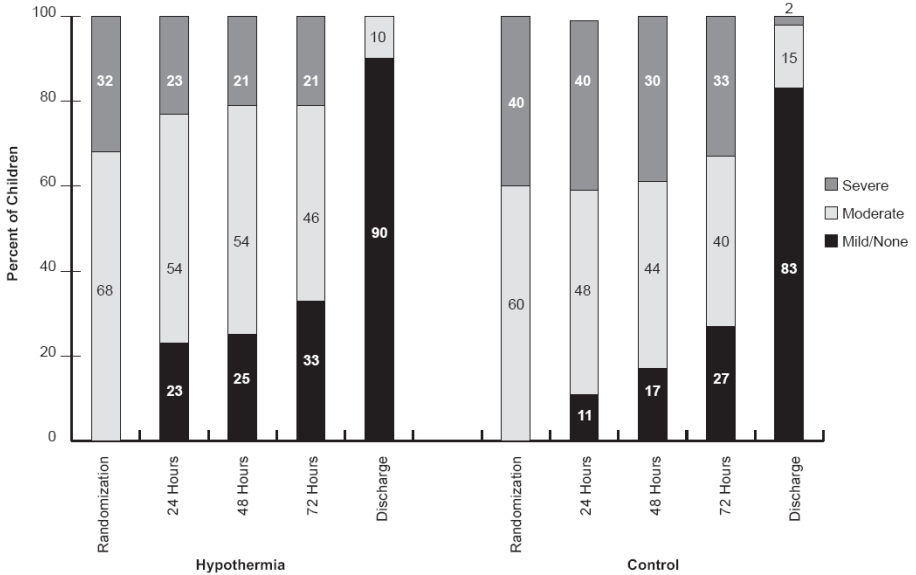
Delivery Room Management

- A persistently low 10 min Apgar score is associated with death or moderate/severe disability at 18 months and at 6-7 years of age
- Not all infants with a 10 min Apgar score ≤3 had uniformly poor outcome; 20% of children with score of 0 at 10 mins survived without disability at school age.
- *Resuscitation should be continued for >10 min*

Laptook 2009, Natarajan 2013, Shukla 2022

Is there an early biomarker that correlates well with later outcomes?

Evolution of Encephalopathy Among Infants with HIE ± Hypothermia: A Biomarker



Shankaran et al 2012

Evolution of Encephalopathy during Hypothermia for HIE

- Persistence of severe HIE at 72 hours increased risk of death or disability after controlling for treatment group

  OR 60 (15-246)

- Abnormal neuro exam at discharge (tone, clonus, fisted hand, movement, absent gag, ATNR), OR 2.7 (1.1-6.7). Gavage/GT at discharge OR 8.6 (2.7-26.8)

- *Need to perform serial neuro exams*

Shankaran, 2012

Brain Imaging

Is there an early imaging biomarker that correlates well with later outcomes?

Relationship of NICHD NRN Brain Injury MRI score and outcome at 18 m (n=136/208) Shankaran 2012

Summary score	Death or disability		Death		Disability (survivors)		
	n (%)	P	n (%)	P	Mod-Severe n (%)	None-Mild n (%)	P
NICHD SCORE:		<0.0001		.05			<0.0001
0	5 (9)		2 (3)		3 (5)	53 (95)	
1A	0 (0)		0 (0)		0 (0)	6 (100)	
1B	1 (25)		0 (0)		1 (25)	3 (75)	
2A	3 (38)		1(13)		2 (29)	5 (71)	
2B	35(70)		10(20)		25 (63)	15 (38)	
3	8 100)		2 (25)		6 (100)	0 (0)	

Specific Areas of Brain Injury in Neonatal MRI and 6-7y Outcome: Shankaran 2015

	IQ ≥70 N=76	IQ <70 N=28	P
Any Cerebral	33%	82%	<0.0001
Frontal	24%	64%	
Temporal	20%	64%	
Parietal	25%	64%	
Occipital	17%	64%	
Basal ganglia thalamus	24%	75%	<0.0001
Putamen	22%	75%	
Globus pallidus	13%	54%	
or Lenticular nucleus			
Caudate	3%	18%	0.01

Specific Areas of Brain Injury in Neonatal MRI and 6-7y Outcome

	IQ ≥70 N=76	IQ <70 N=28	P
ALIC Abnormal	9%	54%	<0.0001
PLIC Abnormal	9%	54%	<0.0001
Watershed			0.002
No area of infarction	93%	71%	
Extensive WS	4%	36%	
Hemispheric	0%	11%	0.01
Hippocampus	0%	7%	0.07
Cerebellar	1%	11%	0.06

Brain injury on MRI in TOBY RCT

Rutherford 2010

- 131 of 325 had MRI
- Hypothermia group had reduction in BGT, WMI, PLIC abnormalities
- OR (95%CI) of MRI of predicting death or disability at 18m was 0.84 (0.74-0.94) cooled and 0.81 (0.71-91) in non-cooled group

Brain injury on MRI in ICE RCT

Cheong 2012

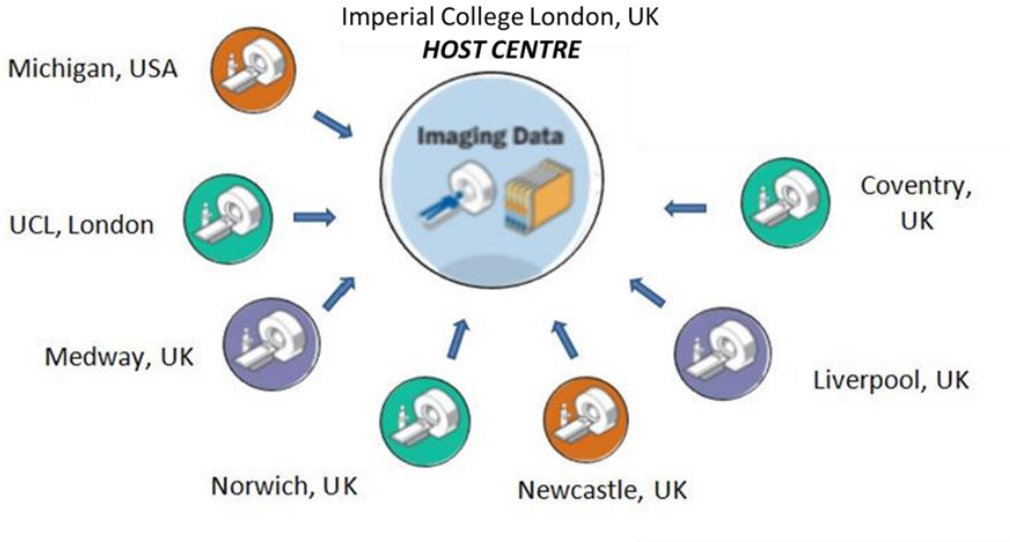
- 128 of 221 in RCT had MRI & DWI
- Hypothermia reduced WMI or cortical GM abnormalities
- Greatest predictive value for 2y outcome was PLIC and BGT abnormalities

The Expanded NICHD NRN Brain injury score (n=298 of 367) correlated with death or disability in the longer, deeper cooling RCT. Outcomes were similar following WS and BGT injury

Shankaran JAMA Pediatrics 2025

Magnetic Resonance Spectroscopy (n=223)

Biomarkers in Neonatal Encephalopathy (MARBLE Study)



MR spectroscopy biomarkers

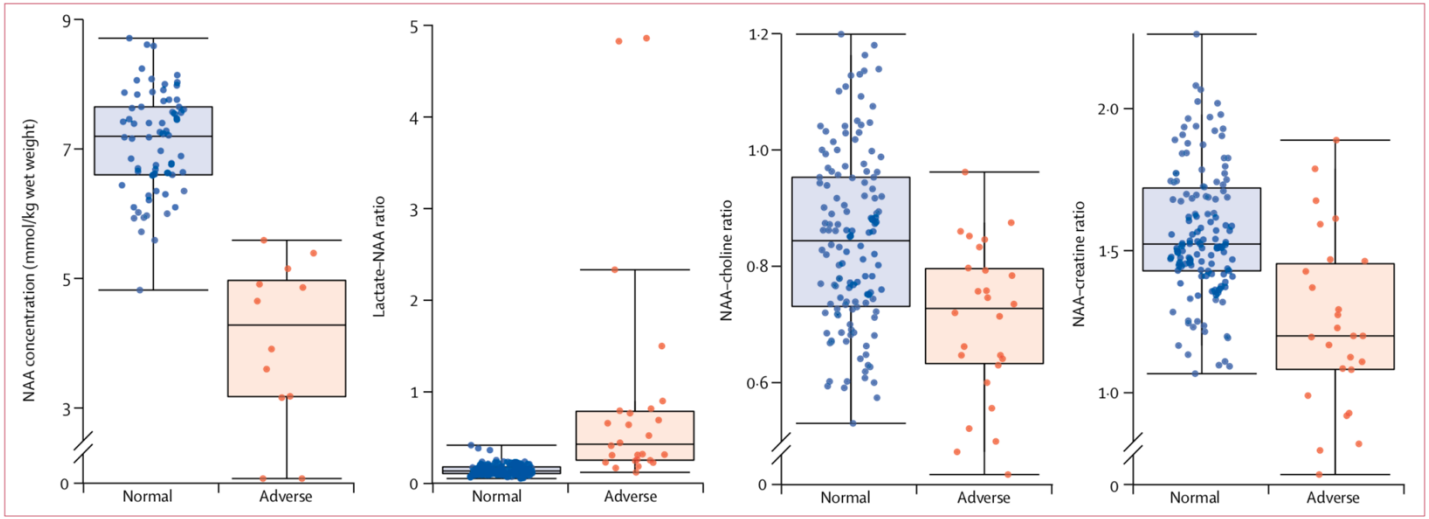
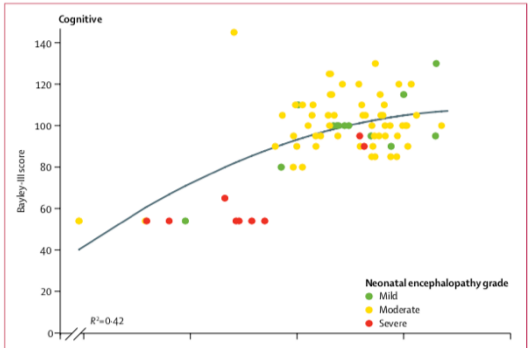
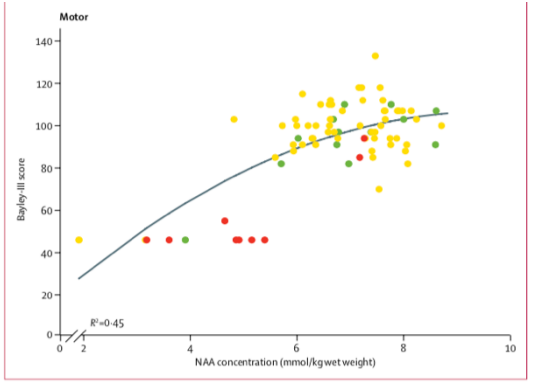


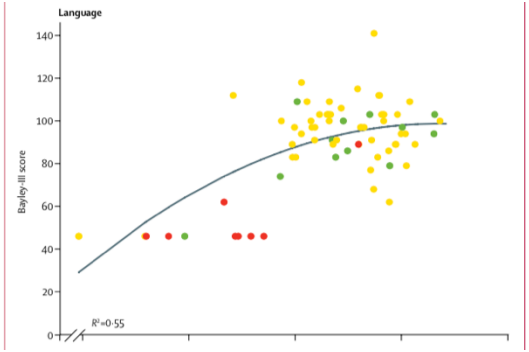
Figure 3: **Box plots of proton MRS biomarker values for children with normal compared with adverse neurodevelopmental outcome at 2 years**
Box plots show the spread of the datapoints overlaying the median and IQR. Medians are indicated by horizontal lines; boxes outline the upper and lower quartiles; and the whiskers indicate 1·5×IQR from upper and lower quartiles. Outliers are indicated with dots lying beyond the whiskers. p<0·0001 for all analyses. NAA=N-acetylaspartate.

Lally et al Lancet Neurology 2019

Correlation with Bayley scores at 2 years







Is Hypothermia effective for moderate or severe HIE in Low-and Middle-Income Countries (LMIC) ?

Hypothermia for Moderate or Severe Neonatal Encephalopathy in LMIC:HELIX

Thayyil et al Lancet Global Health 2021

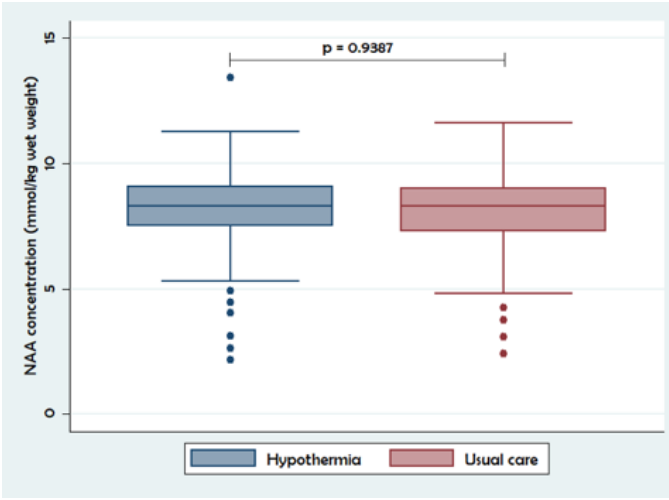
Design	Open label phase III RCT with masked outcome assessments
Inclusion	408 term babies with moderate or severe encephalopathy from 7 tertiary neonatal units in South Asia
Control group	Intensive care with avoidance of hyperthermia (core temperature of 36.5 C)
Intervention group	Whole body cooling (33.5 C) x 72 hours using Tecotherm Neo
Primary outcome	Death or moderate or severe disability at 18 to 22 months

Outcomes at 18 to 22 mos

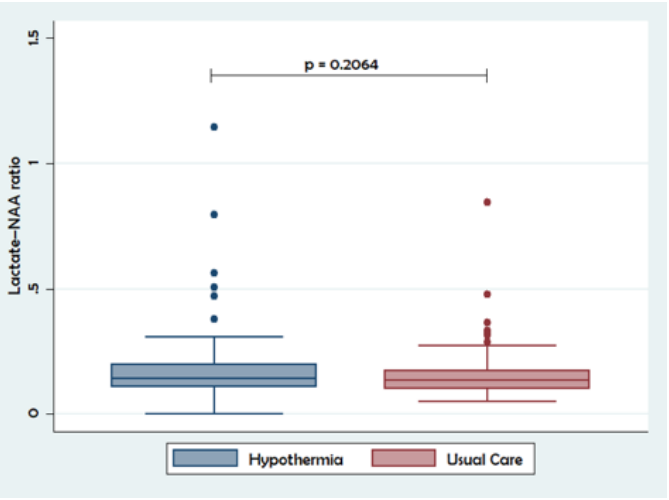
	Hypothermia (N=202)	Usual care (N=206)	Risk ratio (95% CI)	P value
Death or moderate or severe disability	98 (50%)	94 (47%)	1.1 (0.87, 1.3)	0.6
Death until 18 months	84 (42%)	63 (31%)	1.4 (1.1, 1.8)	0.02
Severe disability among survivors	14 (13%)	28 (21%)	0.6 (0.3, 1.1)	0.1
Microcephaly	33 (30%)	37 (27%)	1.1 (0.7, 1.6)	0.7
Survival without neurodisability	47 (42%)	47 (35%)	1.2 (0.9, 1.7)	NS
Persistent seizure disorder	3 (3%)	9 (7%)	0.4 (0.1, 1.4)	NS
Blindness	5 (4%)	10 (7%)	0.6 (0.2, 1.7)	NS
Hearing impairment	3 (3%)	6 (4%)	0.6 (0.2, 2.4)	NS

Proton MR spectroscopy

Thalamic [NAA]



Lactate/NAA



What about Preterm Infants with Moderate or Severe HIE?

Therapeutic Hypothermia at <36 wks GA

- Two RCTs with follow-up at 12-24 mos (Eicher 2005; Jacobs 2011) included enrollment at 35^0-35^6 wks
  - Total randomized 35 wk infants: N = 7
    - Control: 1 death, 1 normal survivor
    - Cooled: 2 deaths, 2 survivors with moderate disability, **1 normal survivor**

DJ Eicher et al, Pediatr Neurol 2005, 32:11
SE Jacobs et al, Arch Pediatr Adolesc Med 2011, 165: 692

Preemi Hypothermia Primary Outcome

- Death **or** disability (severe or moderate)
  - Severe disability: **any** of Bayley III cognitive score <70, Gross Motor Function (GMF) 3-5, blindness, or hearing loss despite amplification
  - Moderate disability: Bayley III cognitive score 70-84 **and** any of GMF 2, seizure disorder, or hearing loss corrected with amplification
- Assessment targeted for 18-22 months
- Trained, certified examiners blinded to group assignment performed assessments

Sample Size and Pre-Specified Analyses

- Sample size, N=168, pre-defined
  - Largest feasible estimate of available patients
- Bayesian analysis pre-defined: probability that the hypothesis is true based on the observed data
- Analyses adjusted for level of encephalopathy and center
- Enrollment July 2015 to Dec 2022, Results published Feb 2025 JAMA Peds

Outcomes: Posterior Probability, Neutral Prior

	Cooled (n=88)		Non-cooled (n=80)		Bayesian results	
	#	%	#	%	aRR (95% credibility interval)	Probability of treatment harm*
Death or disability	29/83	35	20/69	29	1.11 (0.74-2.00)	74%
Death	18/83	22	9/69	13	1.38 (0.79-2.85)	87%

*Probability of treatment harm = Area under curve RR>1.0

What about Hypothermia Plus Therapies?

Neuroprotection trials: Evidence Based Data

- Hypothermia Plus Epo not beneficial (HEAL)
- Melatonin, UCB cells, Allopurinol being evaluated
- Xenon, Mag Sulfate, Topiramate RCTs not beneficial
- Future studies should have adequate sample size as rate of death or moderate/severe disability is 29%
- Gold standard still neurodevelopmental outcome at 18-24 mos

High-Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL) Wu 2022

- N=501 infants with moderate/severe encephalopathy
- Epo 1000 U/Kg or saline within 26h and 2,3,4,7days. Primary outcome death or any NDI 22-36m
- PO: 52.5% Epo and 49.5% placebo groups, RR 1.03 (95% CI 0.86-1.24)
- Mean n of SAE/child 0.86 vs.0.67, RR 1.26 (1.01-1.57)

RCT of Hypothermia for Mild HIE needed

- Infants at highest risk: acidosis/resuscitation
- Defined criteria for neurological examination for mild HIE
- Use current depth and duration of cooling
- Evaluate cognitive and behavioural outcomes with robust measures at 5y; sample size would be ~420

- If cooling safe and effective, offer cooling
- If not safe and effective, treatment can be discontinued

Chawla, Bates and Shankaran 2020

Conclusions: Evidenced Based Update in Therapeutic Hypothermia

- Hypothermia at 33.5C for 72 h is safe and effective for moderate and severe HIE in infancy and childhood in HIC
- Early biomarker of outcome in infancy and childhood include neuro exam, neonatal MRI and MRS
- Sedatives and analgesics should be used with caution
- Neither safety nor efficacy of hypothermia for HIE noted in HELIX RCT in LMIC, will specific groups benefit?
- Hypothermia not neuroprotective for 33, 34, 35 weeks GA with moderate/severe HIE

NICHD Neonatal Research Network Centers

- Brown University
- Case Western Reserve University
- Children's Mercy Hospital, Missouri
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Indiana University
- Nationwide Children's Hospital/ Ohio State University
- RTI International
- Stanford University
- Tufts Medical Center
- University of Alabama at Birmingham
- University of California - Los Angeles
- University of Iowa
- University of New Mexico
- University of Pennsylvania
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center
- University of Utah
- Wayne State University
- Yale University

Questions?

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