



The Northern Neonatal Network
An Operational Delivery Network
Website - www.nornet.org.uk



Chair: Deborah Jenkins

deborah.jenkins@stees.nhs.uk

Clinical Lead: Dr Sundeep Harigopal

sharigopal@nhs.net
P.A. 0191 2825755

Nurse Lead: Lynne Paterson

lynne.paterson@stees.nhs.uk
(01642) 854871

Manager: Martyn Boyd

Northern Neonatal Network, Trust Headquarters (Room 248), Sunderland Royal Hospital,
Kayll Road, Sunderland, SR4 7TP

martyn.boyd@chsft.nhs.uk
Office line (0191) 541 0139
Mobile 07795062535

Guideline for the use of Neonatal Therapeutic Hypothermia (“Cooling”)

V3 April 2024

Due for review – March 2027

Northern Neonatal Network guideline

Therapeutic hypothermia in newborn infants with probable hypoxic ischaemic encephalopathy

1) Purpose

This guideline covers the potential role of therapeutic hypothermia (TH) for infants born within or referred in to the Northern Neonatal Network with Hypoxic Ischemic Encephalopathy (HIE)

2) Key Points

- Therapeutic hypothermia (TH) should be considered in infants ≥ 36 weeks gestation with moderate to severe clinical encephalopathy and a history suggestive of HIE.
- The earlier TH commences the greater the likely efficacy
- Passive cooling (i.e. stop active warming) can be commenced at the hospital of birth whilst awaiting transfer but must be carefully monitored, preferably with a rectal temperature probe
- TH is currently provided in each of the three Network NICUs – RVI, JCUH, and Sunderland.
- Early contact with the tertiary centres offering TH is advised via the usual transport ‘hot-line’ number: **RVI 0191 2303020**

3) Background

There is good animal evidence that Cooling after hypoxic insults results in an improvement in cerebral damage as measured by both histological and behavioural changes. This appears to be modulated by interference with the cascade of events that leads to secondary metabolism failure and later cell death. Human neonatal data is now supportive of a similar effect.

From 1998 human studies have been undertaken to try and assess whether cooling reduces (the combined outcome) death or disability in newborn infants believed to have sustained a recent cerebral hypoxic insult^{1,2,3,4} and measures of neurologic outcomes⁴. These studies used either clinical² or combined clinical and cerebral function^{1,3,4} (CFM) entry criteria. The UK cooling trial was the TOBY study⁴ a randomised controlled trial of standard intensive care with or without whole body cooling in infants >36 weeks gestation identified by combined clinical and CFM criteria. Systematic reviews and metaanalysis have shown that 72 hours of therapeutic hypothermia in moderate to severe HIE significantly reduces the combined outcome of mortality or major neuro-developmental disabilities at 18 months of age⁵.

3.1) Evidence for cooling

The published evidence to date suggests the following⁵:

- Cooling to a target temperature of 33-34°C is feasible and the physiological changes are well tolerated by the majority of infants
- Individually, the trials show the following effect of whole body cooling for combined death or disability:

Study/Year	Number of participants	Risk Ratio
Eischer 2005 ²	52	0.62 (0.41-0.92)
NICHD 2005 ³	205	0.71 (0.54-0.93)
TOBY 2009 ⁴	325	0.86 (0.68-1.07)
NEO.nEURO 2010 ⁶	111	0.62 (0.46-0.82)
ICE 2011 ⁷	208	0.77 (0.62-0.98)

- Systematic review on these studies involving whole body cooling showed an overall risk ratio of 0.75 (0.66-0.84) for death or major disabilities in survivors⁵.
- TH is now considered standard of care in NHS. With current practice of TH, mortality due to HIE has reduced from 25% in the clinical trials to 9% and disability from 20% to around 16% with a reduction in the rate of cerebral palsy (BAPM 2020)⁸

4) Management

4.1) Eligibility for therapeutic Hypothermia

Suitable infants are likely to be those who are identifiable as coming from the group of infants studied so far, i.e. those with:

Criterion A

Gestational age \geq 36weeks gestation with at least **one** of the following:

- *Apgar score of \leq 5 at 10 minutes after birth*
- *Continued need for resuscitation, including ET or mask ventilation, at 10 minutes after birth*
- *Acidosis within 60 minutes of birth (pH from cord, capillary or arterial sample of $<$ 7.00)*
- *Base deficit \geq 16mmol/l in any sample (cord, arterial, venous or capillary) within 60 minutes of birth*

PS: TH for infants less than 36 weeks should only be undertaken after careful consideration and after discussion with the cooling centres.

Infants who meet any of the above **Criteria A** will then be assessed for whether they meet the neurological abnormality entry criteria (**Criteria B**)

Criterion B

Moderate to severe encephalopathy, consisting of altered state of consciousness (lethargy, stupor or coma) **AND** at least **one** of the following:

- *Hypotonia*
- *Abnormal reflexes including oculomotor or pupillary abnormalities*
- *An absent or weak suck*
- *Clinical seizures*

IF INFANTS HAVE ONE OR MORE OF THE SIGNS FROM CRITERION A AND THEN ONE OR MORE FROM CRITERION B, THEY SHOULD BE DISCUSSED URGENTLY WITH ONE OF THE COOLING CENTRES

BAPM⁸ recommends using amplitude integrated EEG (aEEG) or cerebral functioning monitor (CFM) as *Criteria C* for infants meeting *Criteria A and B*. aEEG/CFM should be read by trained personnel. **Abnormal aEEG if available can be very helpful, but the lack of availability should not delay discussion regarding cooling with cooling centres. This should also not delay the initiation of cooling in infants with moderate to severe clinical encephalopathy.**

Criteria C : If Criteria C is being used, at least 30 minutes of a EEG recording should be taken. There must be one of the following:

- Normal background with some seizures
- Moderately abnormal activity
- Suppressed activity
- Continuous seizure activity

4.2) Assessment: Appendix 1

Use the structured neurological examination sheet to perform and document a full neurological examination, including reflexes and level of consciousness on at least a daily basis over the first few days.

The ultimate decision to cool rests with the responsible clinician, and occasional babies may be felt to potentially benefit from cooling outside these criteria. This should be carefully documented. **Infants born in hospitals that are unable to deliver active cooling but whom the referring clinician feels might benefit from cooling should be discussed as soon as possible with NNeTs via the transfer request pathway.**

4.3) Timing and location of cooling

Current evidence is highly suggestive that the earlier the cooling is initiated the greater the potential benefit. You can stop active warming and if needed open incubator doors but NOT by the use of fans or ice) and target temperatures (33.5 °C +/- 0.5 °C) can be achieved this way (this was undertaken before arrival at a cooling centre). Focus should be to avoid hyperthermia, maintain airway and breathing, monitoring of oxygen saturation and other regular clinical observations. Active cooling is ideally initiated within the first 6 hours. Hence, every effort should be made to identify infants who may benefit from cooling as soon as possible. Active cooling is continued for 72 hours followed by gradual re-warming. Cooling for more than 72 hours or lower temperatures (32 C) is not recommended and is associated with higher mortality⁹.

It is important to avoid excessive hypothermia and temperatures must be monitored carefully (ideally using a rectal probe) and suitable adjustments made to the environment whether cooling is actively or passively undertaken. Infants who are being cooled may benefit from earlier respiratory support and secure arterial and venous access and this aspect should also be discussed with the cooling centre.

4.4) Parental information

The clinical reason for offering TH and the accompanying parental discussion should be captured in the notes.

4.5) Cooling protocol

Active cooling is currently usually undertaken in accordance with the guidance produced by the TOBY trial¹⁰.

Brief cooling summary includes:

- Target temperature is 33.5°C +/- 0.5°C
- Commence as soon as possible
- Duration of cooling is generally 72 hours
- Re-warming should be no more than 0.5°C per hour to 37 +/- 2 C

References

1. Gluckman PD, Wyatt JS, Azzopardi D, *et al.* Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005;**365**:663–70
2. Eicher DJ, Wagner CL, Katikaneni LP, *et al.* Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. *Pediatr Neurol* 2005;**32**:11–17
3. Shankaran S, Laptook A, Ehrenkranz RA, *et al.* Whole body hypothermia for neonates with hypoxic ischemic encephalopathy. *N Engl J Med* 2005;**353** (13):1574–84
4. Azzopardi D *et al.* Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Eng J Med* 2009;**361**:1349-1358
5. Jacobs SE, Berg M, Hunt R, *et al.* Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database of Systematic Reviews* 2013, Issue 1. Art. No.: CD003311. DOI: 10.1002/14651858.CD003311.
6. Simbruner G, Mittal RA, Rohlmann F, Muche R, neo.nEURO.network Trial Participants. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. *Pediatrics* 2010;**126**(4):e771-8.
7. Jacobs SE, Morley CJ, Inder TE, *et al.* Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. *Archives of Pediatrics and Adolescent Medicine* 2011;**165**(8):692-700.
8. Therapeutic Hypothermia for neonatal encephalopathy. A framework of practice. British Association of Perinatal Medicine Nov 2020.
9. Shankaran S, Laptook AR, Pappas A, McDonald SA, Das A, Tyson JE, *et al.* Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. *JAMA*. 2017;**318**(1):57-67.
10. Azzopardi D, Brocklehurst P, Edwards D, Halliday H, Levene M, Thoresen M, Whitelaw A; TOBY Study Group. The TOBY Study. Whole body hypothermia for the treatment of perinatal asphyxial encephalopathy: a randomised controlled trial. *BMC Pediatr*. 2008 Apr **30**;8:17

NEUROLOGICAL EXAMINATION WITHIN 6 HOURS OF AGE					
CATEGORIES (TOTAL 6)		SIGNS OF NEONATAL ENCEPHALOPATHY (NE) IN EACH CATEGORY (Circle the most appropriate level)			
		NORMAL	MILD NE	MODERATE NE	SEVERE NE
1. LEVEL OF CONSCIOUSNESS		0 ALERT, RESPOSIVE TO EXTERNAL STIMULI (STATE DEPENDENT e.g., POST FEEDS)	1 HYPER-ALERT, HAS A STARE, JITTERINESS, HIGH-PITCHED CRY, EXAGGERATED RESPONSE TO MINIMAL STIMULI, INCONSOLABLE	2 LETHARGIC	3 STUPOR / COMA
2. SPONTANEOUS ACTIVITY		0 CHANGES POSITION WHEN AWAKE	1 DECREASED with or without periods of excessive activity	2 DECREASED ACTIVITY	3 NO ACTIVITY
3. POSTURE		0 PREDOMINANTLY FLEXED WHEN QUIET	1 MILD FLEXION OF DISTAL JOINTS (FINGERS, WRIST USUALLY)	2 MODERATE FLEXION OF DISTAL JOINT, COMPLETE EXTENSION	3 DECEREBRATE
4. TONE		0 STRONG FLEXOR TONE IN ALL EXTREMITIES AND STRONG FLEXOR HIP TONE	1 NORMAL OR SLIGHTLY INCREASED PERIPHERAL TONE	2a HYPOTONIA (FOCAL OR GENERAL) 2b HYPERTONIA	3a FLACCID 3b RIGID
5. PRIMITIVE REFLEXES	SUCK	0 STRONG, EASILY ELICITABLE	1 WEAK, POOR	2 WEAK OR HAS BITE	3 ABSENT
	MORO	0 COMPLETE	1 PARTIAL RESPONSE, LOW THRESHOLD TO ELICIT	2 INCOMPLETE	3 ABSENT
6. AUTONOMIC SYSTEM	PUPILS	0 IN DARK: 2.5-4.5 mm. IN LIGHT: 1.5-2.5 mm.	1 MYDRIASIS	2 CONSTRICTED	3 DEVIATION/DILATED/ NON-REACTIVE TO LIGHT
	HEART RATE	0 100-160 bpm	1 TACHYCARDIA (HR > 160)	2 BRADYCARDIA (HR < 100)	3 VARIABLE HEART RATE
	RESPIRATION	0 REGULAR RESPIRATION	1 HYPERVENTILATION (RR > 60/min)	2 PERIODIC BREATHING	3 APNOEA OR REQUIRES VENTILATOR
* SEIZURE		NONE	NONE	YES / NO	YES / NO
TOTAL SCORE					
FINAL ALLOCATED NE STAGE (PLEASE TICK ONE)		<input type="checkbox"/> NO NE	<input type="checkbox"/> MILD NE	<input type="checkbox"/> MODERATE NE	<input type="checkbox"/> SEVERE NE

Calculation (see next page)

- 6 Categories with 9 clinical aspects in 4 domains (normal, mild, mod, severe)
- If 2 or more categories are not normal (in any domain of HIE) then neonate has at least mild HIE
- If more or equal to 3/6 catogies are moderate or severe, then neonate has mod/HIE HIE
- If an equal number in mod/sev, then category 1 (level of Consciousness) dictate te grade)

Document Control

Document Ref. Number	NNNGUIDE03
Title of document	Guideline for the use of Neonatal Therapeutic Hypothermia (“Cooling”)
Original author’s name	Dr Janet Berrington Dr Sundeep Harigopal
Author’s job title	Consultant Neonatologist, RVI (Newcastle)
Department/type	Network guideline
Document status	V.1.5
Based on	New guideline
Signed off by Board	October 2011
Publication date	October 2011
Next review date	April 2027
Distribution	Board and Website

Consultation History

Version	Date	Consultation
V 1.0	June 2010	Network for comment
V 1.1	February 2011	Network Management Team
V 1.2	September 2011	Network Guideline Group
V 1.2	October 2011	Network Board
V 1.3	March 2015	Network Guideline Group
V 1.4	February 2018	Sundeep Harigopal
V 1.5	June 2021	Vrinda Nair
V 1.6	April 2024	Vrinda Nair