



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



Chair: Deborah Jenkins

kindlingltd@msn.com

Clinical Lead: Dr Sundeep Harigopal

sundeep.harigopal@nuth.nhs.uk
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”)

V2.1 February 2018

Due for review – February 2019

Northern Neonatal Network guideline

Therapeutic hypothermia in newborn infants with probable hypoxic ischaemic encephalopathy

Purpose

This guideline covers the potential role of therapeutic hypothermia for infants born within or referred in to the Northern Neonatal Network with an encephalopathy that is likely to be of a hypoxic-ischaemic origin. It includes the meta-analysis and guidance from NICE that was disseminated in May 2010.

It does *not* cover investigations or management of neonatal encephalopathy, but wider guidance based on the RVI guideline is available below

[Link 1 - further guidance on Cooling](#)

Summary

- Cooling should be considered in infants ≥ 36 weeks with clinical encephalopathy and a history suggestive of a hypoxic-ischaemic insult. Use the TOBY entry criteria (see below) to identify those babies who should be discussed as soon as possible.
- The earlier cooling commences the greater the likely efficacy
- Passive cooling can be commenced at the hospital of birth whilst awaiting transfer but must be carefully monitored, preferably with a rectal temperature probe
- Active cooling treatment is currently provided in each of the four Network NICUs – RVI, JCUH, Sunderland & North Tees.
- Early contact with the tertiary centres offering cooling is advised via the usual transport ‘hot-line’ number:
 - RVI 0191 2303020

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 study (<https://www.npeu.ox.ac.uk/toby>) 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. Outcome data at 18 months of age were published in October 2009⁴; later outcomes will also be made available.

Evidence for cooling

Careful consideration of the published evidence to date suggests the following⁵:

- Cooling to a target temperature of 33.5°C is feasible and the physiological changes are well tolerated by the majority of infants
- Individually, the trials show the following effect of cooling for combined death or disability:
 - Coolcap¹ (n=228) OR 0.82 (95% CI 0.66-1.02)
 - Eicher² (n=52) OR 0.62 (95% CI 0.41-0.92)
 - NICHD³ (n=208) OR 0.72 (95% CI 0.56-0.95)
 - TOBY⁴ (n =325) OR 0.86 (95% CI 0.68-1.07)
- Using meta-analysis on studies 1, 3 and 4 above the odds ratio for combined death or disability was 0.81 (95% CI 0.71-0.93)⁵.

Neurological outcomes after therapeutic hypothermia

A range of (pre-specified) secondary outcomes assessing neurological status after cooling have also been subject to meta-analysis⁵ including the rate of survival without neurologic abnormality (no CP, normal MDI and PDI): this was significantly increased OR 1.53 (95%CI 1.22-1.93) with a number needed to treat of 8, and for CP alone 0.67 (95%CI 0.54-0.89) with a number needed to treat also of 8.

There are still some methodological considerations that clinicians need to be aware of. The cooling studies are thought to have the potential for withdrawal bias affecting the combined outcome data (the study cannot be 'blinded')⁶, but in TOBY there were actually more withdrawals in the cooled group.

Based on these findings many clinicians feel that therapeutic hypothermia is now appropriate. Data collected on infants y cooled in the UK using the TOBY register (<https://www.npeu.ox.ac.uk/tobyregister>)⁷ showed 120 infants cooled as per the TOBY protocol, in infants from 34-44 weeks gestation, without apparent adverse events and with an improvement in their encephalopathy score.

NICE have also produced guidance on therapeutic hypothermia for clinicians (IPG 347, May 2010 - <https://www.nice.org.uk/guidance/ipg347>) and an information for parents is available [here](#)

Management

Suggested approach to cooling

Suitable infants:

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 1

Gestational age ≥ 36 w with at least **one** of the following:

- *Apgar score of ≤ 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 ≥ 16 mmol/l in any sample (arterial, venous or capillary) within 60 minutes of birth*

Infants who meet any of the above criteria will then be assessed as to whether:

Gestational age < 36 w: Cooling has now taken place down to 34 weeks in some situations.

Criterion 2

They show 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 1 AND THEN ONE OR MORE FROM CRITERION 2, THEY SHOULD BE DISCUSSED URGENTLY WITH ONE OF THE COOLING CENTRES

Abnormal CFM (if available can be very helpful, but the lack of availability should not delay discussion/cooling: no CFM was used at entry to the Eicher study²)

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.

[Link 2 - actions for referring hospitals](#)

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.

Timing and location of cooling

Current evidence is highly suggestive that the earlier that cooling is initiated the greater the potential benefit. Cooling can commence passively (i.e. by stopping active warming, opening incubator doors etc 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 TOBY centre as part of the TOBY study).

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 either the RVI or NNeTS via the normal transfer request mechanisms.

TOBY has produced guidance on both passive cooling, and transportation during cooling, available at <https://www.npeu.ox.ac.uk/tobyregister/transport>. This guidance suggests that passive cooling should not be undertaken until a formal cooling bed has been located. The Northern Network feels that the benefits of earlier cooling are significant and suggest that passive cooling should commence as soon as possible.

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.

[Link 3 - Passive Cooling Flow Chart](#)

[Link 4 - Transport Cooling Flow Chart](#)

Parental information

The clinical reason for offering cooling and the accompanying parental discussion should be captured in the notes. Parents should also be made aware of the cooling registry (which captures anonymised data), but this can be done at a later stage.

Cooling protocol

Active cooling is currently usually undertaken in accordance with the guidance produced by the NPEU TOBY team, which is available at <https://www.npeu.ox.ac.uk/toby/protocol>

Brief cooling summary:

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 at maximum 0.3°C per hour (Azzopardi et al 2010)

Structured Neurological Examination

Appendix 1

References

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 NORMAL OR DECREASED	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

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. Edwards D *et al.* Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data *BMJ* 2010; 340:363
6. Ziino AJA. Palliation bias is being overlooked in neonatal hypothermia trials. *Arch Dis Child*. Published Online First: 27 Feb 2006, doi: 10. 1136/adc. 2006. 097394
7. Azzopardi D *et al.* Treatment of asphyxiated newborns with moderate hypothermia in routine clinical practice: how cooling is managed in the UK outside a clinical trial. *Archives of Diseases in Childhood Fetal and Neonatal Edition* 2009; **94**:F260-F264

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.2.1
Based on	Revision based on previous version
Signed off by Board	October 2011
Publication date	October 2011
Next review date	February 2019
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 2.0	March 2017	Author for update and revision/Clinical Lead
V 2.1	February 2018	Sundeep Harigopal