Initiating Therapeutic Hypothermia (cooling) in Hypoxic Ischaemic Encephalopathy (HIE)

University Hospitals of Leicester NHS Trust

Caring at its best

Trust ref: C25/2009

1. Introduction and Who Guideline applies to

This guideline is aimed at all Health care professionals involved in the care of infants within the Neonatal Service.

Key Points

- Evidence from multi-centre studies has shown demonstrated improved outcomes for infants with moderate and/or severe hypoxic ischaemic encephalopathy (HIE) after early body cooling to a core temperature of 33.5°C for 72 hours (Grade A evidence)
- Therapeutic moderate hypothermia is therefore the standard of care for newborn infants with moderate or severe HIE.
- This guidance is designed to aid decision-making around the initiation of therapeutic hypothermia in asphyxiated newborn infants.

2. The decision to cool (Gestation, Postnatal Age, TOBY Criteria ABC)

Gestational age

- **Infants over 36 weeks gestational age**
- **Infants between 35 and 36 weeks gestation** will also be considered for active cooling, but at consultant discretion (and parental discussion).
- **Infants at less than 35 weeks gestation age** will not normally be offered cooling as this is outside the range of the published therapeutic hypothermia trials that have demonstrated benefit. Evidence of effectiveness in this patient population is awaited.

Postnatal age

- **Newborn infants less than 12 hours of age and ideally less than 6 hours of age**
    - Cooling is a preventative treatment so the earlier it is started the better. Maximum benefit occurs in infants less than 6 hours. There is some limited benefit in infants up to 12 hours of age but currently no clear evidence of benefit for those over 12 hours of age.

TOBY Criteria - ABC [1, 2, 10]

A. Is there evidence of 'asphyxia' as defined by:

1. Apgar score ≤ 5 at 10 minutes
2. and / or continued need for resuscitation (including endotracheal or mask ventilation) at 10 minutes
3. and / or acidosis within 60 minutes of birth defined as a cord, arterial or capillary pH <7.00 at any point
4. and / or a Base deficit ≥ 16mmol/L in cord or other blood sample within 60 minutes of birth. (Consideration may be given to base deficit ≥ 12 or lactate ≥ 12 dependent on the clinical picture)

B. Is there evidence of moderate or severe encephalopathy as defined by:

Evidence of altered conscious state (lethargy, stupor or coma) plus one of either:

- hypotonia
- abnormal reflexes including oculomotor or pupillary abnormalities
- absent or weak suck
- seizures

Infants must fulfil both plus at least one of the criteria from each of sections (A) and (B) to be considered for cooling as well as being at the appropriate gestation and postnatal age (but see section below on 'cooling outside TOBY criteria').

Further evidence for cooling MUST be sought by use of an aEEG (Amplitude-integrated EEG / CFM – cerebral function monitor) monitor as soon as possible. However, lack of immediate availability of aEEG should not delay the decision to cool. It is better to instigate cooling and then stop early once additional information from aEEG or other investigations is available rather than prolong the starting of cooling, thus missing the window of opportunity for maximum effectiveness.

C. Is there evidence of encephalopathy on aEEG (CFM)?

aEEG recordings should be performed for a minimum of 30 minutes and ideally for more than 60 minutes to aid with interpretation. Supporting evidence for HIE includes:

- Normal background with evidence of seizure activity
- Moderately abnormal activity
- Suppressed activity
- Continuous seizure activity

3. When cooling may not be appropriate

- If the infant appears moribund or has persisting extremely severe encephalopathy such that further treatment is likely to be futile e.g. with an isoelectric aEEG beyond 12-24 hours postnatal age [1,2].
- If there are other abnormalities indicative of poor long-term outcome [2].
- Cooling after 12 hours post-hypoxic insult is unlikely to effective [7] and so not appropriate.
- Currently there is insufficient evidence to recommend therapeutic hypothermia for clinically diagnosed mild encephalopathy.

Cooling outside TOBY criteria may also be considered where:

- The infant is between 35 and 36 weeks gestation and other criteria are met
- Base deficit ≥ 12 or lactate ≥ 12, dependent on the clinical picture (the cut-off for base deficit was 16 in the TOBY trial)
- Postnatal ward collapse, particularly if less than 48 hours old.
- aEEG shows normal voltages, but with an absence of sleep-wake cycling together with clinical encephalopathy

Cooling *may* be discontinued

- If the aEEG is normal with a normal clinical examination at around an hour of age [2].
- Previously it was indicated that if the aEEG was normal and infant no longer encephalopathic by 6 hours, then the need for cooling could be reconsidered [2].Our current approach is to continue cooling if the aEEG was abnormal at any stage even if the abnormality was present before six hours.

Logistics of the cooling decision making process

Infants on delivery suite

If a sick term infant is felt to be at high risk of HIE:

a. Consider switching off the radiant heater on the resuscitaire – passive cooling (but only after resuscitation 'ABC' and infant stabilised)
b. A rectal temperature probe is required if cooling is being commenced.
c. Once stable transport infant to NNU
d. If using transport incubator keep incubator temperature turned off

Uncontrolled hypothermia is potentially dangerous and the main aim during resuscitation, stabilisation and transport is to prevent hyperthermia/pyrexia. A core temperature of no greater than 36.5°C is recommended.

For Infants meeting above clinical criteria for cooling

- Commence active cooling (cooling jacket) to a core temperature of 33.5°C (a rectal temperature probe is essential)
- Attach aEEG leads and commence monitoring
- Review appropriateness of continuing cooling once sufficient aEEG tracing available (at least 30 minutes)

- Complete stabilisation including insertion of central lines, rectal temperature probe, urinary catheter, etc. in a timely fashion (NB. Once an infant is cooled peripheral line insertion will be more difficult)
- Ensure adequate sedation – heart rate should be no more than 110bpm
- Inform parents at the earliest opportunity.
- Arrange and perform early cerebral ultrasound imaging
- **Ensure there is a daily documented assessment of encephalopathy**
- On warming do not increase by more than 0.3ºC an hour or remove cooling jacket until normothermia has been achieved and temperature is stable for several hours. Continue rectal temperature monitoring for 24 hours

General intensive care measures:
- Maintain stable and protected airway
- Aim for normocarbia (pCO_2 4-6 kPa) on blood gases
- Review acid-base balance and consider whether it is starting to resolve or requires correction
- Keep fluid restricted (40ml/kg/day) and monitor fluid balance closely
- Maintain good cardiac output with inotrope use. Avoid excessive use of volume expanders
- Treat seizures actively
- Trophic feeds can be cautiously introduced after 24hours if the infant has stabilised

Cooling during transport:
Cooling equipment is now available to the transport service to enable active cooling during transport.

However when the specific equipment is not available during transport a few suggested methods to control hypothermia include:
- Keep incubator switched off or at the lowest setting
- Use of a rectal thermometer probe
- Management of cabin temperature in back of the ambulance
- No wrapping or limited wrapping of baby

For outborn infants, do ensure a record of the decision to cool is made (may be through the CenTre Transport team).

Neonatal Outreach to referral units:
If logistically feasible consideration should be given to neonatal outreach for difficult cases. An experienced neonatologist may travel to referral centre with CFM if required in order to assess appropriateness of retrieving an infant for cooling. Always bear in mind that time is of the essence.

MRI:
Cranial MRI scans should normally be performed between days 5 and 14 [9]. Earlier MRI scanning may be considered to support decision-making around critical care

treatment. Although information from MRI scanning can be of key importance, decisions to discontinue intensive care should be largely based on clinical grounds.

4. Safety Notice

Seizures:
Seizures should be treated as per unit policy. The following advice is added on recommendations from the TOBY register, June 2011. However note that Lidocaine is not currently in routine use for neonatal seizures on the UHL Neonatal Units.

We have heard of instances of severe bradycardia occurring during infusion of lidocaine (lignocaine) for the treatment of seizures during treatment with cooling. It is well recognised that lidocaine toxicity can occur during infusion, even in normothermic infants. There are no data on which to base a recommended infusion dose during hypothermia, but it would seem sensible to use lidocaine cautiously. The following suggested schedule for treating cooled infants was provided by Professor DeVries from Utrecht. If an infant becomes severely bradycardic whilst receiving lidocaine infusion it is essential to stop the infusion immediately. Adrenaline and/or other inotropes may also be required; continuation of cooling should be reviewed case by case.

Lidocaine infusion	
Time	Dose
0 hrs//start	2mg/Kg over 10 minutes
10 minutes	4mg/kg/hour for 6 hours
6 hours	2mg/kg /hour for 12 hours
18 hours///stop	Stop infusion

5. Education & training

None

6. Audit Criteria

1. Infants will be less than 12 hours post insult when cooling is commenced (100%)
2. All infants will have aEEG recording within two hours of being commenced on cooling (100%) or within two hours of admission for outborn infants.
3. Temperature will be maintained between 33-34ºC (100%)

Evidence according to RCPCH

Grade A	At least 1 randomised controlled trial addressing specific recommendation
Grade B	Well conducted clinical trials but no randomised trial on specific topic
Grade C	Expert committee report or opinions

7. Supporting References

1. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, Kapellou O, Levene M, Marlow N, Porter E, Thoresen M, Whitelaw A, Brocklehurst P; TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009 Oct 1;361:1349-58. doi: 10.1056/NEJMoa0900854.
2. UK TOBY Cooling Register Clinician's Handbook. Version 4, May 2010
3. Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury. Interventional procedures guidance [IPG347] Published date: May 2010
4. Laptook AR. Brain Cooling for the Neonatal Encephalopathy: Should it Be Used for Whom and By Whom in Neonatology: Questions and Controversies Series: Neurology 1st Edition Ed. Perlman JM Saunders 2008
5. Laptook AR. Chapter 5 - The Use of Hypothermia to Provide Neuroprotection for Neonatal Hypoxic-Ischemic Brain Injury Neurology: Neonatology Questions and Controversies (2nd Edition) Ed. Perlman JM. Elsevier 2012 p63-76
6. Shankaran S. Therapeutic Hypothermia for Neonatal Encephalopathy. Curr Treat Options Neurol 2012 December; 14: 608–619. doi:10.1007/s11940-012-0200-y
7. Laptook AR, Shankaran S, Tyson JE et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. JAMA. 2017 Oct 24;318(16):1550-1560. doi: 10.1001/jama.2017.14972
8. Kariholu U, Montaldo P, Markati T, et al. Therapeutic hypothermia for mild neonatal encephalopathy: a systematic review and meta-analysis. Archives of Disease in Childhood - Fetal and Neonatal Edition Published Online First: 19 December 2018. doi: 10.1136/archdischild-2018-315711
9. Fetal & Neonatal Brain Magnetic Resonance Imaging: Clinical Indications, Acquisitions and Reporting. BAPM Framework for Practice (2016)
10. Therapeutic Hypothermia for Neonatal Encephalopathy: BAPM Framework for Practice (Nov 2020)

8. Key Words

aEEG, Encephalopathy, Neonatal, Temperature, TOBY

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS			
Guideline Lead (Name and Title) **Authors:** A Currie – Consultant, R Miralles – Consultant & M Hubbard Neonatal Research Nurse **Clinical guidelines lead:** S Mittal - Consultant			**Executive Lead** Chief medical officer
Details of Changes made during review:			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
Sept 2009	**1**		Original Guideline
June 2011	**2**	Neonatal Guidelines Group	Revised
Oct 2015	**3**	Guidelines lead Neonatal Guidelines Group Neonatal Governance Group	Reviewed / Amendments
Jan 2019	**4**	Neonatal Guidelines Group	
Jan 2020	**5**	Neonatal Governance Group	Revision of Criteria in line with TOBY criteria, additional updates
May-Jun 2022	**6**	Neonatal Guidelines Group Neonatal Governance Group	Revisions made to cooling outside of TOBY criteria considerations, indications for discontinuing cooling and general intensive care monitoring