The Northern Neonatal Network
An Operational Delivery Network
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Guideline for the use of Neonatal Therapeutic Hypothermia ("Cooling")

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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 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.

2) Key Points

- Cooling should be considered in infants ≥ 36 weeks gestation with moderate to severe 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 three Network NICUs – RVI, JCUH, and Sunderland.
- Early contact with the tertiary centres offering cooling 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 outcomes[4]. These studies used either clinical[2] 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. Systematic reviews 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 age[5] .

3.1) Evidence for cooling

The published evidence to date suggests the following[5]:

- 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 partipants	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 survivors[5].
- Therapeutic Hypothermia 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 ≥ 36weeks gestation 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 ≥16mmol/l in any sample (cord, arterial, venous or capillary) within 60 minutes of birth*

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

Infants who meet any of the above ***Criteria A*** will then be assessed for wether 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 occulomotor 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

BAPM[8] recommends using amplitude integrated EEG (aEEG) or cerebral functioning monitor (CFM) as ***Criteria C*** for infants meeting ***Criteria A and B.*** aEEG 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.**

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 either the RVI or NNeTs via the transfer request mechanisms.**

4.3) Timing and location of cooling

Current evidence is highly suggestive that the earlier the 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). Focus should be to avoid hyperthermia, maintain airway and breathing, monitoring of oxygen saturation and other regular clinical observations. Active cooling is ideally instigated with in the first 6 hours. Hence, every effort should be made to identify infants 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 mortality[9].

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.

4.4) Parental information
The clinical reason for offering cooling 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 NPEU TOBY team, which is available at https://www.npeu.ox.ac.uk/toby/protocol

5) 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[10]

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Structured Neurological Examination Appendix 1

NEUROLOGICAL EXAMINATION WITIHIN 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)**		☐ NO NE	☐ MILD NE	☐ MODERATE NE	☐ SEVERE NE

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