Hypoxic-Ischemic Encephalopathy: Diagnosis, Management and Prognosis in 2022

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Diagnosis of hypoxic-ischemic encephalopathy (HIE)

Selection of infants with moderate or severe HIE for hypothermia therapy

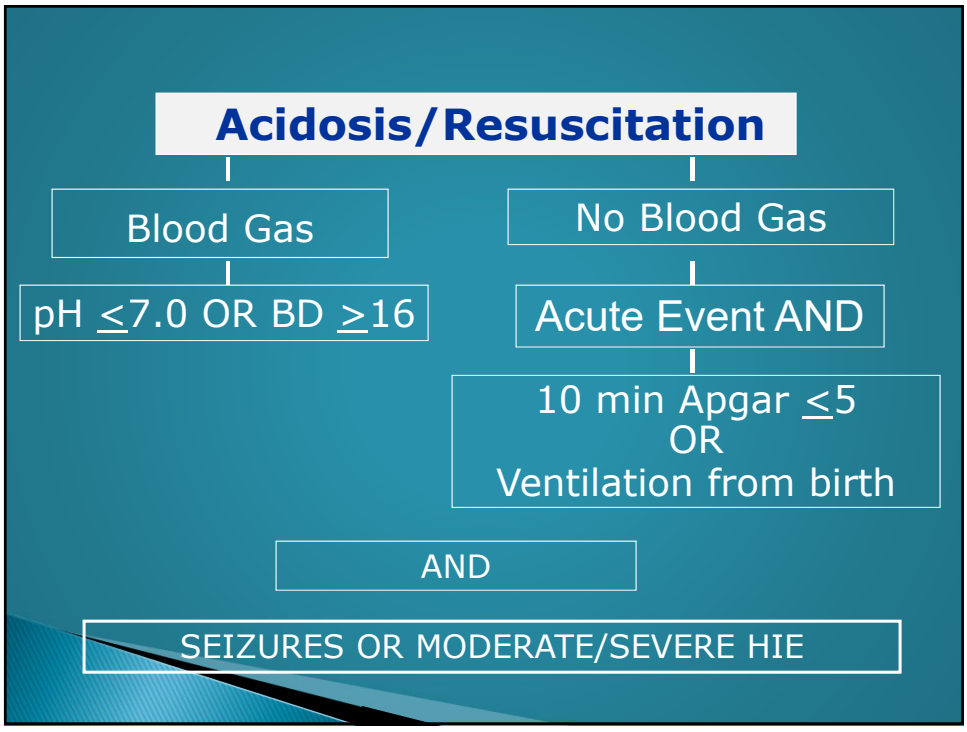
Selection of Neonates for Hypothermia

≥ 36 weeks gestation

< 6 hours of age

2 Steps selection criteria

- Severe birth acidosis and need for resuscitation
- Moderate or Severe encephalopathy



Challenges of Neurological Exam

- Impact of maternal anesthesia, analgesia
- Severity and timing of injury
- Ability of neonate to recover
- Associated conditions
- Response to resuscitation

Natarajan, Laptook, Shankaran 2018

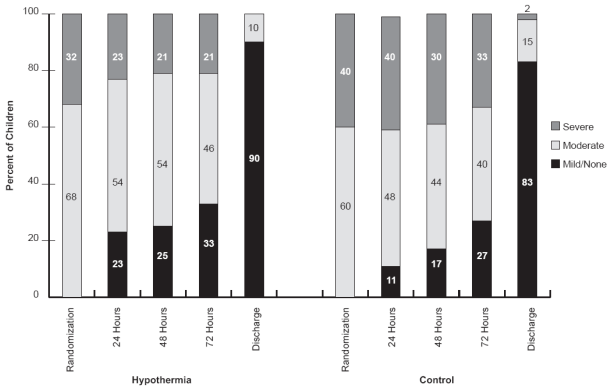
CATEGORY	MODERATE HIE	SEVERE HIE
1. Level of consciousness	2 = Lethargic	3 = Stupor/coma
2. Spontaneous Activity	2 = Decreased activity	3 = No activity
3. Posture	2 = Distal flexion, complete extension	3 = Decerebrate
4. Tone	2a = Hypotonia (focal or general) 2b = Hypertonia	3a = Flaccid 3b = Rigid
5. Primitive Reflexes Suck Moro	 2 = Weak or has bite 2 = Incomplete	 3 = Absent 3 = Absent
6. Autonomic System Pupils Heart rate Respiration	 2 = Constricted 2 = Bradycardia 2 = Periodic breathing	 3 = Deviation/dilated/ or nonreactive to light 3 = Variable HR 3a = on vent with spontaneous respirations 3b = on vent without spontaneous breaths

Neurological Examination

- 3 of 6 categories have to be moderate or severe
- Definitions for categories of exam
- Certification of new examiners
- Annual refresher course

Hypothermia only for infants meeting moderate or severe HIE criteria

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

Management of Infants with Moderate or Severe HIE receiving TH

Optimization of TH for infants with moderate or severe HIE

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 $\leq$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

Elevated Temperature management

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
- *Need to avoid elevated temperatures before and after hypothermia therapy*

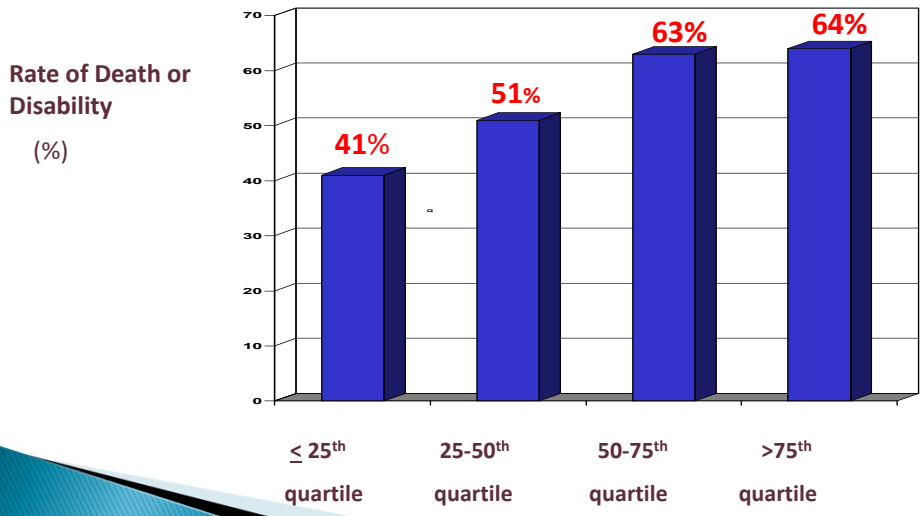
Wyatt 2007, Laptook 2013

Hemodynamic Stability during TH

- Link between cerebral ischemia and cardiac dysfunction unclear
- HIE is associated with myocardial dysfunction or injury
- Troponin levels are reduced with TH
- *Need to stabilize blood pressure during induction and maintenance phases* among the smaller, *sicker neonates requiring pressor agents*

Shankaran 2012
Liu 2011,
Geisinger 2017

NICHD Trial: Hypocarbia and 18 mos outcome: Pappas 2011



Relationship of PCO_2 and Outcome

Cool Cap Trial data

- Available on 196 of 243 infants enrolled
- 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*

Lingappan 2016

Hyperoxemia within first hour of life in HIE

- 120 term infants with birth acidosis
- Infants with hyperoxemia, n=36, (PaO2 >100 mmHg compared with those without hyperoxemia
- 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

Sedatives, Analgesics?

- Preclinical data has shown that hypothermia was effective only in sedated model
- Pediatric and adult patients are sedated during hypothermia therapy (because of shivering)
- No data in neonatal HIE that has demonstrated efficacy of sedation/analgesia
- Accumulation of morphine reported
- *Need to use sedation/analgesia with caution*

Tortorici 07, Roka 08, Wassinik 2015

Cerebral function monitoring <6 hrs

- 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
- *Most Neuro-ICUs now have EEG capability within 6h*

Wyatt 2007, Azzopardi 2007, Thoresen 2010, Shankaran 2011

Prognosis

Prognosis after hypothermia for moderate/severe HIE

Hypothermia RCTs High-Income-Countries (HICs) Primary Outcome: Death or Disability at 18 to 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%

Does neuro-protection persist to childhood in HICs?

2) NICHD 6 to7-year outcomes, Shankaran 2014

Primary Outcome: Death or IQ <70

Hypothermia N=97	Control N=93	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
46 (47%)	58 (62%)	0.76 (0.58,0.99)	0.78 (0.61,1.01)

Secondary Outcomes: NICHD RCT

Outcomes at 6-7 years	Hypothermia N=97	Control N=93	Adjusted RR (95% CI)
Death	27 (28%)	41 (44%)	0.66 (0.45,0.97)
Death or CP	41 (43%)	56 (60%)	0.75 (0.57,0.99)

3) TOBY: Primary Outcome IQ ≥85

Azzopardi 2014

Hypo N=163	Control N=162	RR (95% CI)	P value
75/145 (52%)	52/132 (39%)	1.31 (1.01-1.71)	0.04

NICHD Hypothermia RCT: CP and Growth at 6-7 years: Vohr et al 2013

Characteristics at 6-7 year	Mod/Severe CP N=23	No CP N=92
Gastrostomy feeds	52%	0%
Physical therapy	87%	7%
Occupational therapy	83%	9%
Re-Hospitalization	78%	25%
Full Scale IQ < 70	96%	10%
Full Scale IQ < 55	87%	2%
		All P < 0.05

NICHD Hypothermia RCT: CP and Health at 6-7 years

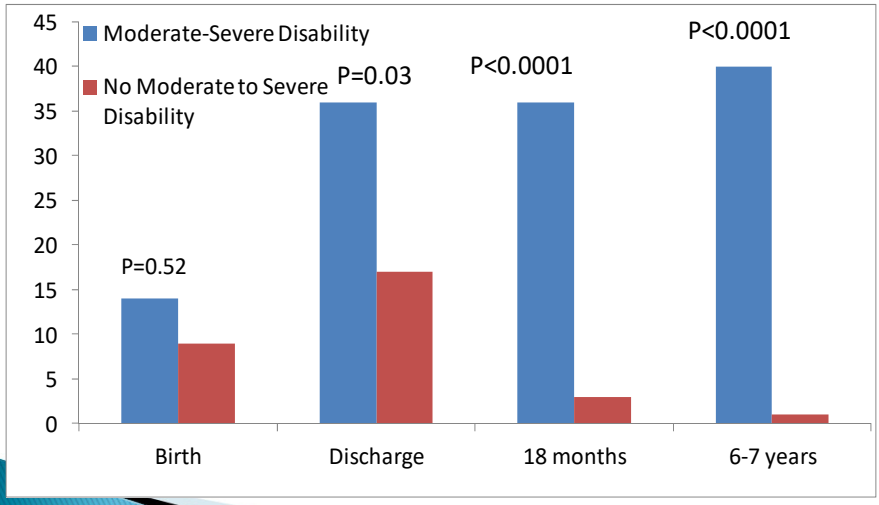
Re-hospitalization at 18-22 mos for CP group:

- 23% for intractable seizures
- 54% gastrostomy or fundal plication

Re-hospitalization at 6-7y for CP

- 61% pneumonia
- 56% surgery / tendon releases
- 44% reflux / dehydration
- 56% seizures
- 22% failure to thrive

NICHD: Disability and Growth: Weight <10 perc



Cognitive Outcome after Neonatal HIE: NICHD RCT

- Almost all children with CP had IQ<70 (96%)
- 9% of children without CP had IQ <70 and 31% had scores 70-84
- Children with IQ <70: 23% had normal gait, 6-16% had ability to perform complex motor function and 10% intact fine motor coordination

Pappas 2018

Rates of Special Education Services

	18-22 Months	6-7 Years
Hypothermia Group	**63**	**63**
Early Intervention/ Special education	30%	32%
Speech therapy	17%	30%
Behavior problems	21%	7%
Questionable	15%	N/A

Impact on the Family in Childhood after Hypothermia as Neuroprotection for Neonatal HIE: NICHD RCT

Natarajan et al 2014

18-month Functional Status Decreases with Disability

Variable	No/Mild Disability N=74	Mod/Severe Disability N=37
Birth		
Severe HIE	15%	32%
18 Month		
Public Insurance	47%	78%
Functional Status Score mean (SD)		
Independence	98 (8)	54 (35)
General Health	98 (6)	87 (14)

All $P < 0.05$

18-month Family Resources Decrease with Disability

Variable	No/Mild Disability N=74	Mod/Severe Disability N=37
18 Month Family Resource Scale, mean (SD)		
Total	134(16)	127(19)
Money	23(5)	20(7)

$P < 0.05$;
Basic needs, Time for self, Time for family: NS

18-month Impact on Family Increases with Disability

Variable	No/Mild Disability N=74	Mod/Severe Disability N=37
18 month Impact on Family Scale mean (SD)		
Total	26(8)	33(9)
Financial Impact	4(2)	5(2)
Duration of planning	9(3)	12(3)
Caretaker Burden	6(2)	8(3)
Family Burden	7(2)	9(3)
All $P < 0.05$, Coping was not different		

Optimum depth and duration

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

Higher in-hospital mortality with longer or deeper cooling

Shankaran 2014, 2017

Primary Outcome: 72 vs.120 h

	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

	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

Brain Imaging

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

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

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)	

Brain injury on MRI in TOBY & ICE RCT

TOBY Rutherford 2010

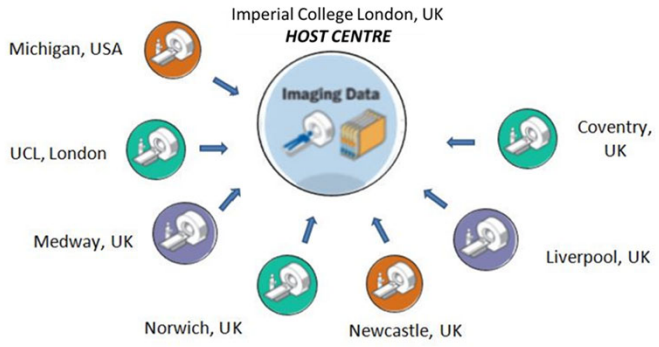
- 131 of 325 had MRI
- Hypothermia group had reduction in BGT, WMI, PLIC abnormalities
- OR (95%CI) of MRI of predicting death or disability at 18m was 0.84 (0.74–0.94) cooled and 0.81 (0.71–91) in non-cooled group

Brain injury on MRI in TOBY & ICE RCT

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

Magnetic Resonance Spectroscopy (n=223)
Biomarkers in Neonatal Encephalopathy (MARBLE Study)



MR spectroscopy biomarkers

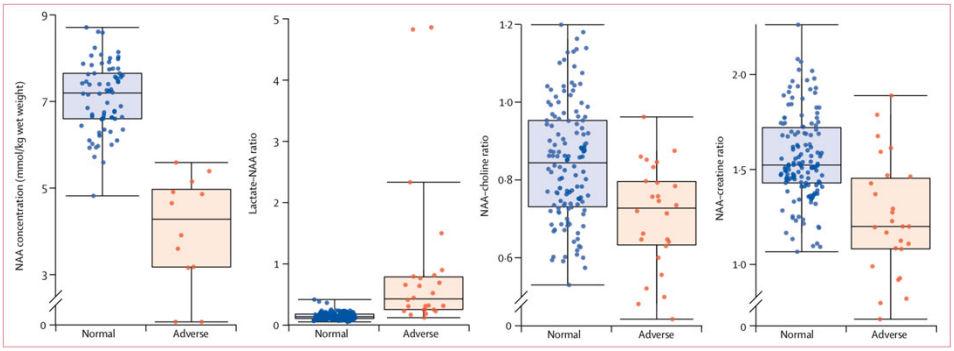
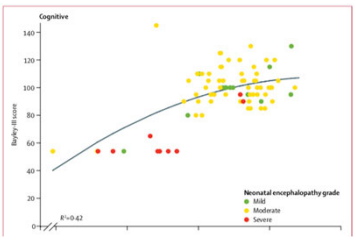
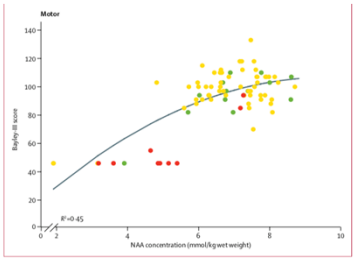


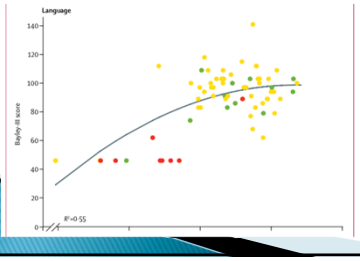
Figure 3: **Box plots of proton MRS biomarker values for children with normal compared with adverse neurodevelopmental outcome at 2 years**
Box plots show the spread of the datapoints overlaying the median and IQR. Medians are indicated by horizontal lines; boxes outline the upper and lower quartiles; 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

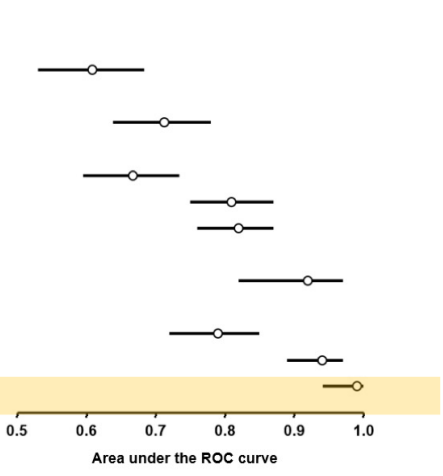






Prognostic accuracy of MR biomarkers

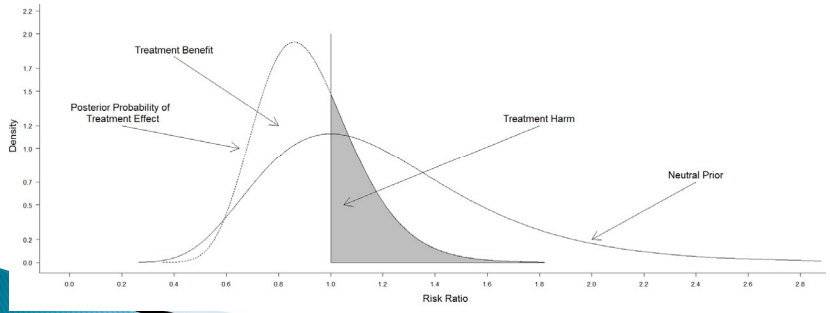
	Sensitivity	Specificity
Clinical assessment		
Discharge neuro. exam	26 (10, 48)	95 (90, 98)
Cerebral function monitor		
aEEG	45 (27, 64)	92 (86, 96)
MRI appearance		
Cortex	48 (30, 67)	81 (74, 87)
Basal ganglia/thalami	71 (52, 86)	88 (82, 93)
PLIC	71 (52, 86)	90 (84, 94)
Diffusion MRI		
Fractional anisotropy	75 (19, 99)	98 (91,100)
MR Spectroscopy		
NAA/Cr	65 (44, 83)	89 (82, 94)
Lac/NAA	89 (70, 98)	91 (85, 95)
[NAA]	100 (74,100)	97 (90,100)



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

Posterior Probability of Reduced Death or Disability with onset>6h (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**



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 be powered based on rate of death or moderate/severe disability of 29%

Gold standard still neurodevelopmental outcome at 18-24 mos.

High-Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL) NEJM July 14 2022

- N=501 infants with moderate/severe encephalopathy
- Epo 1000U/Kg or saline within 26h, primary outcome death or any NDI 22-36m
- Death or NDI: 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)

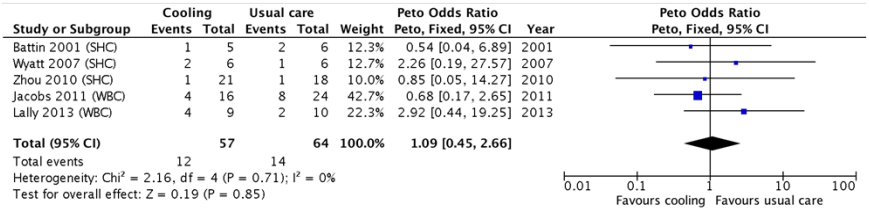
Controversies in use of Hypothermia

Controversies in Therapeutic Hypothermia

- Cooling for Mild HIE
- Cooling Preterm Infants
- Postnatal collapse
- Severe Surgical Conditions, NEC
- Use of Sedatives and Analgesics during Hypothermia for HIE

Therapeutic hypothermia for mild neonatal encephalopathy: a systematic review and meta-analysis

Ujwal Kariholu,[1,2] Paolo Montaldo,[1] Theodora Markati,[1,2] Peter J Lally,[1] Russell Pryce,[1,3] Justinas Teiserskas,[2] Natasha Liow,[2] Vânia Oliveira,[1] Aung Soe,[3] Seetha Shankaran,[4] Sudhin Thayyil[1]



Study or Subgroup	Cooling Events	Cooling Total	Usual care Events	Usual care Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year
Battin 2001 (SHC)	1	5	2	6	12.3%	0.54 [0.04, 6.89]	2001
Wyatt 2007 (SHC)	2	6	1	6	12.7%	2.26 [0.19, 27.57]	2007
Zhou 2010 (SHC)	1	21	1	18	10.0%	0.85 [0.05, 14.27]	2010
Jacobs 2011 (WBC)	4	16	8	24	42.7%	0.68 [0.17, 2.65]	2011
Lally 2013 (WBC)	4	9	2	10	22.3%	2.92 [0.44, 19.25]	2013
Total (95% CI)		**57**		**64**	**100.0%**	**1.09 [0.45, 2.66]**	
Total events	12		14				

Heterogeneity: Chi² = 2.16, df = 4 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)

Arch Dis Childhood 2020

Hypothermia for Mild HIE

- Surveys note many centers in US, UK and Europe use hypothermia for mild HIE
- Registry data: VON, TOBY, CHND etc: >1000 mild HIE infants have been cooled prior to 2020
- No outcome data has been presented from majority of these reports

Murray 2016, Murthy 2014, Chevallier 2013, Pfister 2012, Mehta 2017, Oliviera 2018, Conway 2018, Gagne-Loranger 2016, Massaro 2015, Kracer 2014, Kariholu 2018, Walsh 2017, Goswami 2019

Trends in the incidence and management of hypoxic-ischaemic encephalopathy in the therapeutic hypothermia era: a national population study

Lara Shipley [1], Chris Gale [2], Don Sharkey [3]

To cite: Shipley L, Gale C, Sharkey D. *Arch Dis Child Fetal Neonatal Ed* 2021;**106**:F529–F534.

- 3511 babies with mild encephalopathy admitted to neonatal units between 2011 and 2016 (approx. 700 per year)
  - 1050 (30%) were cooled
  - 2330 (66%) were not cooled.

Registry based data on mild encephalopathy

Characteristics and short-term outcomes of neonates with mild hypoxic-ischemic encephalopathy treated with hypothermia

Ipsita R. Goswami[1] · Hilary Whyte[1] · Pia Wintermark[2] · Khorshid Mohammad[3] · Sandesh Shivananda[4] · Deepak Louis[5] · Eugene W. Yoon[6] · Prakesh S. Shah[6,7] · on behalf of the Canadian Neonatal Network Investigators

Variables	Hypothermia group ($N = 393$)	Standard care group ($N = 696$)	P value
Received opioid infusion[a]	264 (67%)	86 (12%)	<0.01
Length of hospital admission (days)[b]	9 (7–12)	6 (4–9)	<0.01
Duration of any respiratory support (days)[b]	2 (0–5)	1 (0–2)	<0.01
Duration of invasive respiratory support (days)[b]	0 (0–2)	0 (0–1)	<0.01
Gavage feeding at discharge from level III NICU[a]	88 (22%)	89 (13%)	<0.01
Persistent pulmonary hypertension[a]	43 (11%)	46 (7%)	0.01
Renal failure[a]	52 (13%)	56 (8%)	<0.01
Disseminated intravascular coagulation[a]	33 (8%)	12 (2%)	<0.01
Hepatic dysfunction[a]	89 (23%)	74 (11%)	<0.01
Cardiac dysfunction[a]	32 (8%)	17 (2%)	<0.01
Seizure at any time during admission[a]	69 (18%)	141 (20%)	0.28

Registry based data on mild encephalopathy

Neonates with mild hypoxic–ischaemic encephalopathy receiving supportive care versus therapeutic hypothermia in California

Yieh L, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2021;**0**:F1–F5.

Table 2 Short-term outcomes of infants with mild hypoxic–ischaemic encephalopathy

Variable, n (%)	Supportive care (N=397)	Therapeutic hypothermia (N=967)	P value
Conventional ventilator	180 (45)	580 (60)	<0.0001
High frequency ventilator	45 (11)	96 (10)	0.44
Duration of intubation			<0.0001
≤4 hours	15 (4)	89 (9)	
≥4 hours	167 (42)	487 (50)	

Imaging in infants with mild HIE

- Evidence of brain injury on MRI noted among 11–40% of infants with mild HIE,
- Depending whether retrospective or prospective reports or if cooling provided
- Injury occurred in watershed areas as compared to the basal ganglia

Gagne-Loranger 2016, Massaro 2015, Walsh 2017, Walsh 2018

Mild HIE Treated with Darbepoetin

- Phase II multicenter placebo-controlled feasibility trial (n=21)
- Darbepoetin 10mcg/kg/single dose or normal saline IV within 24 h
- Primary Outcome: Neurodevelopmental outcome at 12m
- Results: no adverse events, Bayley III scores average in both groups
- Dupont 2021

Ongoing/Upcoming Studies on Infants with mild HIE

1) Comparative Effectiveness for Cooling Prospectively Infants with Mild HIE: COOL PRIME

- Multicenter Longitudinal Observational study
- Receipt of TH or no cooling based on center practice
- 460 participants
- Start date Dec 1, 2022
- Primary outcome: Comparison of Bayley IV domains between TH and normothermia infants
- PI Lina Chalak UT Southwestern

2) TH for Infants with Mild Encephalopathy: TIME

- RCT of TH vs. Targeted Temperature Management
- Primary Outcome at 12-14m: a) Warner Initial Developmental Evaluation of Adaptive and Functional skills (WIDEA -FS) and b) Alberta Infant Motor Scale (AIMS)
- 68 participants
- PIs: Sonia Bonifacio and Krisa Van Meurs, Stanford Univ.
- Updated March 2020

Summary: To Optimize Care during TH

- Hypothermia should be provided for moderate/severe HIE; perform serial neuro exams
- Avoid hypocarbia, hypoxemia, hyperoxemia
- Maintain blood sugar in normal range
- Use sedation with caution
- Avoid temperature elevations pre & post-cooling
- MRI within first week
- Standardized FU to minimum of 18 mos
- Referrals to Early Intervention Programs
- Focus on nutrition among disabled children

Thank You

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