# HIE – an Update

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# What's in a name? Does it matter?

- Neonatal Encephalopathy (NE) has been defined by the American College of Obstetricians and Gynecologists/ American Academy of Pediatrics (ACOG-AAP) as a
- "clinical syndrome of disturbed neurologic function in the first week after birth in an infant born at or beyond 35 weeks of gestation, manifested by an abnormal level of consciousness or seizures, often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes."
- NE is a descriptive diagnosis.
- An early diagnosis of NE does not imply a specific or known etiology
- A specific etiologic diagnosis is highly desirable because of implications for treatment, prognosis, and family planning.
- The more thorough the diagnostic process, the more likely it is that an underlying contributing or determinative pathology is identified

*Obstet Gynaecol 2014*

# Hypoxic Ischaemic Encephalopathy (HIE)

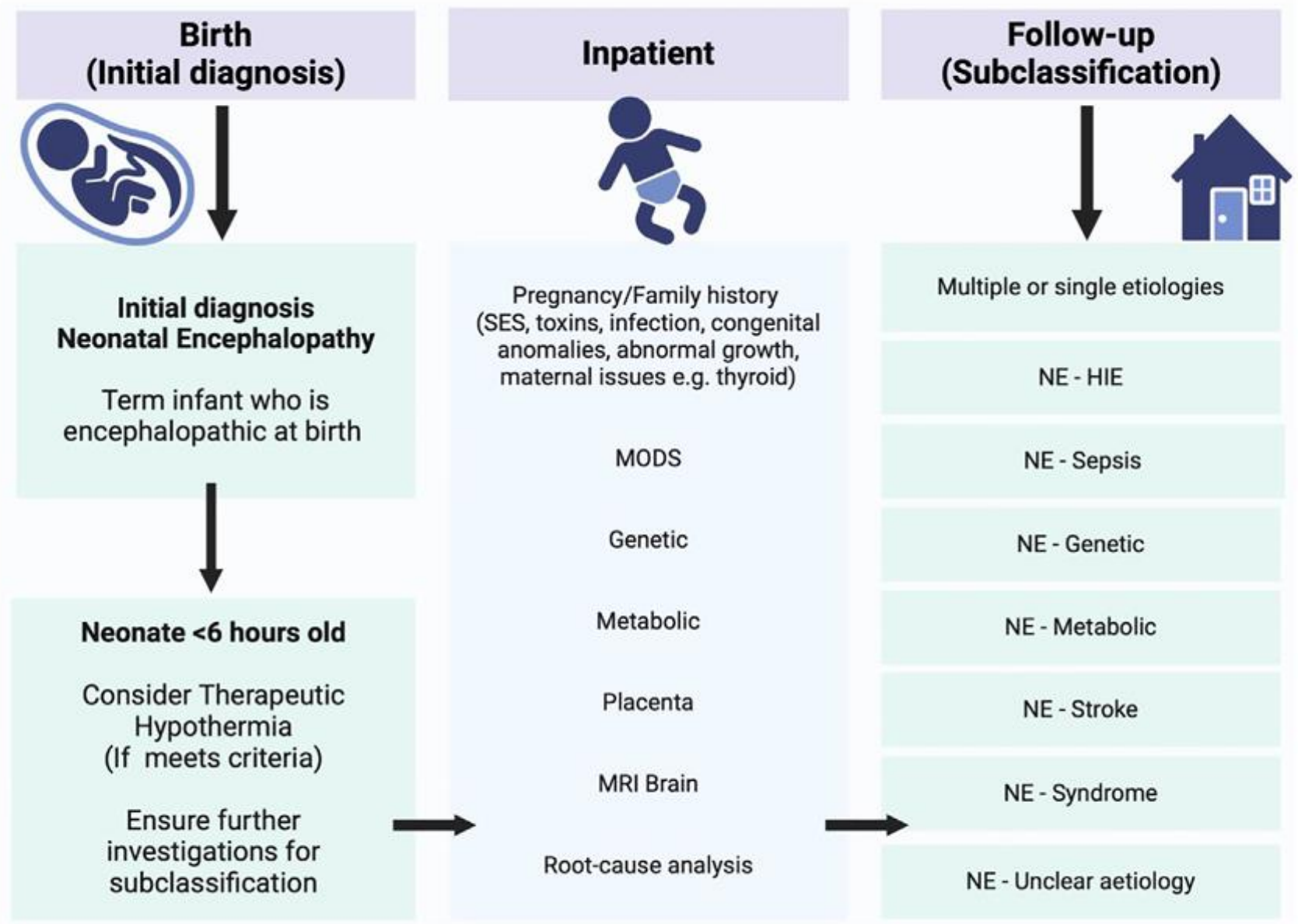
- HIE is a subgroup of neonatal encephalopathy
- The occurrence of a “sentinel event” around the time of birth, such as a cord accident or uterine rupture, suggest HIE,
- Low Apgar scores and acidosis are consistent with HIE but are themselves consequences of prior processes not the nature of the initiating process.
- ACOG-AAP recommend that HIE be used as a final diagnosis only when diagnostic studies have been completed.
- Diagnosis may not be made until many years later or following the birth of another sibling with a similar presentation.

# HIE vs NE

- Don’t use NE and HIE interchangeably – rather use the term NE
- HIE – when
  - Apgar scores < 5 at 5 and 10 minutes
  - Foetal acidaemia – pH < 7.0 and BD 12mmol/l
  - Neuroimaging evidence – on MRI of acute brain injury
  - Multi organ dysfunction
  - Associated factors – sentinel hypoxic or ischaemic event that occurs  before or during labour or at birth
  - Foetal heart rate monitor patterns consistent with acute peripartum or intrapartum event
  - Timing and type of injury pattern observed on imaging consistent with an aetiology of an acute peripartum or intrapartum event
  - Developmental outcome of spastic quadriplegia or dyskinetic cerebral palsy
- ‘A rose by any other name would smell as sweet’ - William Shakespeare

Molloy E et al. *Pediatric Research* 2023

# Moving from initial diagnosis to final diagnosis




Branagan et al Clinics in Perinatology 2024

# Mimickers of HIE

**Table 1**
**Clinical features of selected mimickers of hypoxic-ischemic encephalopathy**

| Disorder | Similarities | Differences |
|---|---|---|
| SSRI withdrawal syndrome | Hypotonia<br>Encephalopathy<br>Tremors<br>Tachycardia<br>Respiratory distress | Hypoglycemia<br>SSRI exposure<br>Onset day of life 1–4 |
| Inborn errors of metabolism | Encephalopathy<br>Poor feeding<br>Hypotonia<br>Seizures<br>Brain injury patterns on MR diffusion-weighted imaging | Dysmorphisms/congenital malformations<br>Metabolic laboratory abnormalities<br>Disease specific changes on MR spectroscopy |
| Enterovirus encephalitis | Acute symptomatic seizures<br>Encephalopathy<br>Periventricular white matter restricted diffusion | Elevated inflammatory markers<br>Exanthem<br>Prodrome<br>Affected sibling/exposure |
| Vector-borne encephalitis | Acute symptomatic seizures<br>Encephalopathy<br>Periventricular white matter restricted diffusion on MR imaging | Fever<br>Thrombocytopenia<br>Hepatomegaly<br>Exanthem<br>Intracranial Hemorrhage |
| Spinal cord injury | Hypotonia<br>Decreased extremity movements<br>Respiratory distress | Areflexia<br>Paradoxic breathing<br>Spinal cord level on examination |

Barsh GR et *al Clin Perinatol* 2025

# Suggested investigations for Neonatal Encephalopathy

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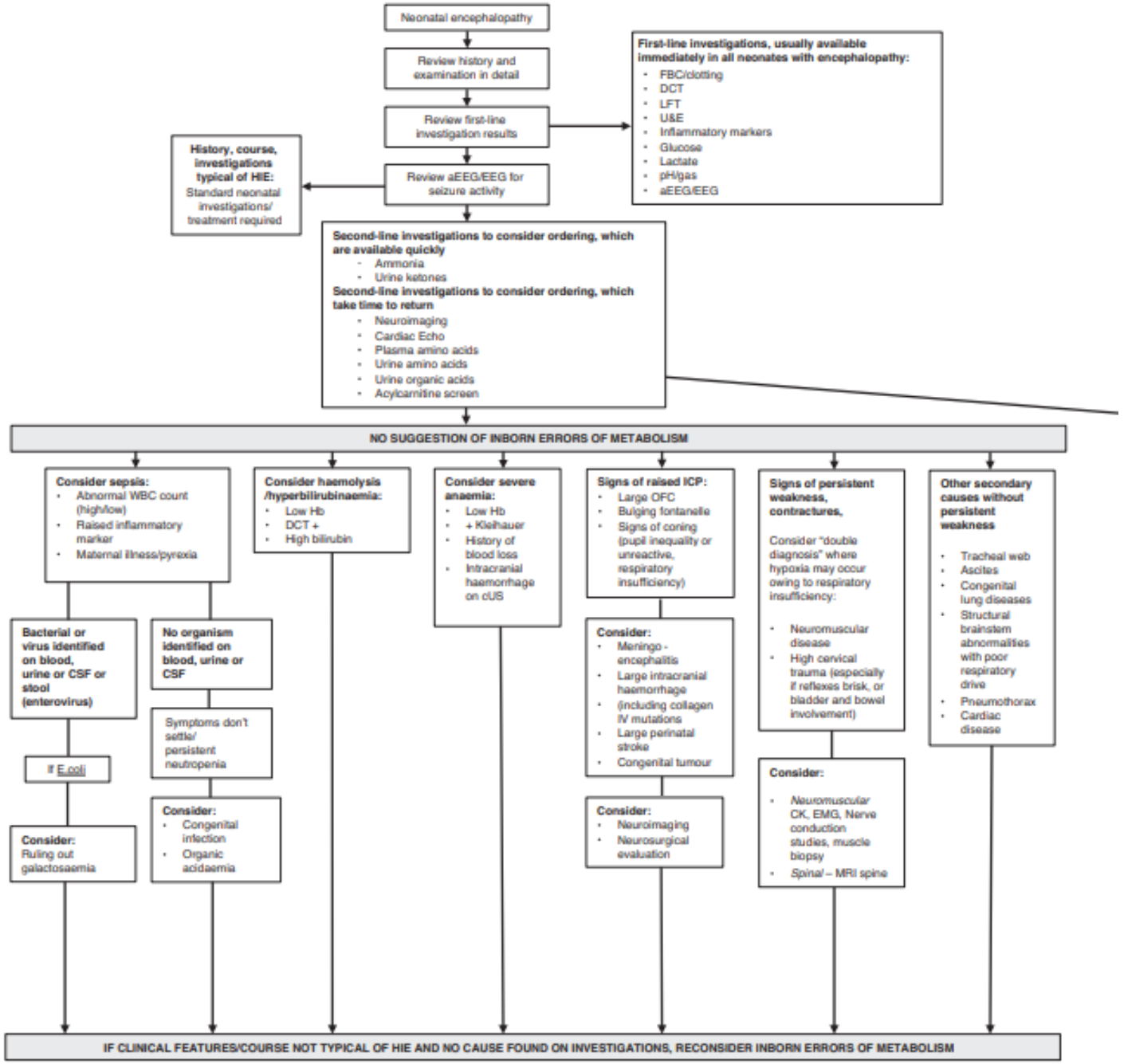
**Table 2**
**Suggested investigations for neonatal encephalopathy**

| | |
|---|---|
| Pregnancy/ birth history | Maternal medication/Drug exposure<br>Fetal movements<br>IUGR<br>Delivery complications<br>Apgar scores |
| Family history | Consanguinity<br>Early fetal or neonatal death<br>Metabolic/genetic conditions |
| Physical examination | Dysmorphisms and congenital malformations<br>Level of consciousness<br>Cranial nerve examination<br>Brainstem and primitive reflexes<br>Tone, peripheral reflexes, contractures<br>Sensory examination<br>Skin examination<br>Formal ophthalmologic examination for infectious or metabolic etiologies |
| Baseline testing | Umbilical or arterial blood gas, anion gap<br>Serum electrolytes and calcium<br>Complete blood count<br>Liver enzymes<br>Plasma lactate<br>Plasma ammonium<br>Urine ketones<br>Head Ultrasound<br>MRI brain<br>MR spectroscopy |
| Second tier laboratories | CSF cell count, glucose, protein<br>CSF culture, meningitis/encephalitis PCR panel, parvovirus PCR, parechovirus PCR<br>Plasma amino acids<br>Urine organic acids<br>Plasma carnitine and acylcarnitine profiles<br>Urine amino acids<br>Urine reducing substances<br>CSF amino acids |

# When to consider Mimickers of HIE

- SSRIs - Consider monitoring and providing supportive care for symptoms like hypotonia, hypertonia, tremors, tachycardia, respiratory distress, and hypoglycemia in neonates who may be experiencing selective serotonin reuptake inhibitor **(SSRI) withdrawal**.
- Ensure a thorough evaluation for **inborn errors of metabolism (IEMs)** in neonates presenting with seizures, encephalopathy, or abnormal muscle tone, including the possibility of conducting extensive investigations beyond the standard newborn screening.
- Include **viral infections**, particularly vector-borne infections, in the differential diagnosis for neonates presenting with encephalopathy.
- Maintain a high level of suspicion for conditions that mimic encephalopathy, such as **spinal cord injuries**, when assessing affected neonates.

# Diagnostic Algorithm of Neonatal Encephalopathy




Chakkarapani E. et al *Pediatric Research* 2025

# Criteria to Cool

- Appropriate **gestational age, birth weight** and postnatal age (all of these)
  - Born at ≥ 36 weeks
  - Weighing ≥ 1800 g
  - ≤ 6 hours of age at initiation AND
- Any ONE of the following: **metabolic criteria, Apgar scores, resuscitation**
  - pH **<7.00** or base deficit **≥16 mmol/L** based on an arterial or venous blood gas done within **60 minutes of birth** or
  - pH between **7.00 and 7.15** or base deficit between **10-16 mmol/L** and an **acute perinatal event** (e.g. late or variable decelerations, cord prolapse, uterine rupture, maternal haemorrhage or cardiorespiratory arrest)
  - Apgar score **≤5 at 10 minutes** after birth
  - Continued **need for resuscitation** (including endotracheal and/or bag mask ventilation) for **≥10 minutes**

# Criteria to Cool

- **Moderate or severe encephalopathy** on clinical examination (Thompson score >10) AND
- **Abnormal amplitude-integrated electroencephalography** (aEEG) of at least 30 minutes duration. Abnormalities could be any of the following:
  - Moderate abnormal background (upper margin of the band above 10µV and lower margin below 5 µV)
  - Severe abnormal background (upper margin of the band below 10µV and lower margin below 5 µV)
  - Normal background with seizure activity
  - (**Note**: If aEEG is not available but patient meets the other three criteria, cooling should still be considered).

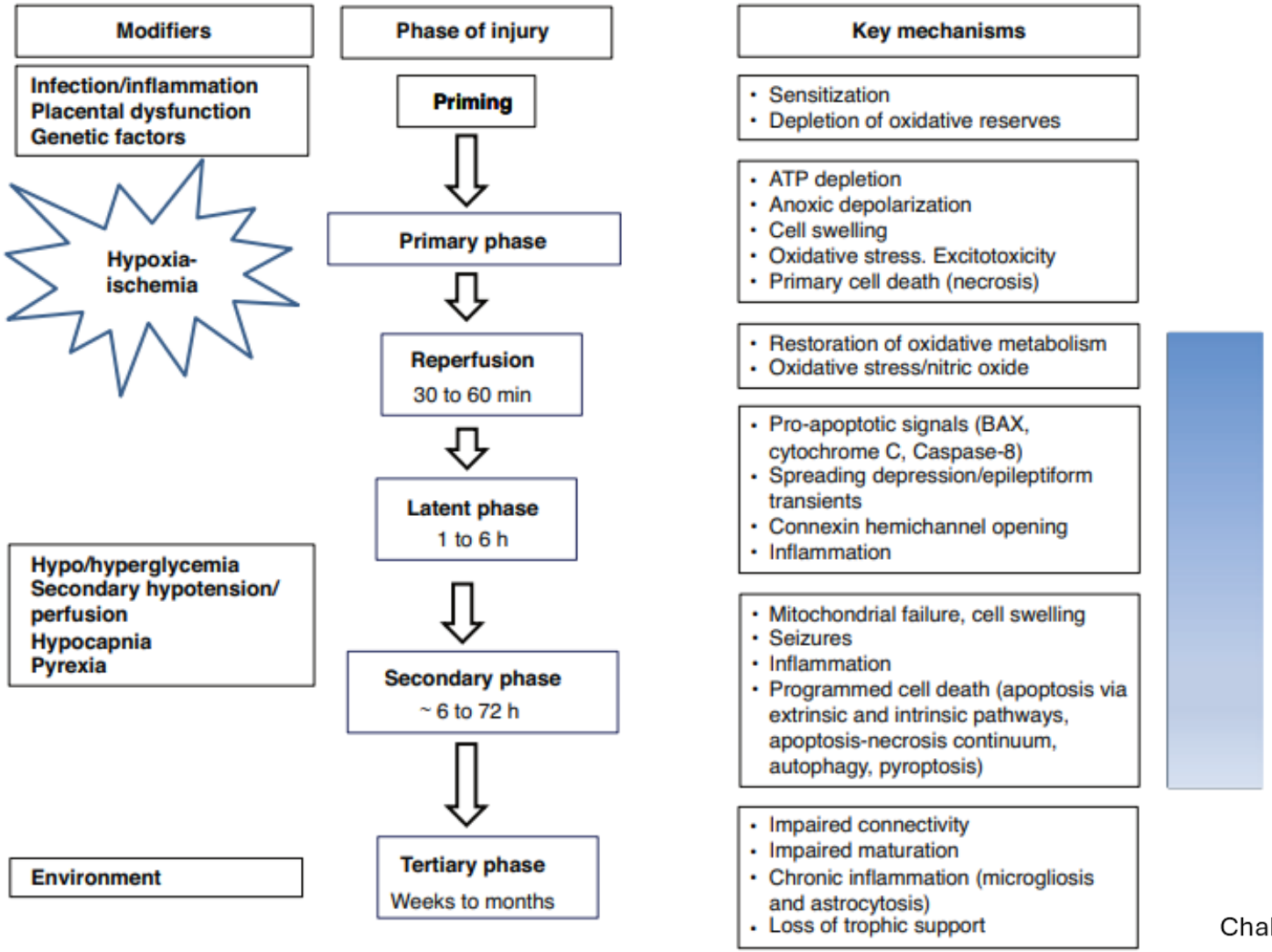
# Major trials of therapeutic hypothermia

**Table 2**
Entry criteria used in different trials of hypothermic neuroprotection after perinatal asphyxia.

| Study | CoolCap ($n = 235$)<br>TOBY ($n = 325$)<br>≥36 WG<br>≤5.5 h/6.0 h | NICHD trial ($n = 208$)<br>≥36 WG<br>≤6.0 h | Eicher trial ($n = 67$)<br>≥35 WG<br>≤6.0 h | NeonEuro ($n = 129$)<br>≥36 WG<br>≤6.0 h | ICE ($n = 204$)<br>≥35 WG<br>≤6.0 h |
|---|---|---|---|---|---|
| Metabolic | • 1 out of 4 (below)<br>• Apgar 10: ≤5<br>• pH <7.00<br>• BE ≤−16<br>• Ventilated/resuscitated by 10 min | • 1 out of 4 (below)<br>• Apgar 10: ≤5<br>• pH <7.00<br>• BE ≤−12<br>• Ventilated/resuscitated by 10 min (or fetal distress) | • 1 out of 6 (below)<br>• Apgar 5: ≤5<br>• pH <7.00/7.1<br>• BE ≤−13<br>• Ventilated/resuscitated by 10 min<br>Bradycardia ≤80 bpm,<br>Postnatal HI event | • 1 out of 4 (below)<br>• Apgar 10: ≤5<br>• pH <7.00<br>• BE ≤−16<br>• Ventilated/resuscitated by 10 min | • 2 out of 4 (below)<br>• Apgar 10: ≤5<br>• pH <7.00<br>• BE ≤−12<br>• Ventilated/resuscitated by 10 min |
| Neurology | • Consciousness; lethargy, stupor or coma<br>• And 1 out of 3:<br>• Hypotonia<br>• Abnormal reflexes<br>• Abnormal suck<br>• or Clinical seizures | • 3 out of 6:<br>• Consciousness (abnormal)<br>• Tone<br>• Autonomic reflexes<br>• Primitive reflexes<br>• Activity<br>• Posture<br>• or: Seizures | • 3 out of 6:<br>• Consciousness (abnormal)<br>• Tone<br>• Autonomic reflexes<br>• Reflexes<br>• Posture<br>• Seizures | • Moderate or severe encephalopathy<br>• or: Clinical sezures | • Moderate or severe encephalopathy (Sarnat-modified) |
| aEEG | • Abnormal aEEG | • No aEEG | • No aEEG | • Abnormal aEEG | • No aEEG |

WG, weeks of gestation; NICHD, National Institute of Child Health and Development; BE, base excess mmol/l; HI, hypoxic–ischaemic.
CoolCap and TOBY trials have identical criteria except entry within 5.5 h (CoolCap) and 6.0 h (TOBY). Data from the NeonEuro and ICE trials are not yet published.

# Time course of Pathophysiological Phases of Injury




Chakkarapani E. et al *Pediatric Research* 2025

**Fig. 2 Schema showing the time course of the pathophysiological phases of injury, key mechanisms, and modifying factors before and after hypoxia-ischemia.** The blue bar shows when therapeutic hypothermia needs to be applied to achieve effective neuroprotection.

# Monitoring and Management

| System | Clinical Features | Monitoring/Investigations | Management Considerations |
|---|---|---|---|
| Neurologic | Abnormal neurologic examination<br>Seizures | aEEG/cEEG<br>NIRS<br>MRI | IV phenobarbital is first-line ASM, should be used for EEG-confirmed seizures<br>Avoid systematic prescription of ASM at discharge |
| Respiratory | Hypoxemia<br>Hypocapnia<br>Respiratory acidosis | Cord blood gas<br>Arterial blood gas<br>CXR | Extubate when stable to limit hypocapnia<br>Use pH-stat for temperature-corrected blood-gas values interpretation[7]<br>Use lowest $F_iO_2$ effective to achieve $P_aO_2$ (50–70) mm Hg and $SpO_2 \geq 92\%$ |
| Cardiovascular | Hypotension<br>Shock<br>Arrythmias<br>Heart failure<br>Ischemia | Blood gas<br>Echocardiography<br>Cardiac troponin<br>Lactates | Correct hypotension; adjust treatment according to clinical pictures and lactates[7]<br>Sinus bradycardia is acceptable if adequate cardiac output<br>Consider ECMO if severe pulmonary hypertension |
| Metabolic | Hypoglycemia/hyperglycemia<br>Hypocalcemia<br>Hypomagnesemia<br>Metabolic acidosis<br>Hyponatremia | Blood glucose<br>Calcium<br>Lactates<br>Electrolytes | Start with 10% IV dextrose, customize as needed aiming for ≥2.6 mmol/L, avoid hyperglycemia<br>Customize IV fluids to meet electrolyte requirements |
| Renal | Acute tubular necrosis<br>Oliguria<br>Polyuria<br>Hematuria | Urea<br>Creatinine<br>Fluid balance (body weight, urine output, fluid intake) | Start with 60–70 mL/kg/d of IV fluid with customized electrolytes and glucose<br>Avoid systematic fluid restriction[7]<br>If oliguria, management based on cause of oliguria |
| Hematologic | Elevated nucleated RBCs<br>Thrombocytopenia<br>Bleeding, DIC<br>Thrombosis<br>Anemia | CBC<br>Coagulation profile | Transfuse platelets if needed<br>Transfuse FFP if needed<br>Transfuse cryoprecipitate if needed<br>Give supplemental vitamin K if needed<br>Transfuse PRBC if needed |
| Gastrointestinal | Feeding intolerance<br>GI bleeding<br>Necrotizing enterocolitis | LFTs | NPO during TH, but possible benefit of introduction of enteral breast milk if stable[7] |

# Monitoring and Management 2

| System | Clinical Features | Monitoring/Investigations | Management Considerations |
|---|---|---|---|
| Infectious | Sepsis | CBC<br>Blood culture | Initiate empiric antibiotics until sepsis is excluded |
| Temperature | Hypothermia/hyperthermia | Esophageal or rectal temperature | Start TH as soon as possible within the first 6 h of life<br>Avoid hyperthermia |
| Skin | Subcutaneous fat necrosis | Regular skin examination | Frequent repositioning of neonates on cooling during TH<br>Hyperhydration and diuretic treatment for SFN<br>Monitor for hypercalcemia |
| Comfort & sedation | Discomfort<br>Shivering | | Promote nonpharmacologic approaches (holding, parental presence)<br>Consider low-dose morphine |

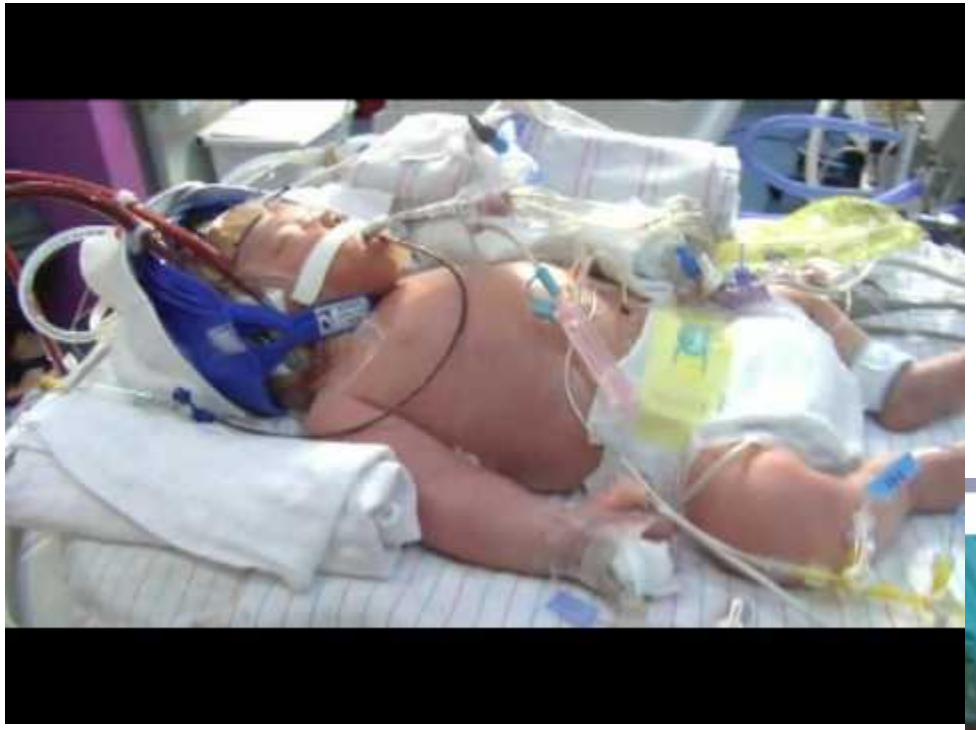
# Methods of Cooling

Whole body cooling(WBC) vs Selective Head Cooling (SHC)

- SHC – adequate neuroprotection with minimal risk of systemic side effects
  - differential temperature gradients in the brain
  - decrease in severe cortical lesions on MRI
  - more effective balance of cooling
  - better protective effect to cortex and cognitive function

- WBC- associated with adverse effects
  - fewer temperature gradients in the brain

Hoque, Paedaitrics 2010




## Methods of Cooling

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# Methods of Cooling

- **Selective Head Cooling**

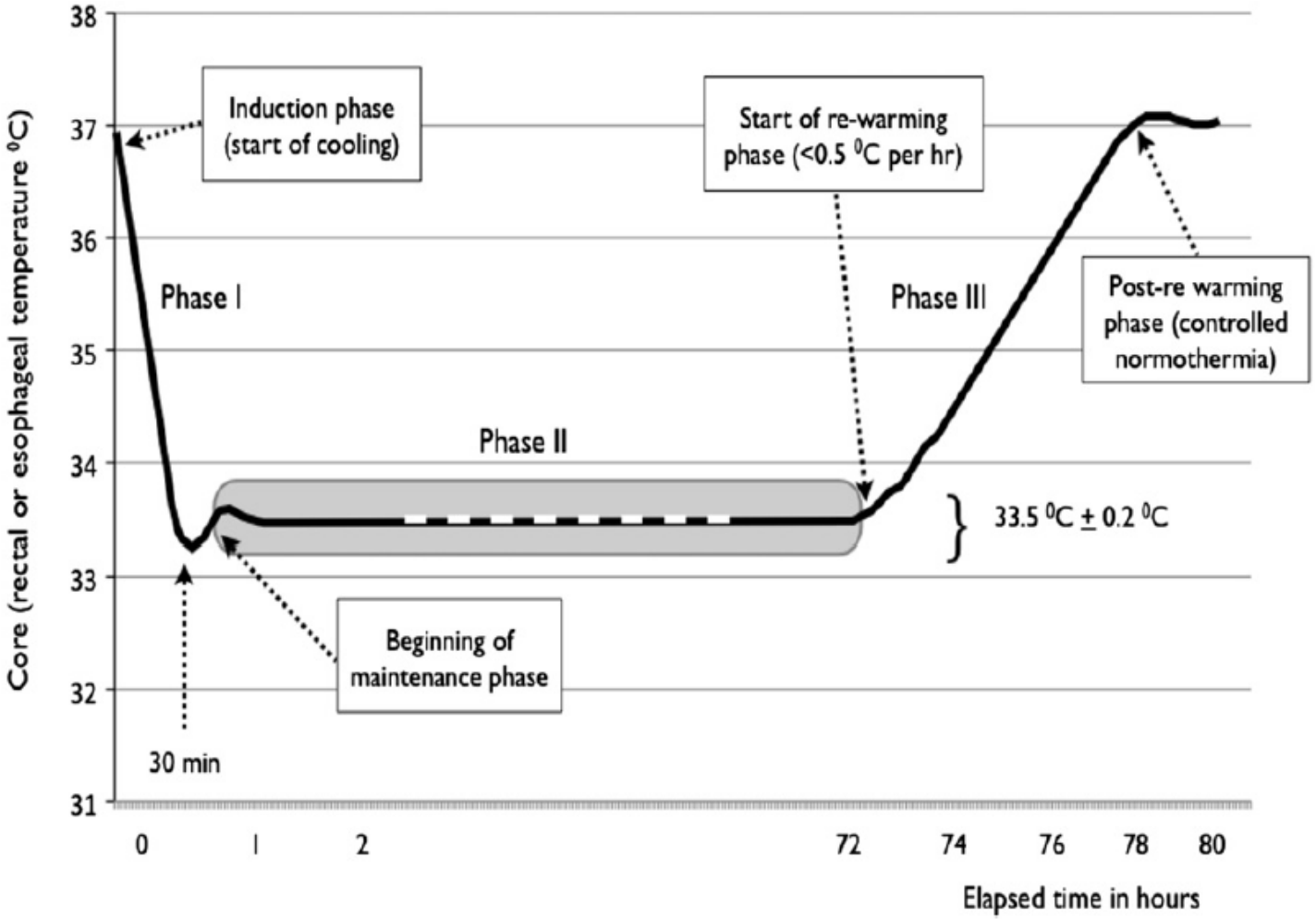
- > thrombocytopaenia
- Less significant decreases mortality, neuromotor disability, developmental delay

- **Total Body Cooling**

- > leukopaenia
- > hypoglycaemia
- > fat necrosis
- > systemic side effects

Pooled results show effect of both methods of cooling however, to be conclusive will need future trials where the two methods are compared head to head

# Phases of Cooling




Robertson N. J. et al. Seminars in Fetal & Neonatal Medicine 2010

# Techniques to Cool – High tech

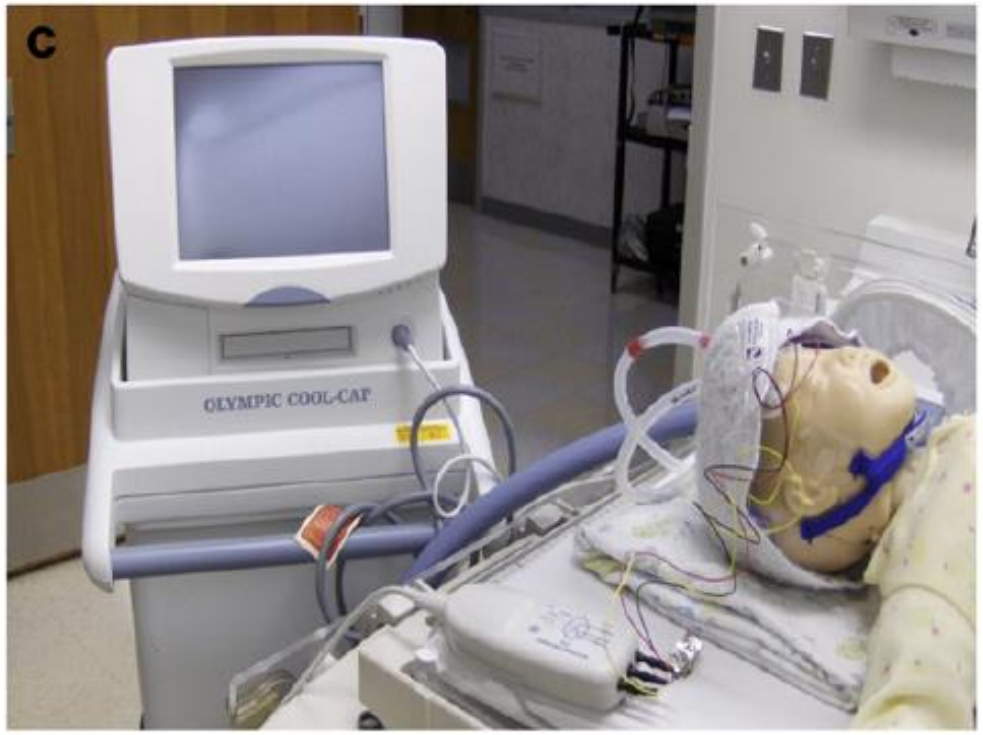
High-tech cooling devices

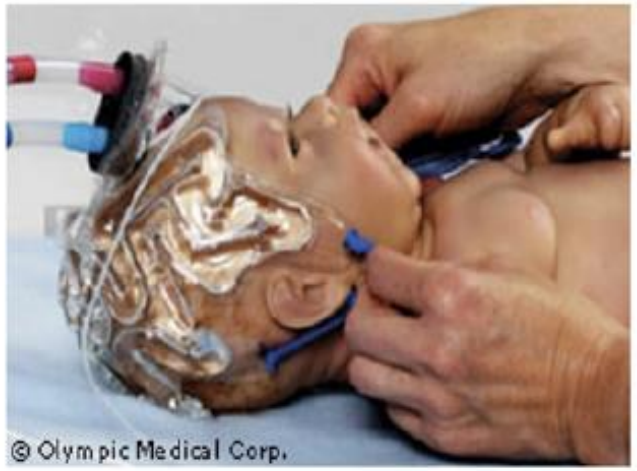
| Parameter | Blanketerol III | Tecotherm TS med 200 | MTRE CritiCool | Cool-Cap | Tecothermo-Servo |
|---|---|---|---|---|---|
| Design | Mattress and wraps | Mattress | Body wraps | Caps over head along with radiant warmers | Mattress (can be wrapped around if required) |
| Coolant | Water | Alcohol-based | Water | Water | Alcohol-based |
| Type of cooling | Whole body | Whole body | Whole body | Selective head cooling | Whole body |
| Precooling required | Yes | No | No | No | No |
| Typical site of record | Oesophageal | Rectal | Rectal | Rectal | Rectal |
| Induction | Rapid, overcooling occurs | Rapid, overcooling occurs | Rapid, overcooling is minimal | | Rapid, overcooling is minimal |
| Maintenance | Low nursing input | High nursing input | Low nursing input | High nursing input | Minimal nursing input (must check that the rectal probe is in situ) |
| Rewarming | Manual | Manual | Semi-automated | Manual | Fully automated |
| User-friendliness of panel | Water flow indicator | Digital temperature display | Graphic and digital displays | LCD touch screen Colour LCD | Graphic and digital displays with three different modes of operation |
| Effective cooling time | Low | Low | High | Low | High |
| Recurrent expenses | Cooling wraps | Nil | Cooling wraps | Cooling cap | Cooling mattress and coolant top-ups |
| Weight (kg) | 55.3 | 10 | 35 | 52 | 7 |
| Portable | No | Yes | No | No | Yes |
| Use in transport | No | No | Yes | No | Yes |
| Battery operation | No | No | No | No | Yes |
| Space required (cm) | 43.2 × 43.2 × 950.2 | 42.0 × 19.0 × 35.0 | 26.0 × 62.5 × 94.0 | 132.1 × 43.4 × 56.6 | 42.0 × 19.0 × 35.0 |

LCD, liquid crystal display.

Robertson N. J. et al. Seminars in Fetal & Neonatal Medicine 2010

# Techniques of cooling - Coolcap

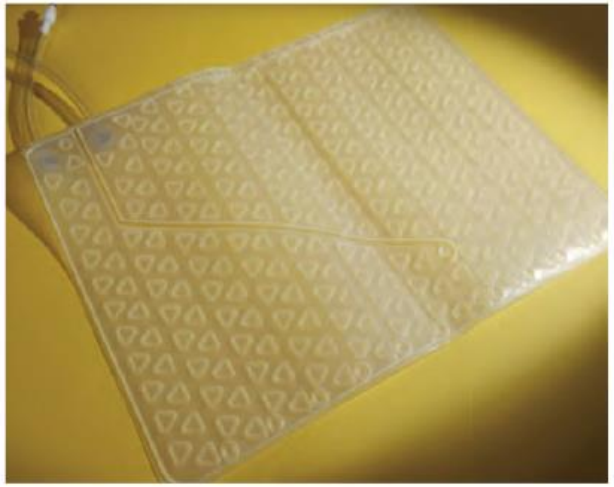


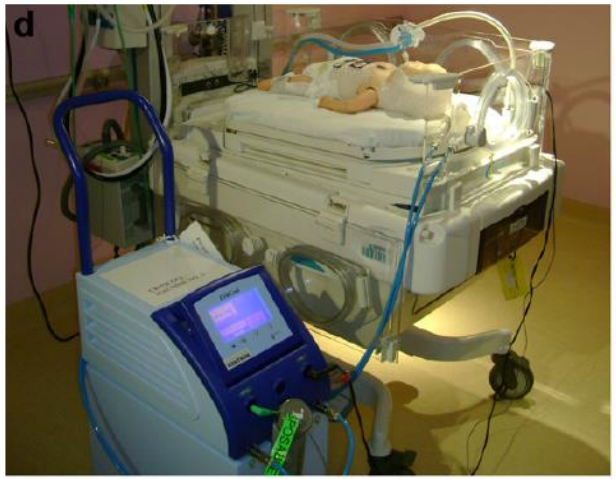



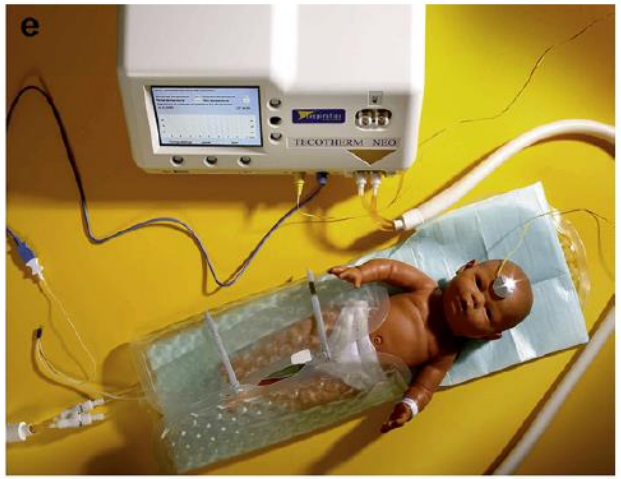

Robertson N. J. et al. Seminars in Fetal & Neonatal Medicine 2010

# Cooling Devices – High Tech








Robertson N. J. et al. Seminars in Fetal & Neonatal Medicine 2010

# Low Tech cooling Devices

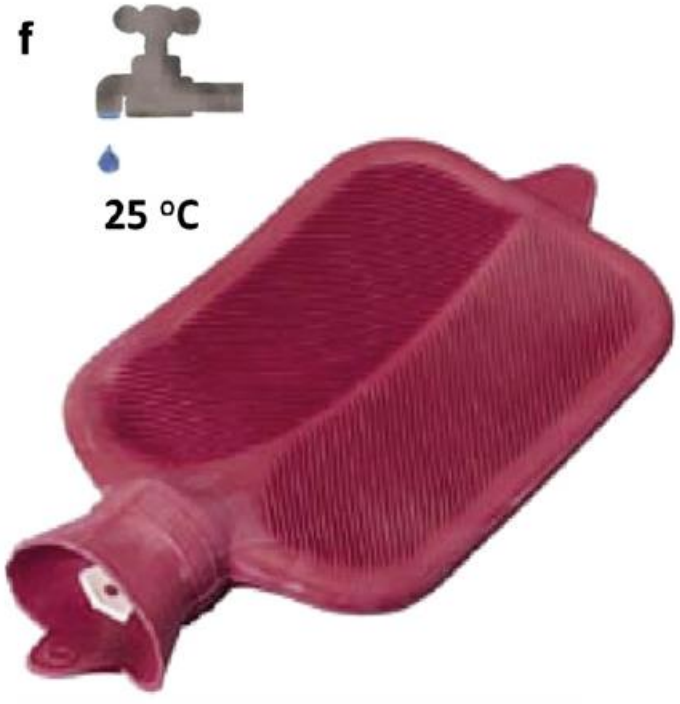
Low-tech cooling devices

| | Natural cooling | Water bottles | Fan | Gels | PCM |
|---|---|---|---|---|---|
| Design | Occurs in settings without radiant warmers | Whole-body cooling with mattress made of three water bottles laid sideways and filled with cool tap water | Servo-controlled fan. Overcooling prevented by servo-controlled radiant warmer | Soft, cold gel bags (12 cm × 12 cm, 250 g, refrigerator kept at 7–10 °C) applied to the head. Infant warmed with radiant warmer | Naked baby on PCM mattress (melting point 32 °C). Blankets used when needed |
| Induction time | Soon after birth | Within 1 h | Within 1 h | Within 1 h | Within 1 h |
| Maintenance | May last up to 15 h, if radiant warmers not used | Core/rectal temp. 33–34 °C | Rectal temp. 33.4–33.7 °C | Rectal temp. at 33–34 °C | Rectal temp. 33–34 °C |
| Rewarming | Passive and slow, generally <0.5 °C/h | Passive and slow, generally <0.5 °C/h | Stepwise increase of radiant warmer | Stepwise increase of radiant warmer | Passive and slow, generally <0.5 °C/h |
| Ambient temperature | <26 °C | 25–26 °C | 24 °C | 24 °C | <30 °C |
| Shivering | No | No | Yes | Yes | No |
| Temperature stability | Poor | Acceptable | Acceptable | Variable | Acceptable |

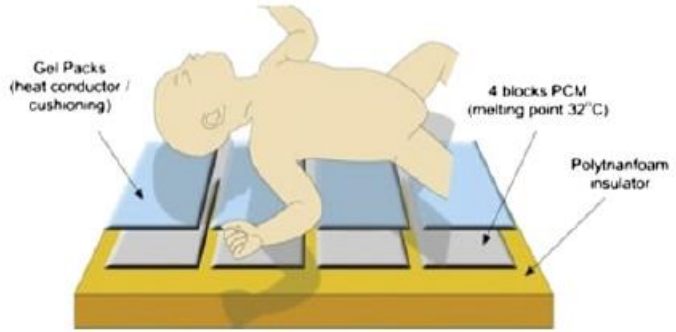
PCM, phase-changing material.

Robertson N. J. et al. Seminars in Fetal & Neonatal Medicine 2010

# Cooling Techniques – Low Tech



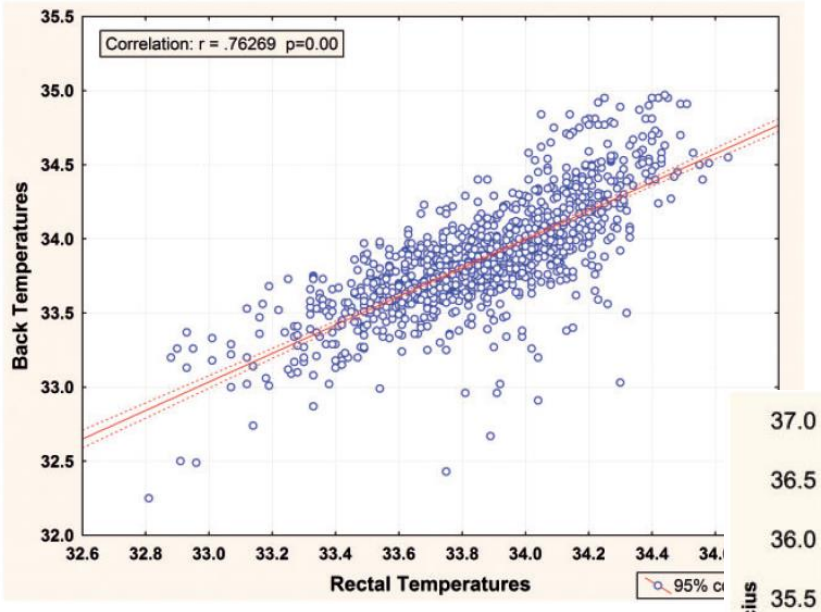


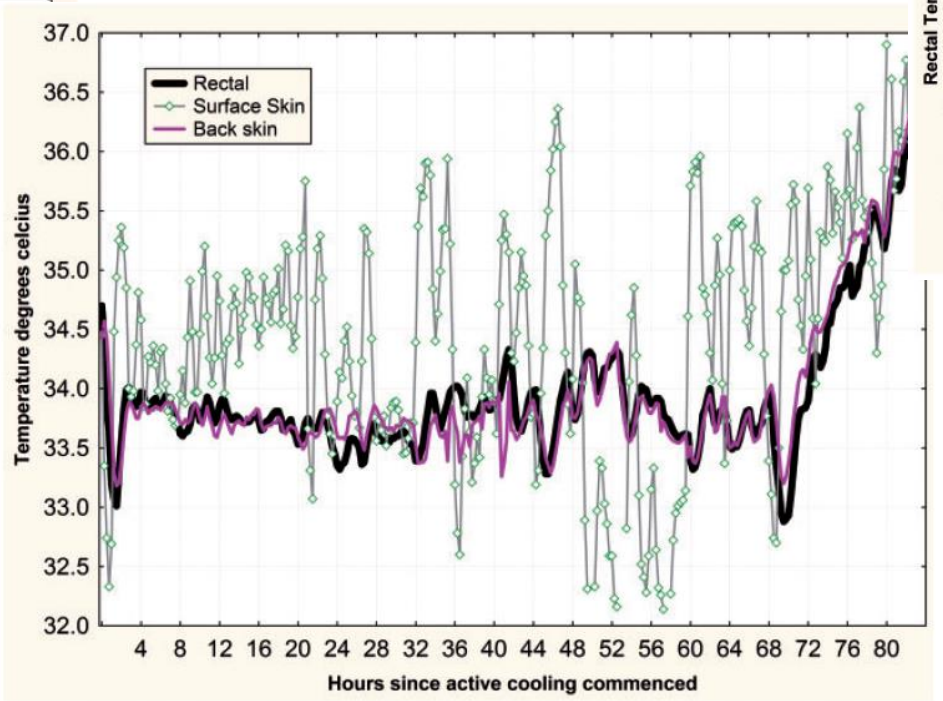


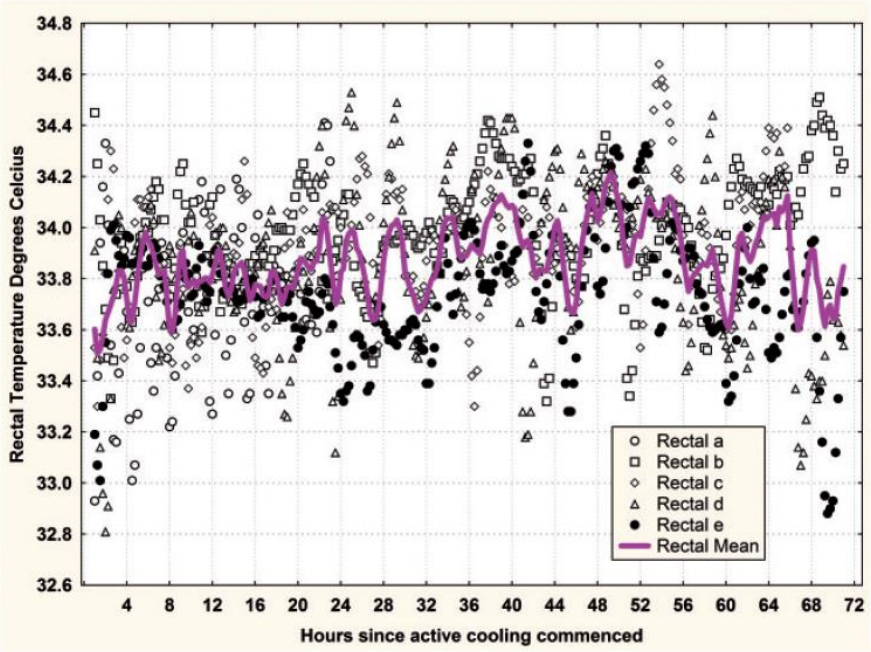

# Manual methods

- Gel bags, Mira cradle – change out the bags, and the phase change material
    - Manually taking temperatures – rectally can use a servo controlled radiant warmer decrease temperature to 34 degrees
    - Staff shortages – over ‘cool’
- Passive cooling
    - Turning off the radiant warmer – needs intensive monitoring - over shoot.
    - Protocol to warm up the patients – blankets, warm bottles - tepid water
- Labour intensive

# Gel Bags - Validation

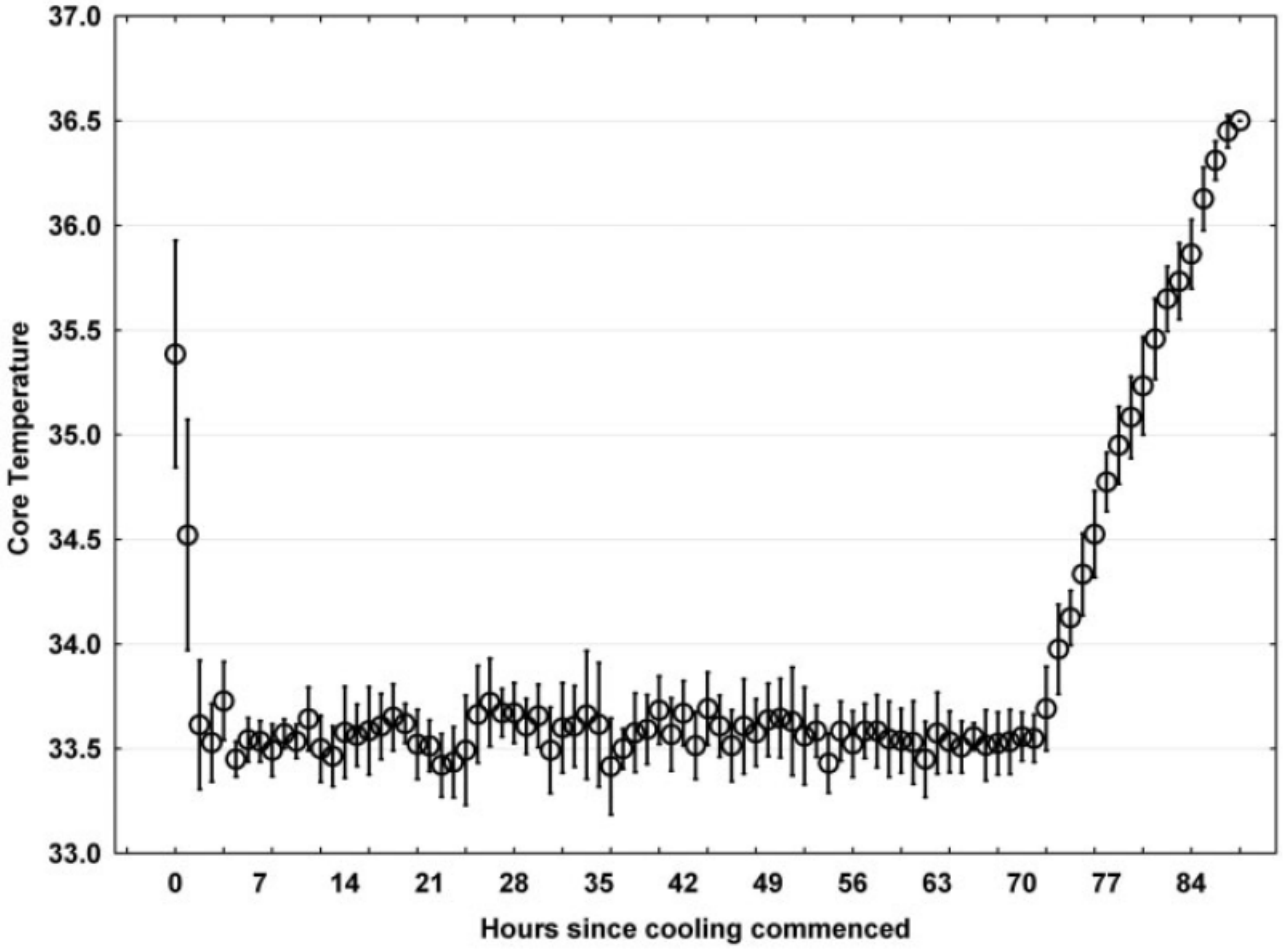



Horn et al. Journal of Tropical Pediatrics 2010

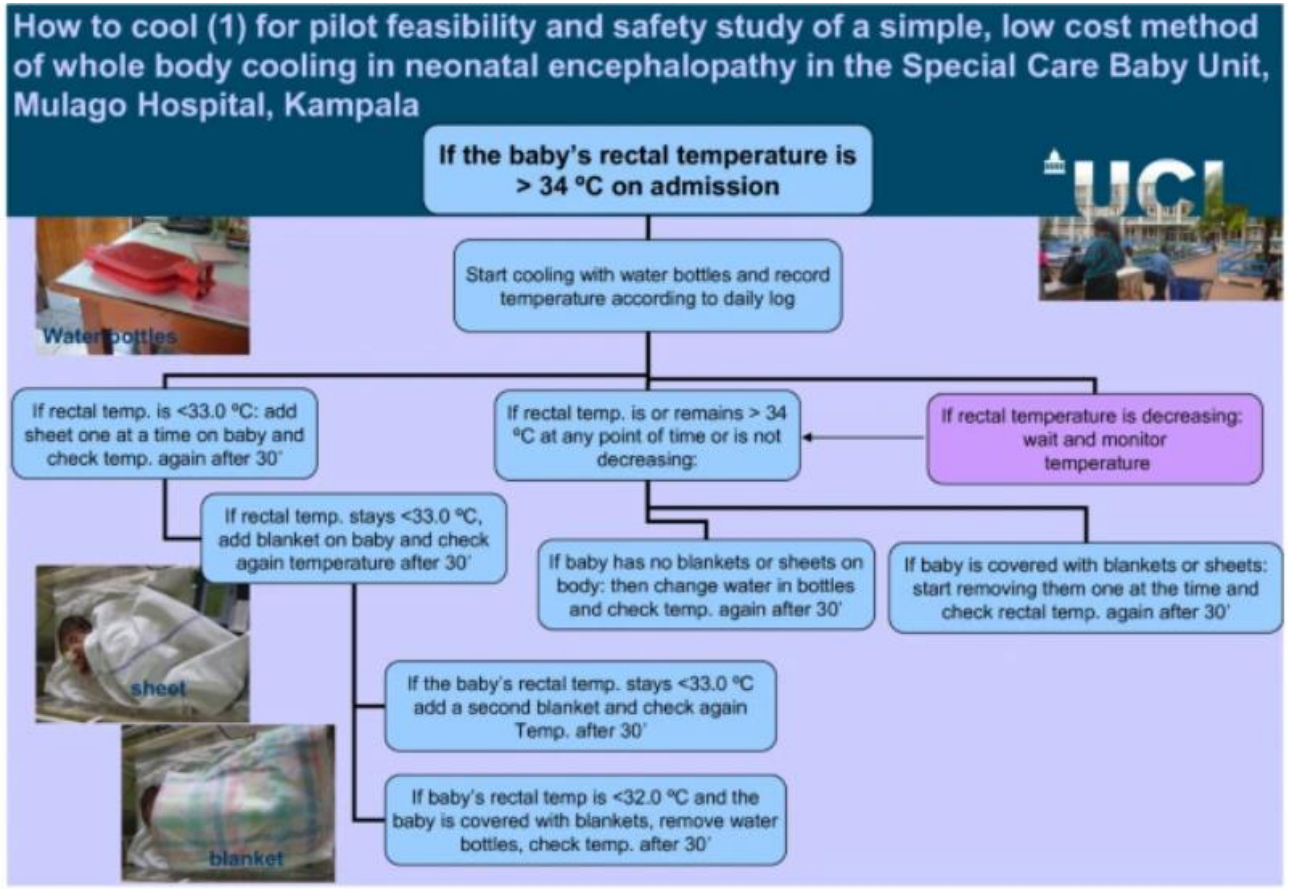
# A Servo-Assisted Gel-Pack Cooling Method for Newborn Infants with Hypoxic-Ischemic Encephalopathy




Horn et. al JOURNAL OF TROPICAL PEDIATRICS, 2011

# Therapeutic Hypothermia in Uganda – water bottles

- TH - water bottle filled with tepid tap water form the neonatal unit is feasible in a low resource setting.
- Higher mortality was seen in the cooled vs the standard care group (risk ratio: 5.0 (95% confidence interval (CI) 0.7-37)
- More infants with severe neonatal encephalopathy were randomized to the cooled group, which could explain the excess deaths;
- No facilities for infection screening at the time.



# Phase Change Material (PCM)

**Phase Changing Material for Therapeutic Hypothermia in Neonates with Hypoxic Ischemic Encephalopathy — A Multi-centric Study**

- 11 Level 3 NNU in India (November 2014 to December 2015)
- The median (IQR) of time taken to reach target temperature was 90 (45, 120) minutes.
- The mean (SD) deviation of temperature during cooling phase was 33.5 (0.39) ºC.
- Temperature readings were outside the target range in 10.8% (5.1% of the readings were <33°C and 5.7% were >34°C).
- Mean (SD) of rate of rewarming was 0.28 (0.13)°C per hour.
- Feasible and safe to provide therapeutic hypothermia to asphyxiated neonates
- Maintenance of target temperature was comparable to standard servo-controlled equipment

Thomas N, *Indian Pediatrics* 2017

# Cochrane review

- 11 randomised trials were included
- 1505 term infants with moderate to severe encephalopathy and evidence of intrapartum asphyxia
- Hypothermia resulted in statistically significant and clinically important reduction in the combined outcome of mortality and major neurodevelopmental disability to 18 -24 months of age
- NNT =7
- Borderline increase in the need for inotropic support and significant increase in bradycardia and thrombocytopaenia

# TH vs Standard Care – Death and Disability

| Study or subgroup | Hypothermia events | Hypothermia total | Standard care events | Standard care total | Weight, % | Risk ratio M-H, fixed (95% CI) |
|---|---|---|---|---|---|---|
| **1.1.1 Selective head cooling with mild systemic hypothermia** | | | | | | |
| Gunn, 1998 | 7 | 18 | 4 | 13 | 1.1 | 1.26 (0.46, 3.44) |
| Cool Cap Study, 2005 | 59 | 108 | 73 | 110 | 17.6 | 0.82 (0.66, 1.02) |
| Zhou, 2010 | 31 | 100 | 46 | 94 | 11.5 | 0.63 (0.44, 0.91) |
| **Subtotal (95% CI)** | | **226** | | **217** | **30.3** | **0.77 (0.64, 0.92)** |
| Total events | 97 | | 123 | | | |
| Heterogeneity: $\chi^2 = 2.46$, d.f. = 2 ($p = 0.29$), $I^2 = 19\%$ | | | | | | |
| Test for overall effect: $Z = 2.78$ ($p = 0.005$) | | | | | | |
| **1.1.2 Whole body cooling** | | | | | | |
| Eicher, 2005 | 14 | 27 | 21 | 25 | 5.3 | 0.62 (0.41, 0.92) |
| NICHD Study, 2005 | 45 | 102 | 64 | 103 | 15.5 | 0.71 (0.54, 0.93) |
| TOBY Study, 2009 | 74 | 163 | 86 | 162 | 21.0 | 0.86 (0.68, 1.07) |
| neo.nEURO Study, 2010 | 27 | 53 | 48 | 58 | 11.2 | 0.62 (0.46, 0.82) |
| ICE Study, 2011 | 55 | 107 | 67 | 101 | 16.8 | 0.77 (0.62, 0.98) |
| **Subtotal (95% CI)** | | **452** | | **449** | **69.7** | **0.75 (0.66, 0.84)** |
| Total events | 215 | | 286 | | | |
| Heterogeneity: $\chi^2 = 4.25$, d.f. = 4 ($p = 0.37$), $I^2 = 6\%$ | | | | | | |
| Test for overall effect: $Z = 4.80$ ($p < 0.00001$) | | | | | | |
| **Total (95% CI)** | | **678** | | **666** | **100.0** | **0.75 (0.68, 0.83)** |
| Total events | 312 | | 409 | | | |
| Heterogeneity: $\chi^2 = 6.89$, d.f. = 7 ($p = 0.44$), $I^2 = 0\%$ | | | | | | |
| Test for overall effect: $Z = 5.53$ ($p < 0.00001$) | | | | | | |
| Test for subgroup differences: $\chi^2 = 0.06$, d.f. = 1 ($p = 0.81$), $I^2 = 0\%$ | | | | | | |

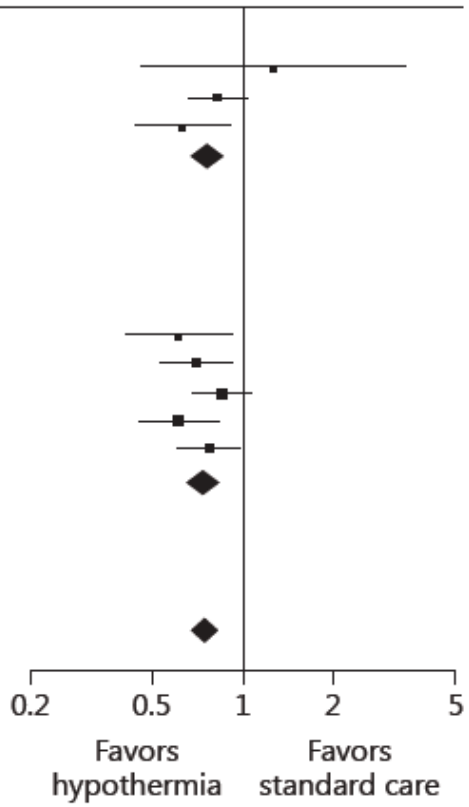



**Fig. 1.** Therapeutic hypothermia versus standard care. Effect on death or disability in survivors assessed (by method of cooling).

Jacobs SE, Cochrane Review 2013

# TH vs standard Care - Death

| Study or subgroup | Hypothermia events | Hypothermia total | Standard care events | Standard care total | Weight, % | Risk ratio M-H, fixed (95% CI) |
|---|---|---|---|---|---|---|
| **1.2.1 Selective head cooling with mild systemic hypothermia** | | | | | | |
| Gunn, 1998 | 3 | 18 | 3 | 13 | 1.4 | 0.72 (0.17, 3.03) |
| Akisu, 2003 | 0 | 11 | 2 | 10 | 1.0 | 0.18 (0.01, 3.41) |
| Cool Cap Study, 2005 | 36 | 108 | 42 | 110 | 16.7 | 0.87 (0.61, 1.25) |
| Lin, 2006 | 2 | 32 | 2 | 30 | 0.8 | 0.94 (0.14, 6.24) |
| Zhou, 2010 | 20 | 100 | 27 | 94 | 11.2 | 0.70 (0.42, 1.15) |
| **Subtotal (95% CI)** | | **269** | | **257** | **31.1** | **0.78 (0.59, 1.04)** |
| Total events | 61 | | 76 | | | |
| Heterogeneity: $\chi^2 = 1.56$, d.f. = 4 (p = 0.82), $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 1.72 (p = 0.09) | | | | | | |
| **1.2.2 Whole body cooling** | | | | | | |
| Shankaran, 2002 | 2 | 9 | 3 | 10 | 1.1 | 0.74 (0.16, 3.48) |
| Eicher, 2005 | 10 | 32 | 14 | 33 | 5.5 | 0.74 (0.38, 1.41) |
| NICHD Study, 2005 | 24 | 102 | 38 | 103 | 15.2 | 0.64 (0.41, 0.98) |
| TOBY Study, 2009 | 42 | 163 | 44 | 162 | 17.7 | 0.95 (0.66, 1.36) |
| neo.nEURO Study, 2010 | 20 | 53 | 33 | 58 | 12.6 | 0.66 (0.44, 1.00) |
| ICE Study, 2011 | 27 | 108 | 42 | 109 | 16.8 | 0.65 (0.43, 0.97) |
| **Subtotal (95% CI)** | | **467** | | **475** | **68.9** | **0.73 (0.61, 0.89)** |
| Total events | 125 | | 174 | | | |
| Heterogeneity: $\chi^2 = 2.92$, d.f. = 5 (p = 0.71), $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 3.18 (p = 0.001) | | | | | | |
| **Total (95% CI)** | | **736** | | **732** | **100.0** | **0.75 (0.64, 0.88)** |
| Total events | 186 | | 250 | | | |
| Heterogeneity: $\chi^2 = 4.72$, d.f. = 10 (p = 0.91), $I^2 = 0\%$ | | | | | | |
| Test for overall effect: Z = 3.59 (p = 0.0003) | | | | | | |
| Test for subgroup differences: $\chi^2 = 0.13$, d.f. = 1 (p = 0.72), $I^2 = 0\%$ | | | | | | |

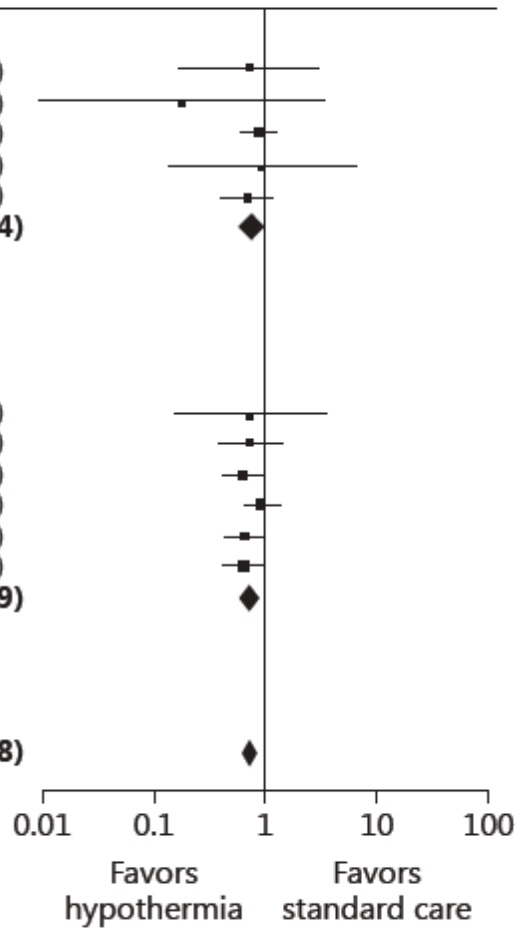



**Fig. 2.** Therapeutic hypothermia versus standard care. Effect on death (by method of cooling).

Jacobs SE, Cochrane Review 2013

# Outcomes in HIE

| Short Term Outcome | Long Term Outcome | |
|---|---|---|
| Seizures | Motor | Cerebral Palsy |
| Feeding Difficulties | Sensory | Hearing loss and Visual impairment |
| Death | Cognitive | Episodic and working memory deficits |
| | | Attention deficits |
| | Educational | Increased Support Requirements |
| | | Lower School Readiness Test scores |
| | Behavioural | Attention Deficits |
| | | Explosiveness and Irritability |
| | Neuropsychiatric | Psychotic symptoms and Schizophrenia |
| | Neurodevelopmental | Autism Spectrum Disorders |

Ahearne CE *World J Clin Pediatr* 2016

# Long term Outcomes (6-7 years)

- NICHD – death or disability was decreased (41% vs 60% P=0.03)
  - survivors – IQ < 70 ( 27% vs 33%) and CP in 17% vs 29% (P=NS)

- Toby – 52% hypothermia patients vs 39% control group
  children survived with an IQ>85 (RR>1.31, P=0.04)
  - number of children that died were 29% vs 30%
  - 45% vs 28 % survived without neurological abnormalities
  (RR 1.61, CI - 1.15-2.22)
  - a decrease in the rate of CP and moderate to severe disability

- CoolCap – status at 18 months was associated with status at 6-7 years ($p<0.001$)
  - CP diagnosed at 18 months was highly associated with
  WeeFim mobility scores at 7-8 years

# Summary of Findings of NICHD and TOBY Trials

| Variable | NICHD trial (2012)[29] | | | TOBY trial (2014)[30] | | |
|---|---|---|---|---|---|---|
| | Hypothermia | Control | *P* value | Hypothermia | Control | *P* value |
| Death, no./total no. (%) | 27/97 (28) | 41/93 (44) | 0.04 | 47/163 (29) | 49/162 (30) | 0.81 |
| Death or IQ score <70, no./total no. (%) | 46/97 (47) | 58/93 (62) | 0.06 | - | - | - |
| IQ score ≥85, no./total no. (%) | - | - | - | 75/145 (52) | 52/132 (39) | **0.04** |
| Death or severe disability, no./total no. (%) | 38/93 (41) | 53/89 (60) | 0.03 | - | - | - |
| Moderate or severe disability, no./survivors' total no. (%) | 24/69 (35) | 19/50 (38) | 0.87 | 21/96 (22) | 31/83 (37) | **0.03** |
| Cerebral palsy, no./ survivors' total no. (%) | 12/69 (17) | 15/52 (29) | 0.14 | 21/98 (21) | 31/86 (36) | **0.03** |
| Survival free of disability, no./survivors' total no. (%) | 28/69 (41) | 21/50 (42) | 0.87 | 65/96 (68) | 37/83 (45) | **0.002** |
| Blindness, no./survivors' total no. (%) | 1/67 (1) | 2/50 (4) | 0.42 | 1/98 (1) | 1/82 (1) | 1.00 |
| Hearing impairment, no./ survivors' total no. (%) | 3/63 (5) | 1/50 (2) | 0.45 | 4/98 (4) | 8/83 (10) | 0.15 |
| Full-scale IQ score, mean±SD | 89.9±23.3 | 75.3±24.4 | 0.23 | 103.6±14.4 | 98.5±18.9 | 0.07 |
| Verbal IQ score, mean±SD | 85.9±19.1 | 86.4±13.7 | 0.88 | 105.2±15.6 | 101.1±17.3 | 0.16 |
| Performance IQ score, mean±SD | 91.3±17.3 | 90.5±16.3 | 0.82 | 101.1±15.0 | 96.7±19.0 | 0.12 |
| Processing speed score, mean±SD | - | - | - | 98.7±12.4 | 95.3±18.7 | 0.22 |

NICHD, National Institute of Child Health and Human Development; TOBY, Total Body Hypothermia for Neonatal Encephalopathy; IQ, intelligence quotient; SD, standard deviation.
Boldface indicates a statistically significant difference with $P<0.05$.

Lee BL et al. *Clin Exp Pediatr* Vol. 64, No. 12, 608–618, 2021

# Novel Therapeutic Agents

| | Neuroprotective | | | | | |
|---|---|---|---|---|---|---|
| Therapies | Antiexcitatory | Antiapoptotic | Anti-inflammatory | Antioxidative | Neurorestorative | Route, Dosing, and Schedule |
| Allopurinol | | | ✓ | ✓ | | Pre: IP, 135 mg/kg immediately post-HI<br>RCT: IV, 20 mg/kg post-HI (30 min after birth)<br>+ 10 mg/kg H12 if TH |
| Azithromycin | | | ✓ | | | Pre: IV or IV, 1.5–150 mg/kg 15 min–4 h post-HI or 2 h post-HI + H24 + H48 |
| Caffeine | | | ✓ | | | Pre: IP or PO, 5–20 mg/kg immediately post-HI<br>RCT: IV, 20 mg/kg post-HI (before 24 h of life)<br>+ 5 mg/kg q24h ×2 doses |
| Erythropoietin | ✓ | ✓ | ✓ | ✓ | ✓ | Pre: IV, 5000 U/kg 3 h post-HI<br>+ 833.3 U/kg/h × 69 h or 1000 U/kg immediately post-HI + H24 + D7<br>RCT: IV, 1000 U/kg post-HI (before 26 h of life) + D2 + D3 + D4 + D7 |
| $MgSO_4$ | ✓ | ✓ | ✓ | ✓ | | Pre: IP, SC, or IV, 100–1000 mg/kg immediately post-HI<br>RCT: IV 250 mg/kg within 6 h post-HI<br>+ H24 + H48 |
| Melatonin | ✓ | ✓ | ✓ | ✓ | | Pre: IP, 10–20 mg/kg immediately post-HI + H24 + H48 or 0.5 mg/kg/h infusion × 2 h or 10–15 mg/kg immediately post-HI<br>RCT: PO or IV, single dose on admission or q2h<br>×8 doses or daily ×3–5 d |

# Novel Therapies for HIE 2

| | Neuroprotective | | | | | |
|---|---|---|---|---|---|---|
| Therapies | Antiexcitatory | Antiapoptotic | Anti-inflammatory | Antioxidative | Neurorestorative | Route, Dosing, and Schedule |
| Sildenafil | | ✓ | ✓ | | ✓ | Pre: IP immediately post-HI or PO 12 h post-HI<br>RCT: PO 2–3 mg/kg q12h × 7 d starting D2/3 |
| Stem cells | | ✓ | ✓ | | ✓ | Variable, usually single dose |
| TH | ✓ | ✓ | ✓ | | | 33.5°C × 72 h started within 6 h |
| Topiramate | ✓ | | | | | Pre: IP 20–100 mg/kg immediately post-HI + H2 or PO 50 mg/kg immediately post-HI<br>+ H2 + q12h × 5 d<br>RCT: PO 5 mg/kg post-HI (at TH initiation) + 3 mg/kg/d × 5 d |
| Xenon | ✓ | ✓ | | | | Pre: Inhaled 50% Xe × 3 h immediately or up to 2 h post-HI<br>RCT: Inhaled 30% Xe × 24 h immediately post-HI |

# Outcomes after Neuroprotective Agents

| Neuroprotective agents | Study | Study group (n) | Control group (n) | Protocol | Findings |
|---|---|---|---|---|---|
| Epo | Wu et al.[41] (2016) | 24 (Epo 1,000 U/kg intravenously plus hypothermia) | 26 (saline plus hypothermia) | Epo at 1, 2, 3, 5, and 7 days of age with hypothermia started within 6 hr of birth, for 72 hr | Brain MRI at mean 5.1 days showed significant lower brain injury score in Epo group; and better motor outcome at mean age 12.7 mo |
| | Juul et al.[43] (2018) | Enrolling 500 (Epo 1,000 U/kg intravenously plus hypothermia) | Recruiting (saline plus hypothermia) | Epo at 1, 2, 3, 5, and 7 days of age with hypothermia started within 6 hr of birth, for 72 hr | Ongoing study: evaluation of neurodevelopmental outcomes and mortality up to 24 mo |
| | Patkai et al.[44,a] (2014) | Enrolling 120 (Epo 1,000 to 1,500 U/kg intravenously plus hypothermia) | Recruiting (saline plus hypothermia) | Epo at day 1 (at <12 hr), 2 and 3 every 24 hr) with hypothermia started within 6 hr of birth, for 72 hr | Ongoing study: evaluation of survival without neurologic sequelae at 24 mo |
| Xenon | Azzopardi et al.[40] (2016) | 46 (30% inhaled xenon plus hypothermia) | 46 (hypothermia alone) | Hypothermia in combination with 30% inhaled xenon for 24 hr commenced a median of 10 hr after birth | No reduction in lactate to N-acetyl aspartate ratio in the thalamus in MRI/MRS; administration of xenon was safe but did not enhance the neuroprotective effect of hypothermia |
| Melatonin | Aly et al.[39] (2014) | 15 (melatonin 10 mg/kg plus hypothermia) | 15 (hypothermia alone) | Melatonin 10 mg/kg daily for a total of 5 enteral doses with hypothermia | Melatonin/hypothermia group had fewer seizures, fewer white matter abnormalities on MRI and better mortality rate at 6 months without neurodevelopmental abnormalities |
| Stem cell | Cotten et al.[38] (2014) | 23 (fresh autologous UCB cell plus hypothermia) | 82 (hypothermia alone) | Infusion of 4 doses of UCB, 1–5×$10^7$ cells/dose (the first dose after birth, and at 24, 48, and 72 postnatal hours) with hypothermia | UCB cell administration with hypothermia therapy was safe but did not provide long-term neurodevelopmental outcomes at 12 mo |
| Topiramate | Filippi et al.[42] (2018) | 21 (topiramate plus hypothermia) | 23 (hypothermia alone) | Topiramate administration by orogastric tube, at the dosage of 10 mg/kg/day at 1, 2, and 3 days of age with hypothermia | Topiramate was safe but did not reduce the combined frequency of mortality and severe neurological disabilities at 18–24 mo |

Epo, erythropoietin; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; UCB, umbilical cord blood.
[a]Quoted from Rangarajan and Juul.[44]

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# Cognitive Outcomes in Late Childhood

| Study | Median or mean age (yr) | Study group (n) | Control group (n) | Measurements | Findings |
|---|---|---|---|---|---|
| Late childhood (5–10 yr) | | | | | |
| Robertson and Finer[12] (1988) | 5.5 | 127 (56 With mild NE, and 71 with moderate NE) | Neonatal comparison group[a]: 71, peer comparison group: 188 | Stanford-Binet Intelligence Scale; accepted norms are 100±16 | Moderate NE group had the lowest mean IQ score.<br>- Moderate NE: 99±18[b]<br>- Mild NE: 106±12<br>- Neonatal comparison: 105±15<br>- Peer comparison: 108 ±14 |
| Robertson et al.[13] (1989) | 8 | 145 (56 With mild NE, 84 with moderate NE, and 5 with severe NE) | Peer comparison group:155 | WISC-Revised (1974) | Lower mean IQ score in moderate impaired and nonimpaired NE group compared with those of the mild NE and peer group.<br>- Moderate nonimpaired NE: 102±17[b]<br>- Moderate impaired NE: 68±27[b]<br>- Mild nonimpaired NE: 106±13<br>- Control: 112±13 |
| Marlow et al[14] (2005) | 7.2 | 50 (32 With moderate NE, and 18 with severe NE) | Peer comparison group: 49 | British ability scales (BAS-II) school-age battery | General cognitive ability scores were lowest in the severe NE group for children without motor disability; Peer and moderate groups had comparable scores.<br>- Severe NE: 103±13[b]<br>- Moderate NE: 112±11<br>- Control: 114±14 |
| van Kooij et al[15] (2010) | 9 10 | 80 (34 With mild NE, and 46 with moderate NE) | Age and sex matched group: 52 | WISC-III (Dutch version) | The mean estimated IQ score of children with moderate and mild NE without cerebral palsy were lower than that of the control group.<br>- Children with CP: 70±18[b]<br>- Moderate NE without CP: 92±20[b]<br>- Mild NE without CP: 99±14[b]<br>- Control: 109±12 |
| van Handel et al[16] (2012) | 9.9 | 81 (32 With mild NE, 39 with moderate NE, and 10 with CP) | Peer comparison group: 53 | WISC-III (Dutch version) | All group differences in mean estimated IQ score were significant except between moderate NE mild NE.<br>- Children with CP: 72±18[b]<br>- Moderate NE: 91±21[b]<br>- Mild NE: 99±14[b]<br>- Control: 109±12 |

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# Cognitive Outcomes in Adolescence

| | | | | | |
|---|---|---|---|---|---|
| Adolescence (11–18 yr) | | | | | |
| Gadian et al[17] (2000) | 12.9 | 5 Without major neurologic deficits | Normal subjects: 35 | Wechsler Memory Scale (Wechsler, 1945) | All 5 patients showed severe impairments of episodic memory (memory for events).<br>- Memory quotient (MQ) of patients with HIE: 83.8±5.4<br>- MQ of normal subjects: 105.8±13.9 |
| Mañeru et al[18] (2001) | 15.6 | 28 (8 With mild NE, and 20 with moderate NE) | Matched healthy adolescents: 28 | Rey's Auditory Verbal Learning Test | Participants with moderate NE showed decreased ability of delayed recall.<br>- Moderate NE: 11.5±1.9[b]<br>- Mild NE: 12.0±1.6<br>- Control: 12.9±1.5 |
| Lindstrm et al.[20] (2006) | 16.8 | 28 With moderate NE without CP | Siblings of school age: 15 | WISC-III | Study group had more cognitive dysfunction (low/borderline IQ and learning disability) compared to their siblings.<br>- Moderate NE: 20/28 (71%)<br>- Control: 2/15 (13%) |
| Perez et al.[3] (2013) | 11.2 | 57 Without CP and severe mental retardation | None | WISC-R (German version) | Full-scale and performance IQ scores were significantly lower in study group than the population norms.<br>- Full-scale IQ mean score: 95 (62–120)<br>- Verbal IQ mean score: 98 (63–123)<br>- Performance IQ mean score: 95 (66–118)<br>- Full-scale IQ score < 85: 14/57 (25%) |
| Lee et al.[21] (2021; in press) | 13 | 16 With NE | None | WISC-IV, V, and WASI-II | Adolescents (n=7) with watershed pattern of injury had lower the mean estimate of overall cognitive ability than those (n=7) with normal imaging (94±21 vs. 113 ±9, *P*=0.04) |

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# MRI Patterns of Injury - BGT

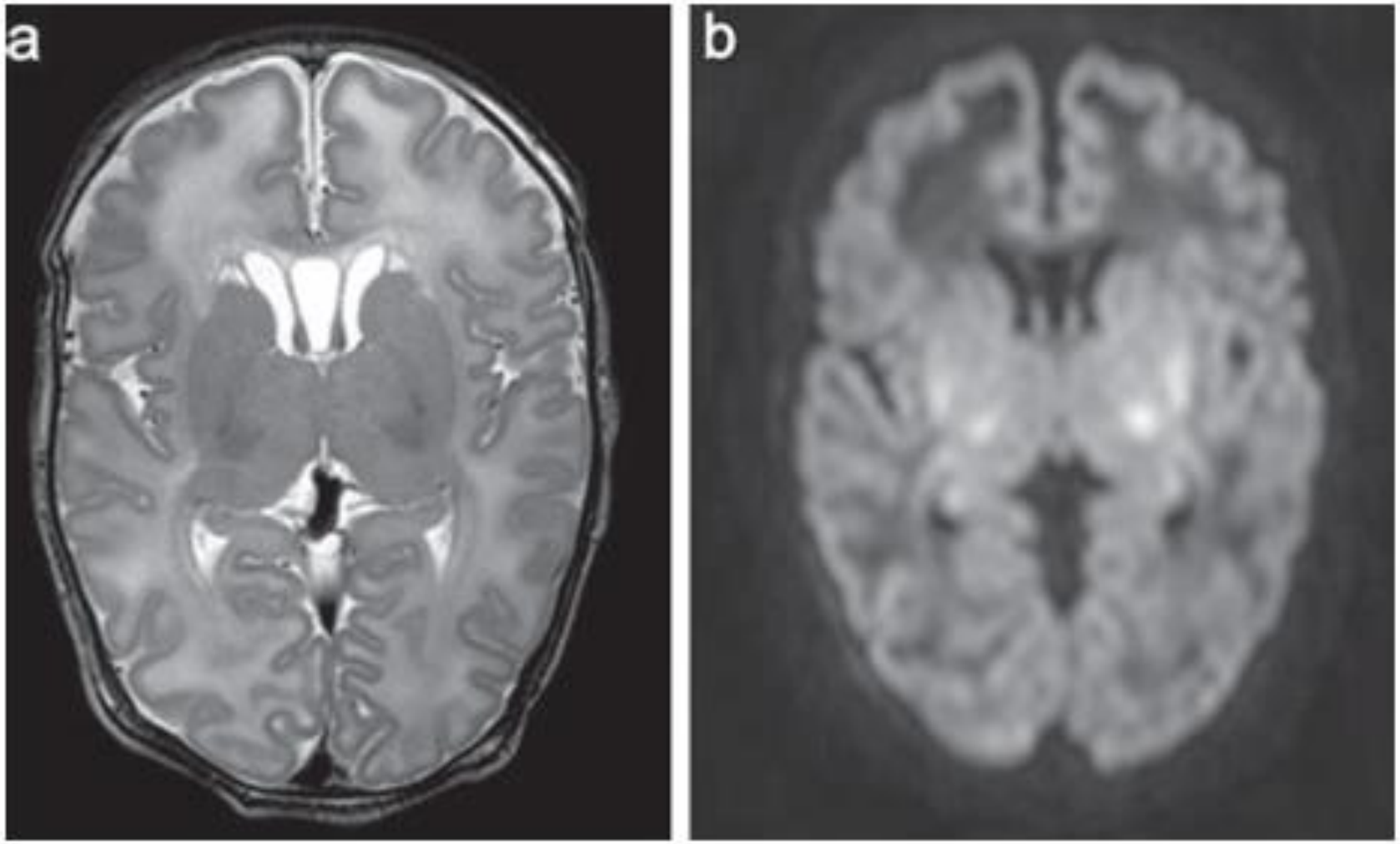
- A basal-ganglia-thalamus pattern (BGT) predominantly affecting bilaterally the central grey nuclei and peri-rolandic cortex.

- Associated involvement of the hippocampus and brain stem is not uncommon
- This pattern of injury is most often seen following an acute sentinel event and is also referred as a pattern following **'acute near total asphyxia**'.

- Using conventional MRI, absence of a normal high signal intensity of the posterior limb of the internal capsule (PLIC) is highly predictive of severe adverse sequelae.

- Neonates with BGT pattern of injury are often so severely disabled that they will not be included in long-term follow-up studies.

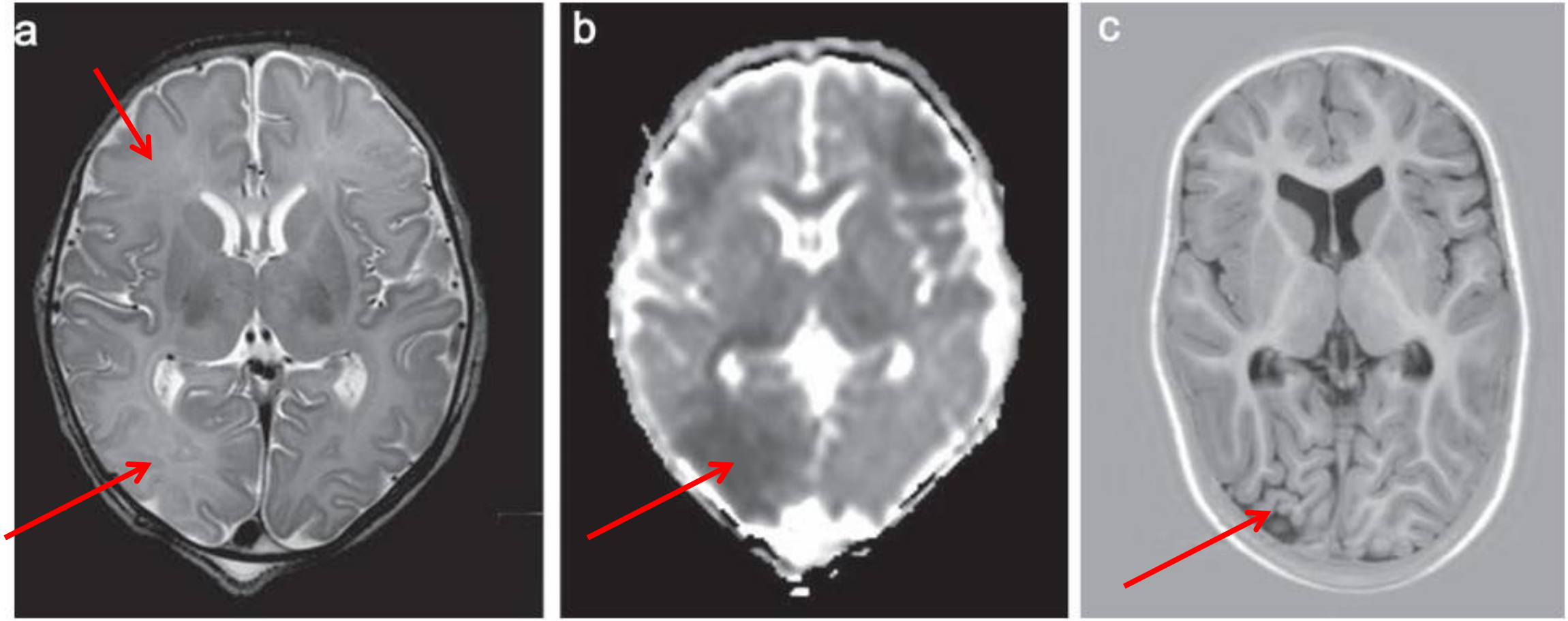
# MRI Of BGT Injury



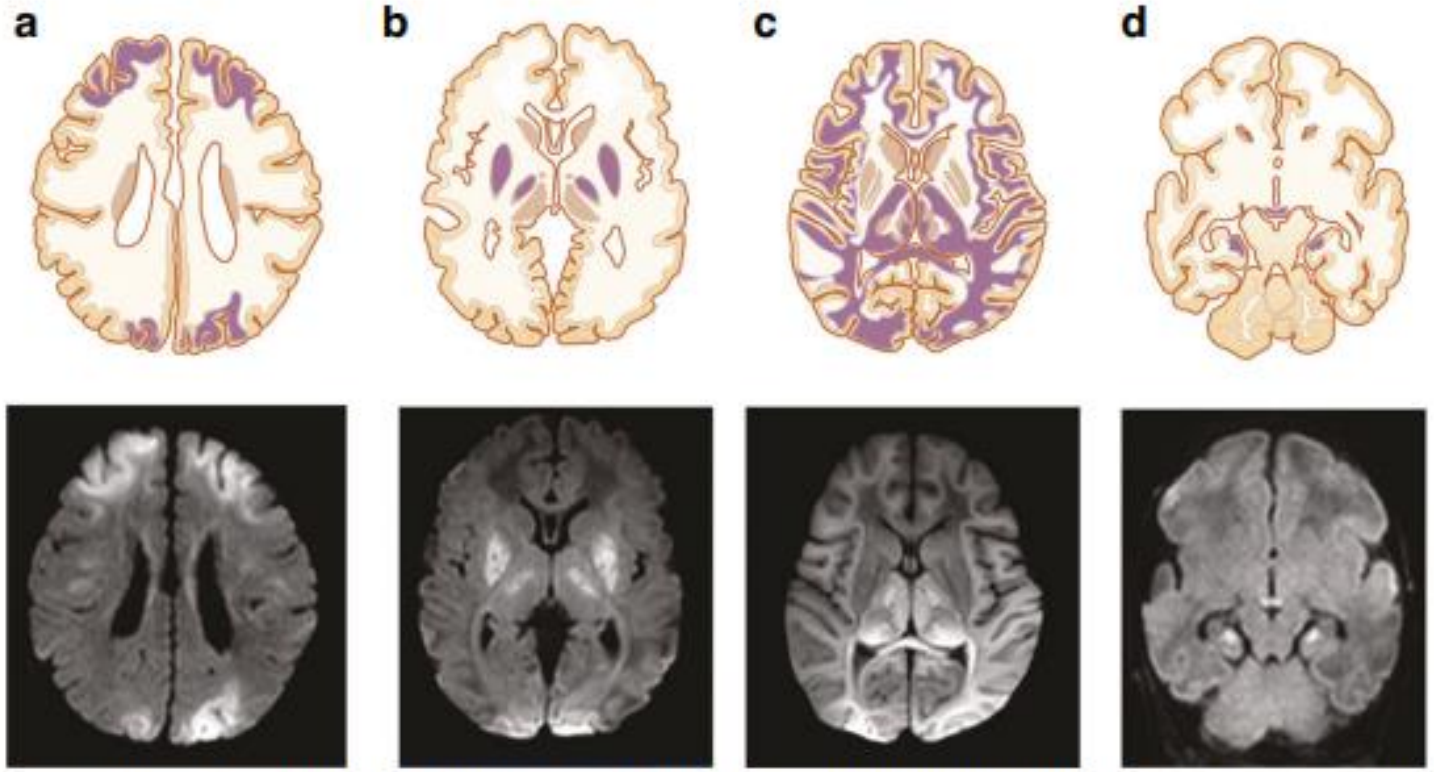
# MRI Patterns of Injury - WS

- The watershed predominant pattern of injury (WS) - pattern seen following '**prolonged partial asphyxia**'.
- The vascular WS zones (anterior-middle cerebral artery and posterior-middle cerebral artery) - white matter and in more severely affected infants also the overlying cortex.
- The lesions can be unilateral or bilateral, posterior and/or anterior.
- A repeat MRI may show cystic evolution, but more often atrophy and gliotic changes will be recognised.
- As (severe) motor impairment is uncommon in this group of infants, they are not uncommonly considered to have an early normal outcome, when seen at 12–18 months and are then discharged from further follow-up.
- However, suboptimal head growth, behavioural problems and delay in language are common

# MRI of WS Injury



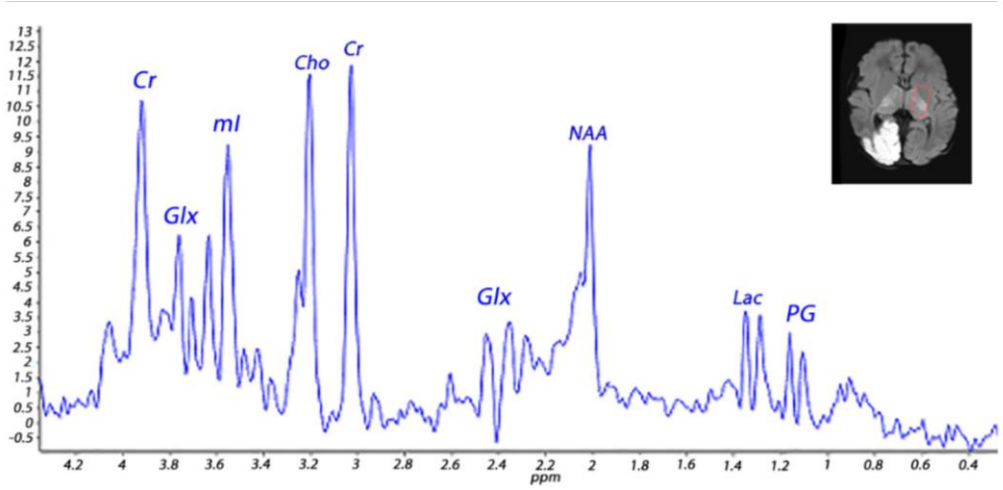
# Representation of Patterns of Injury




**ig. 1 Schematic drawings (top row) and axial MRI-diffusion weighted images taken during the first week of life (bottom row) showing common patterns of brain injury seen in infants with hypoxic-ischemic encephalopathy.** From left to right: bilateral watershed injury (**a**); basal ganglia/thalamic injury (**b**); near total pattern of injury (**c**) and injury to the mammillary bodies and hippocampi (**d**).

# MRI and MRS

- Valuable tool for assessing brain metabolism and predicting neurodevelopmental outcomes
- MRS is used to measure the concentration of various chemical compounds in the brain, such as N-acetylaspartate (NAA), lactate, and creatine.
- Elevated lactate levels and decreased NAA levels are early indicators of brain injury in HIE.
- MRS can assess metabolite ratios like lactate/NAA (Lac/NAA), which can accurately predict adverse neurodevelopmental outcomes.



# Optimizing Cooling (OC) Trial

- NICHD NRN – longer and deeper cooling on death and disability of infants with moderate to severe HIE
- 4 groups – 33.5 C for 72 hours, 33.5 C for 120 hours, 32.0 C for 72 hours and 32.0 C for 120 hours
- Study had to be halted – increase mortality and safety concerns
- Neonates with deeper and longer duration of cooling were at risk of death
- Deeper and longer cooling NOT neuroprotective
- Late Hypothermia Trial
- Initiated at 6 -24 hours
- Did not show benefit or harm

# Preterm Hypothermia

- NICHD NRN – RCT -168 enrolled (88 TH vs 80 NT)
- Average GA - > 34 weeks
- More neonates in the TH demised (35% vs 29%)
- Moderate NNE vs severe NNE – more harm with TH

**Table 5**
**Posterior probabilities of the primary outcome and its components, death alone and survival with disability: neutral prior**

| | Hypothermic (n = 83)[a] | | Normothermic (n = 69)[b] | | Bayesian Results | |
|---|---|---|---|---|---|---|
| | n/N | % | n/N | % | aRR (95% credibility interval) | Probability of treatment harm |
| Death or moderate or severe 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% |
| Survival with moderate or severe disability | 11/83 | 13 | 11/69 | 16 | 0.86 (0.46–1.63) | 32% |

Laptook A, *Clin Perinatol* 2024

# PRIME Study

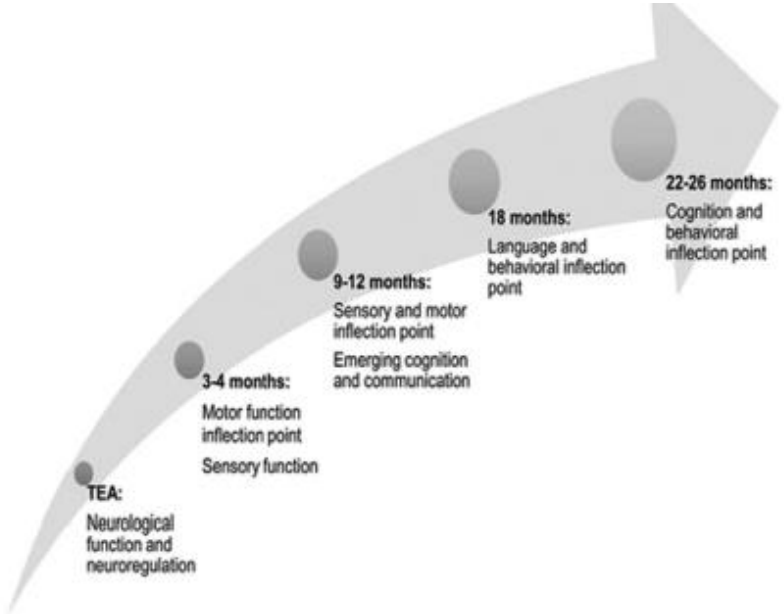
Prospective research in infants with mild encephalopathy identified in the first six hours of life: neurodevelopmental outcomes at 18–22 months

- Multicenter, prospective study of mild HIE defined as ≥1 abnormality using the modified Sarnat within 6 h of birth and not meeting cooling criteria.
- 63 infants enrolled, 51 (81%) were evaluated at 19 ± 2 months and 43 (68%) completed Bayley III (BSID).
- Of the 43 infants, 7 (16%) were diagnosed with disability, including 1 cerebral palsy and 2 autism.
- Bayley scores < 85 in either cognition, motor, or language were detected in 17 (40%): 14 (32%) language, 7 (16%) cognitive, and 6 (14%) motor domain.
- Infants with disability had more abnormalities on discharge examination and brain MRI, with longer hospital stay ($p < 0.001$).
- In this contemporary untreated cohort of mild HIE, disability occurred in 16% of infants at 18–22 months

Chalak L, *Pediatric Research* 2018

# Mild HIE – To Cool?

- CoolPrime Study
- Observational study




***Best Practices***

***What is the current practice for mild HIE?***

- Normothermia and TH for mild HIE are both currently accepted practices in standardized tertiary care, neonatal intensive care settings.

***Best practice/guideline/care path objective(s):***

- A prospective comparative effectiveness cohort investigation emulating a clinical pragmatic trial is the solution to compare benefit and risks of these 2 accepted practices.

***What changes in current practice are likely to improve outcomes?***

- Standardized adoption of TH if superior or normothermia if TH is not shown to be superior.

***Is there a clinical algorithm?***

- TH is the Standard of care treatment for moderate and severe HIE.
- Avoidance of hyperthermia is recommended following HIE.

***Major recommendations:***

- A standardized protocol with neuroimaging and neurodevelopmental follow-up is essential when providing care for any infant with HIE, including mild HIE.
- Universal follow-up of infants with mild HIE into school age for early detection of and intervention for neurodevelopmental impairments.

Chalak L et al. , *Clin Perinatol* 2024

# RCT in LMIC - Helix Trial

- HELIX  trial, conducted across 3 South Asian countries and including 408 neonates,
- Increased mortality among neonates with NE who underwent cooling  compared to the non-cooled group (36% vs 24%; OR 1.50 95% CI:1.04-2.20, p-0.0087).
  - Substantial proportion of small for gestational age (SGA) and low birthweight (LBW) neonates.
  - 73% of the neonates had seizures prior to initiating cooling,
  - Only 11% underwent cord blood gas analysis, and the majority were critically ill
  - 80% requiring inotropic support and 70% needing mechanical ventilation.
  - Cerebral abnormalities indicative of an acute intrapartum hypoxic event were present in only 25% of neonates examined with magnetic resonance imaging (MRI).
  - Fewer neonates in the cohort met the typical criteria of intrapartum hypoxia-ischemia, with only 67% having a 5-min Apgar score of <6, 6% showing fetal heart rate deceleration, and 3% experiencing a prolonged second stage of labor.
  - Survival with neurodisability was comparable between the TH and control groups (42% vs 35%; risk ratio (RR) 1.23 [95% CI: 0.89-1.64]);
  - Trial reported a reduction in disabling cerebral palsy (CP) in the TH group (11% vs 21%; RR 0.53 [95% CI: 0.28–0.98]).

# Cooling in resource poor settings

- Asphyxiated babies would not qualify for ventilation
- Some studies include
    - Passive cooling/accidental cooling
    - Gel packs
    - Servocontrolled cooling fan
    - Use of water bottles
- These studies demonstrate that a cost effective feasible method of cooling can be achieved
- Efficacy still needs to be demonstrated

# Cooling in Transit

- Training of staff – first responders
- Especially in countries with no neonatal retrieval teams
- Studies show if cool en-route – shorter time to reach target temperatures and better outcomes
- 3 methods of passive cooling investigated
  - Passive cooling
  - Gel packs
  - Servo-controlled methods
- Servo controlled superior to other 2 methods – less temperature fluctuations
  - 13 fold (gel packs) and 12 fold (passive cooling) with temperature fluctuations
  - No difference in adverse events between the methods of cooling

# Phase change material (PCM) in transit

- Median rectal temperature upon arrival was 34.5 °C (IQR 33.5–34.8) in PCM-group and 35.1 °C (IQR 34.5–35.9) in control group (*p* = 0.023).
- Median time from birth to reach target temperature was 5.0± 1.4 h and 5.5 ± 1.2 h in the respective groups (p- 0.065).
- 81% PCM versus 62% without **(p = 0.049)** had reached target temperature within the 6-h timeframe.
- No record of overcooling (< 32 °C) in any of the groups.
- No difference in mortality rate between the two groups (33% and 34% respectively (p > 0.05)).

Greater temperature fluctuations with passive and PCM cooling

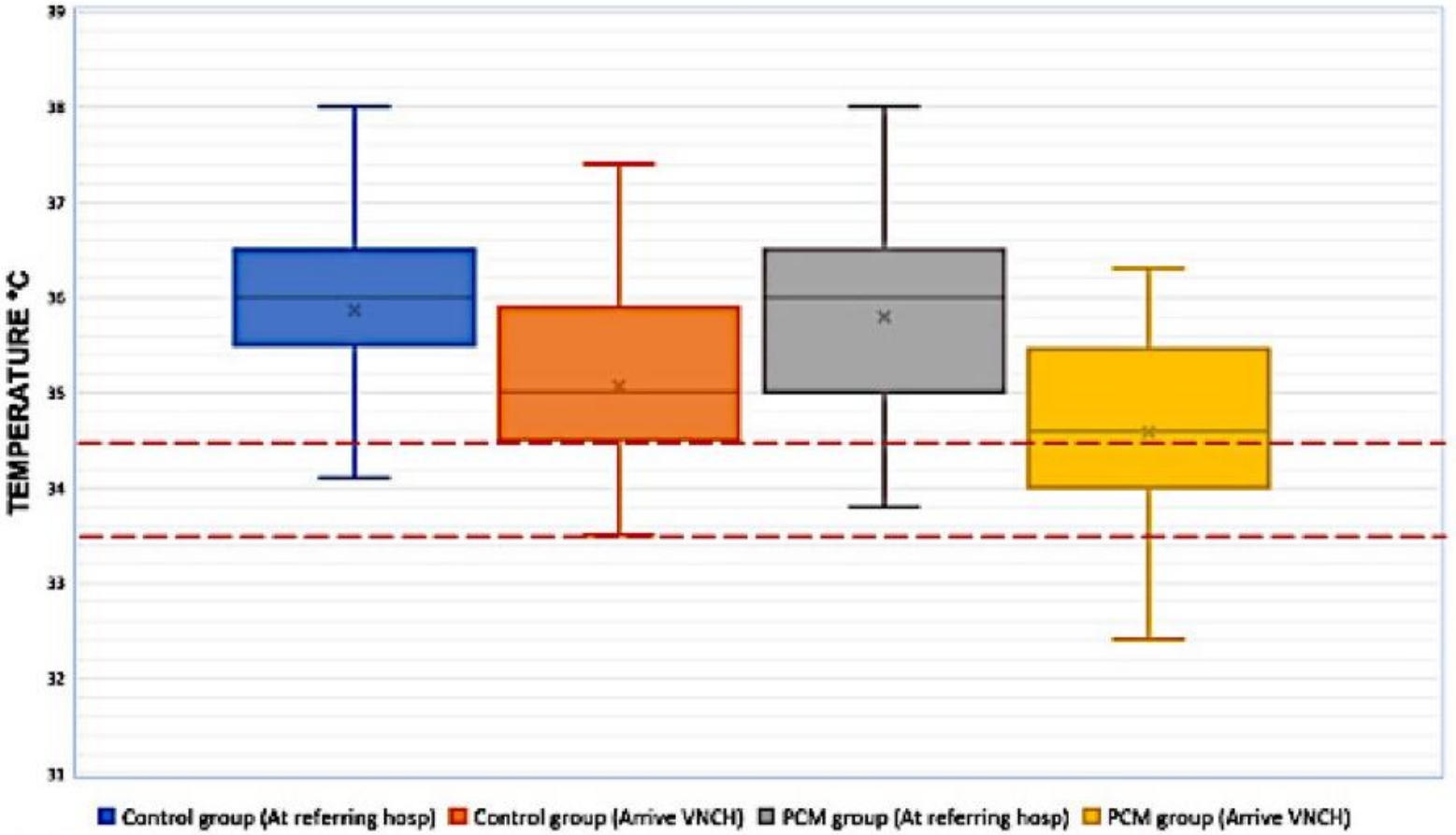



**Fig. 3** Box plot for temperature measurement at referring hospital and on arrival at VNCH. The area between the redlines shows the target temperature range of 33.5 °C to 34.5 °C

Tran TT et al. *BMC Pediatrics* 2024

# Cooling in transit

| Study or Subgroup | any cooling Events | Total | no cooling Events | Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Leon 2020 | 2 | 23 | 10 | 62 | 18.5% | 0.50 [0.10, 2.45] |
| Szakmar 2017 | 14 | 136 | 18 | 78 | 81.5% | 0.38 [0.18, 0.82] |
| **Total (95% CI)** | | **159** | | **140** | **100.0%** | **0.40 [0.20, 0.80]** |
| Total events | 16 | | 28 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.08$, df = 1 (P = 0.77); $I^2 = 0\%$

Test for overall effect: Z = 2.60 (P = 0.009)

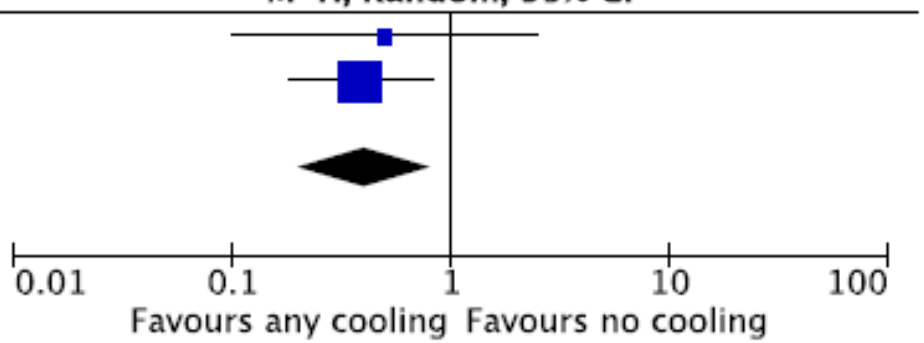



FIGURE 2 Forest plot of comparison: cooling vs. maintaining normal body temperature for outcome: in-hospital mortality

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# Target Temperature and Cooling in Transit

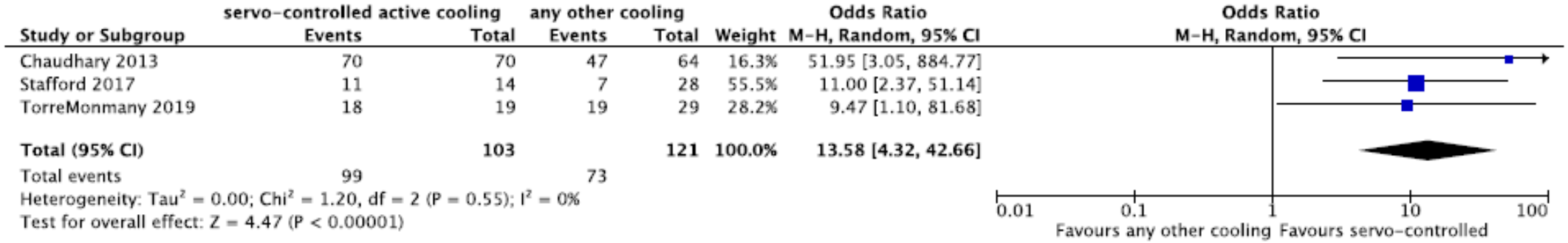


FIGURE 5 Forest plot of comparison: servo-controlled active cooling versus non servo-controlled (active or passive or both) cooling for outcome: proportion of newborns with target body temperature (range 33.0°C–34.0°C) on admission to a referral centre

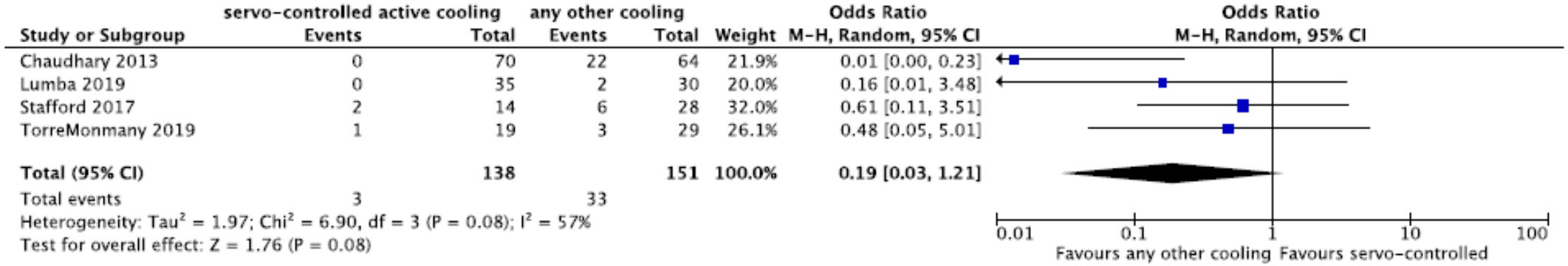


FIGURE 6 Forest plot of comparison: servo-controlled active cooling versus non servo-controlled (active or passive or both) cooling for outcome: the proportion of newborns with a body temperature < 33.0°C on admission to a referral centre

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# Cooling in Transit

| Study or Subgroup | any cooling Mean | SD | Total | no cooling Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Akula 2013 | 25 | 22 | 13 | 30 | 19 | 23 | 33.2% | −0.24 [−0.93, 0.44] |
| Leon 2020 | 13.8 | 8 | 23 | 17.8 | 12.7 | 62 | 66.8% | −0.34 [−0.82, 0.14] |
| **Total (95% CI)** | | | **36** | | | **85** | **100.0%** | **−0.31 [−0.70, 0.09]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0\%$
Test for overall effect: Z = 1.54 (P = 0.12)

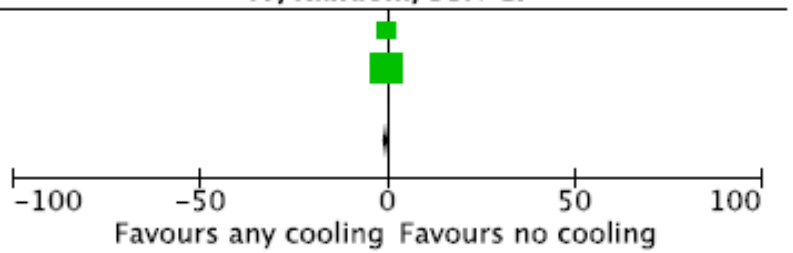


FIGURE 3 Forest plot of comparison: cooling vs. maintaining normal body temperature for outcome: duration of initial hospital stay

| Study or Subgroup | any cooling Mean | SD | Total | no cooling Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Leon 2020 | 3.83 | 1.18 | 23 | 5.12 | 1.32 | 62 | 69.0% | −1.29 [−1.87, −0.71] |
| O'Reilly 2013 | 3.58 | 1.3 | 27 | 5.45 | 1.47 | 16 | 31.0% | −1.87 [−2.74, −1.00] |
| **Total (95% CI)** | | | **50** | | | **78** | **100.0%** | **−1.47 [−1.95, −0.98]** |

Heterogeneity: $Chi^2 = 1.18$, df = 1 (P = 0.28); $I^2 = 15\%$
Test for overall effect: Z = 5.94 (P < 0.00001)

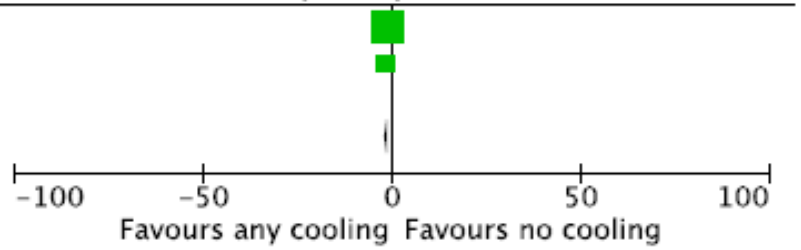


FIGURE 4 Forest plot of comparison: cooling vs. maintaining normal body temperature for outcome: time to achieve target body temperature in hours after birth

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# Cooling during Neonatal Transportation (NT)

- Any cooling is better than no cooling
- Any cooling decreased in-hospital mortality
  - No comparisons between active vs passive cooling
- For every 9 neonates cooled during transport 1 survived compared to no cooling
- Servo-controlled cooling better than PCM or passive cooling
  - Higher proportion reached target temperature of 33 – 34 ◦C (OR – 13.58; 95% CI: 4.32 – 42.66)
  - For every 3 servo-controlled cooled infants during NT – 1 had a body temp between 33 – 34 ◦C
- No long-term Follow-ups analysed – future directions

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# Future Recommendations

- Focus should be the comparison of servo-controlled active cooling devices with other cooling methods in neonatal transport.

- Standardised short-and long-term outcomes should be reported
  - time at which therapeutic hypothermia was initiated,
  - amount of time the body temperature was maintained within the target range during transport until arrival at  referral centre,
  - the adverse effects of hypothermia, in-hospital
  - and later mortality,
  - and neurodevelopmental outcome in childhood.

Sibrect et al. *Acta Pediatrica* 2022

# ICU vs High Care Area

- Most high income countries (HIC) studies conducted in an ICU setting
- Neonates are ventilated in studies in HIC
- Sedation – as infusions – morphine or midazolam

- Outcomes favour TH

# CHBAH

- TH in a high care setting– neonates on nasal cannulae or nCPAP are cooled
- Servo-controlled cooling machine, Monitor temperature, heart rate (HR), blood pressure (BP), Haemoglucotest (HGTs), - continuously
- Sedation is given – morphine orally –
  - 0.05 -0.1mg/kg, titrated against the heart rate (HR)
  - If HR < 85 bpm – naloxone given.
  - Given as stat oral doses
- Seizure medications – phenobarbitone, oral Keppra, lignocaine are given
  - Aim to stop seizure medications before discharge if no seizures
- Feeds – enterally 10mls/kg/day – titrate by 10mls/kg/day based on the severity of the NNE
- Have the option to ventilate – if PPHN or baby decompensates

# Neurodevelopmental outcome in neonates with hypoxic-ischaemic encephalopathy managed with therapeutic hypothermia in a tertiary-level public hospital outside an intensive care unit setting

- TH for 155 (87.1%), 113 of whom (72.9%) received TH.

- At 18– 24 months, 32% had moderate-to-severe disability compared with 6% at 12 months, with the sensitivity and specificity of assessment at 12 months being 50% and 100%, respectively.

- The relatively low prevalence of disability (32%) at 18–24 months suggests that use of TH in a Level 2 nursery is feasible and possibly beneficial. More studies are needed to confirm these findings
- Another South African Study reported an 18% NDI in neonates that were cooled.

Mbatha et al *PAEDIATRICS AND INTERNATIONAL CHILD HEALTH 2021*,
Kali et al *Archives Disease Fetal Neonatal* 2015

Characteristics and outcomes of neonates with intrapartum asphyxia managed with therapeutic hypothermia in a public tertiary hospital in South Africa

- Overall mortality was 29.0%, being 17.0% and 53.4% in cooled and non-cooled infants respectively
- Mortality rate of 17% in cooled neonates observed in this study is similar to rates of 13–20% reported in other observational studies from South Africa, from similar settings with access to mechanical ventilation or intensive care when needed
- This highlights the importance of offering other supportive care that neonates with moderate-to-severe encephalopathy might need in addition to cooling,
- Thus, cooling must not be offered in isolation without other services that these infants might need

*Nakwa et al BMC Pediatrics 2022*

# Who should cool

- Tertiary Academic Hospitals
- Regional Hospitals – provided the infrastructure to support the neonate –
  - Invasive and non-invasive ventilation,
  - inotropic support,
  - seizure medications,
  - rehabilitation team and
  - long term follow up
  - Audit the practices

- All other centres to refer to a Cooling centre

# Therapeutic Hypothermia