

Yorkshire and Humber ODN Pan Network Clinical Guideline

Management of Hypoxic Ischaemic Encephalopathy Including Total Body Cooling

Authors: Adapted from the NTNN and YNN guidelines by Y&H ODN HIE group

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This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire and Humber Neonatal ODN. The appropriate use and interpretation of this guideline in providing clinical care remains the responsibility of the individual clinician. If there is any doubt discuss with a senior colleague.

Recommendations represent widely used evidence-based practice and high quality standards that all Neonatal Units across the Network should implement. However, alternative appropriate local guidelines may also exist.

Aim of Guideline

- To ensure that babies with suspected hypoxic ischaemic encephalopathy (HIE) are appropriately assessed and managed clinically.
- To ensure therapeutic hypothermia is considered and initiated appropriately
- ensure that cooling is managed in a safe and timely manner
- To outline the care pathway for the care of infants with HIE

Cooling should be offered to all babies who achieve at least one criteria A and criteria B See full guideline for “special cases”

Criteria A

Infants \geq 36/40 with at least one of:

- Apgar \leq 5 @ 10 mins after birth
- Continued need for assisted ventilation @ 10 mins after birth
- pH < 7.00 within 60 mins of birth (umb/arterial/capillary)
- Base deficit \geq 16 in umb/cap/venous/art blood sample within 60 mins of birth

Criteria B

- **Seizures**
 - **Moderate to severe encephalopathy i.e.**
 - Altered state of consciousness (lethargy/stupor/coma)
- AND*
- Abnormal tone (focal/generalised hypotonia/flaccid)

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1. Summary of Management of HIE

| | |
|--------------------|---|
| AT DELIVERY | Adequate resuscitation Request arterial and venous umbilical cord gases Request placenta sent for histological examination If encephalopathy suspected and ≥ 36 wks gestation, commence passive cooling by switching off the overhead heater once resuscitation complete. Monitor temperature and avoid overcooling. |
| VENTILATION | Intubate and ventilate to maintain adequate gaseous exchange or if respiratory drive insufficient Maintain PaO ₂ 6-10 kPa, PaCO ₂ 5-7 kPa |
| CVS | Obtain central vascular access (UVC/UAC) Collect FBC, U&Es, Ca, Mg, LFTs, group & save, cultures & clotting If MAP <40mmHg consider single 10ml/kg 0.9% saline bolus If MAP remains low, commence inotropes. Avoid bicarbonate and multiple fluid boluses unless infant has signs of hypovolaemia |
| COOLING | If criteria fulfilled, passive cooling should be continued, and active cooling commenced as soon as possible . Switch off overhead or incubator heater. Insert rectal probe and commence continuous rectal temperature monitoring. Aim to keep temperature between 33 - 34°C and avoid hyperthermia and severe hypothermia (<32°C) . Document rectal temperatures every 15 minutes |
| CNS | Perform a neurological assessment on admission and repeat every 24 hours |
| SEDATION | Consider low dose morphine (10micrograms/kg/hr) to maintain comfort Avoid paralysis unless essential for effective ventilation |
| SEIZURES | 1st line: Phenobarbitol 20mg/kg over 20 minutes. Further dose of 10 mg/kg can be used 40-60 minutes later. <i>Consult local guidance for further management of seizures</i> |
| SEPSIS | Start antibiotics after taking cultures if clinically indicated. If using gentamicin, do pre dose level and wait for result before giving second dose. |
| FLUIDS | Fluid restrict at 40ml/kg/day and monitor blood sugars. May need higher concentration of dextrose if hypoglycaemia is a problem. |
| PARENTS | Senior member of medical team should aim to speak to family as soon as possible to explain level of concerns, mentioning risk of death & disability. (See BLISS information leaflet Appendix 2) |
| TRANSER | If it is considered that the baby may require transfer or advice is needed (e.g. not in a cooling centre or needs tertiary intensive care) call Embrace as early as possible for discussion (0845 147247 2) |

2. Indications for cooling¹

Cooling (therapeutic hypothermia) is an effective therapy for the treatment of newborn encephalopathy. Active cooling should only be conducted in centres that regularly cool infants and have the appropriate equipment and monitoring. Passive cooling should be initiated as soon as possible after delivery, once resuscitation is complete, and can occur in the hospital of birth, using these guidelines. Document time cooling commenced and time therapeutic range reached in the notes.

Cooling should be offered to all babies who achieve at least one criteria A and criteria B

| Criteria A | Criteria B |
|---|---|
| <p>Infants \geq 36/40* with at least one of</p> <ul style="list-style-type: none">• Apgar \leq 5 @ 10 mins after birth• Continued need for assisted ventilation @ 10 mins after birth• pH$<$7.00 within 60 mins of birth (umb/arterial/capillary)• Base deficit \geq 16 in umb/cap/venous/art blood sample within 60 mins of birth | <ul style="list-style-type: none">• Seizures• Moderate to severe encephalopathy i.e.<ul style="list-style-type: none">• Altered state of consciousness (lethargy/stupor/coma) <i>AND</i>• Abnormal tone (focal/generalised hypotonia/flaccid) |

Do not start cooling if infant:

- Is likely to require surgery during first three days after birth
- Has other major congenital abnormalities indicative of poor long term outcome
- Is felt to be dying
- Has a significant intracranial bleed

HIE often co-exists with persistent pulmonary hypertension (PPHN). Cooling may worsen PPHN and risks may outweigh benefits if PPHN is severe. Cool with caution and consider rewarming if oxygenation is poor.

Neurological status can change during first few hours, therefore reassessment is recommended as the baby may subsequently “meet” the cooling criteria. Cooling incurs most benefit if initiated within 6 hours of the insult. Initiating cooling beyond 12 hours from the insult is not usually recommended.

Confirm severity of encephalopathy with cerebral function monitoring (CFM) before cooling if possible, but do not delay cooling for CFM. Normal initial CFM indicates a high probability of normal outcome. In this case cooling is unlikely to be beneficial, and if treatment has been commenced the neonatal consultant may consider discontinuing.

Special cases:

***Infants 34-35 weeks**

There is currently no evidence of any therapeutic benefit from cooling for babies born at 34-35+6 weeks (due to lack of randomised controlled studies in this group). Preterm babies who are therapeutically cooled for HIE have a higher risk of coagulopathy and IVH and a worse combined outcome of death and severe disability.^{2,3,4,5} It is not known whether this is due to increased vulnerability to the effects of hypoxic ischaemia or whether it is the effect of the hypothermia. Cooling in this group cannot currently be recommended routinely. Any decision to actively cool these babies should be made by at least two consultants in conjunction with the parents, after a full discussion regarding the potential risks and benefits.

Postnatal Ward Collapse

Again observational studies and case series' have been reported for infants cooled after postnatal ward collapse. Data extrapolated from adult literature in addition to the current perinatal data gives a good theoretical basis for benefit for these infants. However, there have been no randomised controlled trials. These infants would be best discussed on a case by case basis with a tertiary neonatologist and transport team.^{6,7,8,9} Of note, all these case series' and reviews suggest that significant intracranial haemorrhage should be a contraindication to therapeutic hypothermia in view of the potential impairment in coagulation that cooling may worsen.

3. Criteria for defining moderate and severe encephalopathy:

| Parameter | Moderate Encephalopathy | Severe Encephalopathy |
|------------------------|------------------------------------|--------------------------------|
| Level of consciousness | Reduced response to stimulation | Absent response to stimulation |
| Spontaneous activity | Decreased activity | No activity |
| Posture | Distal flexion, complete extension | Decerebrate |
| Tone | Hypotonia (focal or general) | Flaccid |
| Suck | Weak | Absent |
| Moro | Incomplete | Absent |
| Pupils | Constricted | Variable |
| Heart rate | Bradycardia | Variable |
| Respiration | Periodic breathing | Apnoea |

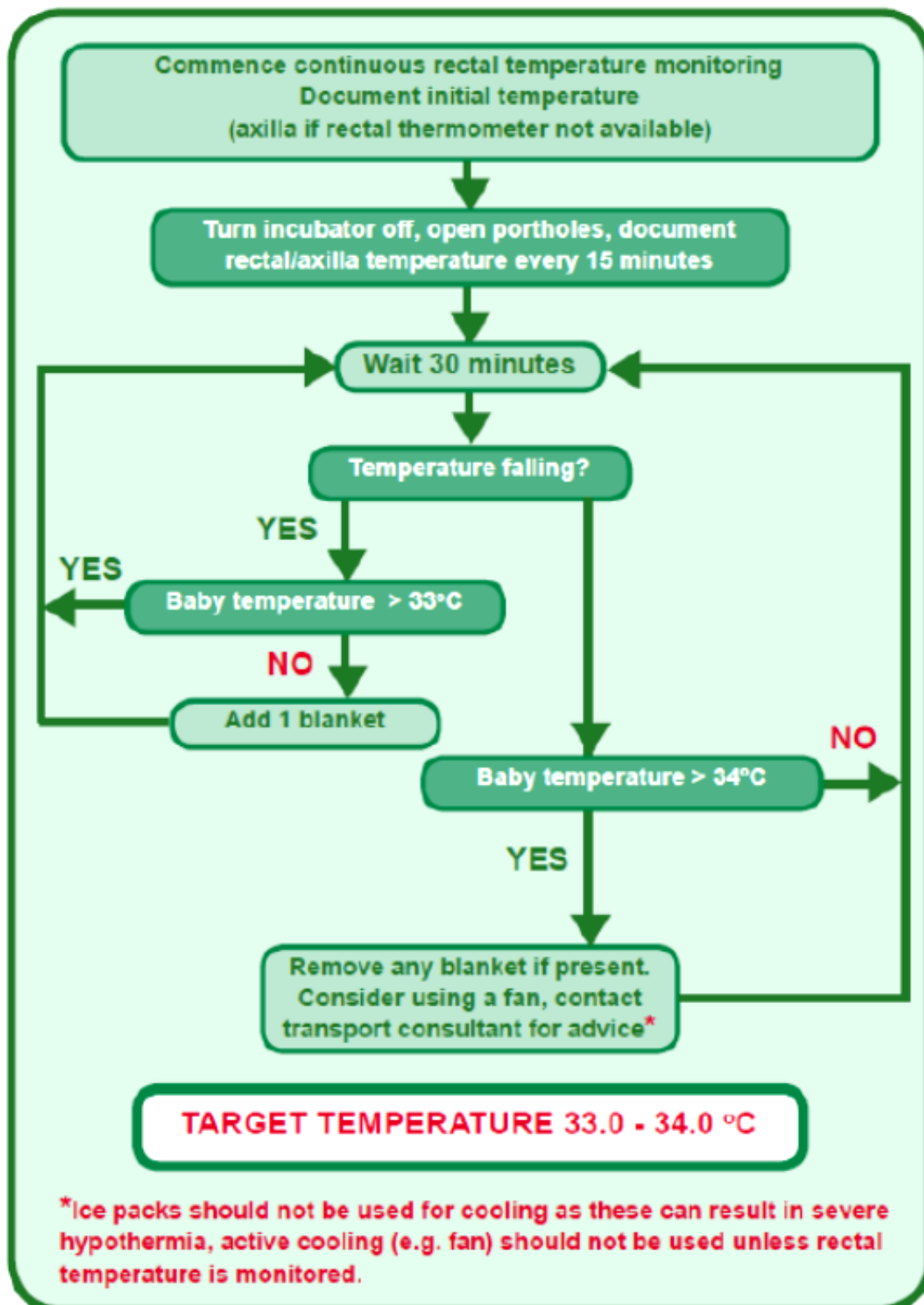
4. Passive Cooling Guideline

- Stop active warming by turning off the heater:
- Monitor and measure the rectal temperature every 15 minutes
- If rectal thermometer unavailable commence continuous skin temperature monitoring or monitor axillary temperature with a low reading thermometer every 15 minutes
- Maintain the rectal temperature between 33.0–34.0°C by passive cooling only (heater off).
- Turn the heater on if the rectal temperature is less than 33.5 °C and continue to closely monitor the rectal temperature.

Do not delay passive cooling to await the arrival of the transport/retrieval team.

Risks and Precautions

- Ensure low reading thermometer is used to check axilla temperatures- some will have a lower limit with leads to false readings.
- Do not allow the temperature to fall below 33°C
- Active cooling with the use of a fan, or using cool bags of fluids can cause overcooling. These methods should only be used with rectal monitoring.
- **Ice packs must not be used to reduce the infant's temperature as they can result in severe hypothermia**



5. Further Supportive Care for infants with Hypoxic Ischaemic Encephalopathy

The main principle of the management of these infants is to maintain normal homeostasis
Good documentation is essential

At delivery

- Adequate resuscitation, as per the Newborn Life Support (NLS) guidelines
- Ask for arterial and venous umbilical cord gases and document in baby's notes
- If encephalopathy suspected and ≥ 36 wks gestation, commence passive cooling by switching off the overhead heater once resuscitation is complete. Monitor temperature if being passively cooled and avoid overcooling
- Ask for placenta to be sent to histopathology

Postnatal collapses - Consider other diagnoses, such as sepsis and metabolic disorders. Refer to BAPM guideline for recommended investigations.¹⁰

Ongoing care

Ventilation

- Consider artificial ventilation to maintain gaseous exchange or if respiratory effort insufficient.
- Maintain PaO₂ 6-10 kPa, PaCO₂ 5-7 kPa.
- Try to avoid iatrogenic hypocarbia. Some babies spontaneously hyperventilate and this cannot easily be prevented, but consider ventilation and sedation if extreme and persistent.
- Low dose morphine (10micrograms/kg/hr) may be used as sedation acutely, but may require to be discontinued later to allow adequate assessment of the baby's neurological status, especially if considering withdrawal of intensive care.
- Avoid paralysis unless essential for effective ventilation.

Cardiovascular system

- Obtain central vascular access, both venous and arterial (UAC/UVC).
- Collect samples for FBC (including the nucleated red cell count) CRP, U&Es, Ca, Mg, LFTs, group & save, cultures & clotting.
- In term infants the mean arterial blood pressure (MAP) should be > 40 mmHg
- If MAP < 40 mmHg consider the following:
 - Single 10ml/kg 0.9% saline bolus
 - Further 0.9% saline bolus or blood product replacement **only** if evidence of hypovolemia e.g. feto-maternal haemorrhage.
 - Only use bicarbonate boluses if prolonged acidosis is causing compromise- the acidosis is usually due to anaerobic metabolism during the hypoxic ischaemic insult and will usually correct without intervention
 - If MAP remains low there may be depressed myocardial function and large volumes of colloid or crystalloid may be harmful, causing worsening hypotension and increasing risk of cerebral oedema.
 - As hypotension likely to be related to myocardial dysfunction suggest start with 5-10 micrograms/kg/min dobutamine, titrated up to a maximum 20 micrograms/kg/min. Add dopamine or noradrenaline if insufficient response
 - Consider performing echo and ECG.

Fluids & Metabolic

- Start 10% dextrose at 40 ml/kg/day, but review carefully in the light of progress at least 3 times in the first 24 hours. Maintain normoglycaemia – increasing glucose concentration rather than volume will avoid fluid overload.
- Monitor and treat hypocalcaemia (due to transient hypoparathyroidism and sick cell syndrome) and hypomagnesaemia.
- Check the lactate soon after admission, but remember the acidosis is usually metabolic due to anaerobic metabolism and will usually correct without volume or bicarbonate.

- Check LFTs and consider full metabolic screen
- Monitor the urine output and have a low threshold for catheterisation.
- Test the urine for blood and protein.
- If urine output is poor treat as renal failure with fluid restriction, but remember that prolonged fluid restriction may exacerbate or even cause renal failure.

CNS & Seizures

- Use CFM early, if available, to establish severity of encephalopathy. It may also be used to monitor seizures.
- Perform a neurological examination, including assessment of pupils, and document the clinical stage of encephalopathy
- Consider requesting a formal EEG.
- Treat clinical and electrographic seizures: Phenobarbitol 20mg/kg over 20 minutes as first line, a further 10mg/kg and then follow local seizure guideline.
- Opisthotonic and tonic generalised seizures after profound asphyxia may have no EEG correlates and may not benefit from anticonvulsants. Prolonged and difficult to treat/intractable seizures must be discussed with the consultant.
- Morphine sedation for comfort during therapeutic hypothermia.

Imaging:

- Early ultrasound may be useful to exclude anatomical abnormalities and intracranial haemorrhage. Ultrasound with cerebral arterial dopplers should be done at 48-72hours after birth to aid prognosis prediction.
- MRI should be performed according to local guideline, ideally at 5-14 days

Sepsis

- Start antibiotics after taking cultures if clinically indicated.
- If using gentamicin, do pre dose level and wait for result before giving second dose, because of risk of acute renal injury.

Feeding:

- Consider minimal enteral feeding (trophic) until re-warmed¹¹
- Mouth care using EBM as available.

Feed intolerance is common as gut circulation may have been compromised, this may increase the risk for necrotising enterocolitis (NEC)¹²

- Breast milk is preferable
- Feeds should be introduced gradually

Monitoring:

Monitoring throughout the cooling and rewarming period should include:

- Continuous invasive blood pressure monitoring
- Continuous oxygen saturation
- Continuous respiratory monitoring
- Continuous electrocardiograph (ECG)
- Continuous amplitude integrated electroencephalography (CFM) commenced as soon as possible, if available. This is prognostic and may assist in guiding therapy (treatment of significant electrical seizures may lessen excitotoxic damage)
- Documented observations including:
 - Urine output
 And hourly:
 - oxygen saturation
 - heart rate and blood pressure
 - respiration rate

Daily investigations (and more frequently if abnormal):

- blood gases, electrolytes, glucose and lactate (may all be obtained from the blood gas sample)
- full blood count including platelets, liver function tests, clotting (which may be sampled from an arterial line)

Parents

Senior member of medical team should aim to speak to family as soon as possible to explain level of concerns mentioning risk of death & disability. Discuss use of CFM and cooling if appropriate (see section 6)

Transfer

Infants who may require transfer for cooling/intensive care should be referred as early as possible to enable the team to mobilise quickly. These infants will require:

- Full documentation (Badger)
- X-rays made available to receiving centre
- 2 points of iv access
- Labelled maternal blood sample for cross match

6. Parental advice regarding therapeutic hypothermia

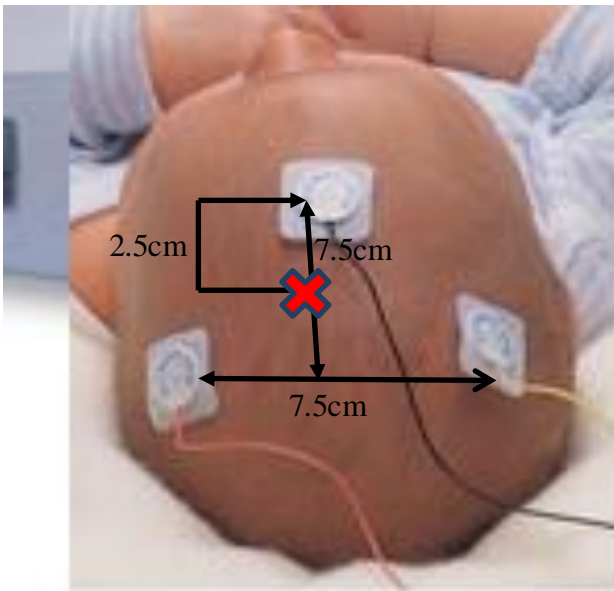
| Criteria | Advice to parent(s) |
|--------------------------------|---|
| Resuscitation | Your baby needed significant resuscitation at birth to help him/her breathe. He/she appears to have suffered from the effects of lack of oxygen and blood supply to the brain |
| Consequences | This can result in brain damage from direct injury and also from ongoing changes that begin around six hours after the injury |
| Prognosis | Babies who survive after this degree of damage to their brain may develop long-term disabilities. These disabilities include cerebral palsy and severe learning difficulties. |
| Treatment | Cooling babies following a period of reduced oxygen and blood supply reduces the secondary brain injury, increases the chances of survival by one fifth and reduces the risk of severe long-term disability by one third. |
| What does the treatment entail | Your baby will receive cooling therapy in addition to standard intensive care support Your baby's temperature will be slowly lowered and kept between 33 to 34°C for 72 hours. Your baby's temperature and other vital signs will be closely monitored throughout the process. If your baby shows any signs of discomfort during cooling he/she will be prescribed medication to reduce this. After 72 hours of cooling, your baby will be gradually rewarmed to a temperature of 37°C |

7. Cerebral Function Monitoring (CFM)

An amplitude-integrated EEG, or Cerebral Function Monitor (CFM), is a device used to measure electrocortical activity in the brain. An abnormal CFM trace in the first six hours of life, after an asphyxial insult, is predictive of abnormalities on acute neurological testing and long term neurodevelopmental outcome.

A three channel single montage aEEG is commonly used. The site of electrode placement is as described below. Needle EEG electrodes are commonly used and the use of glue may be considered to hold the electrodes in place.

Note that interpretation requires some degree of expertise and therefore CFM may not be appropriate in all settings. The indications for the use of therapeutic hypothermia are clinical and CFM only acts as an adjuvant to this.



✘ fontanelle

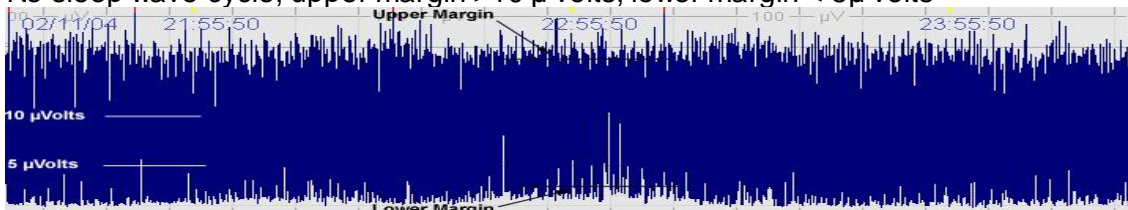
Normal CFM:

Sleep wave cycle, upper margin $>10\mu$ volts, lower margin $>5\mu$ volts, limited variability



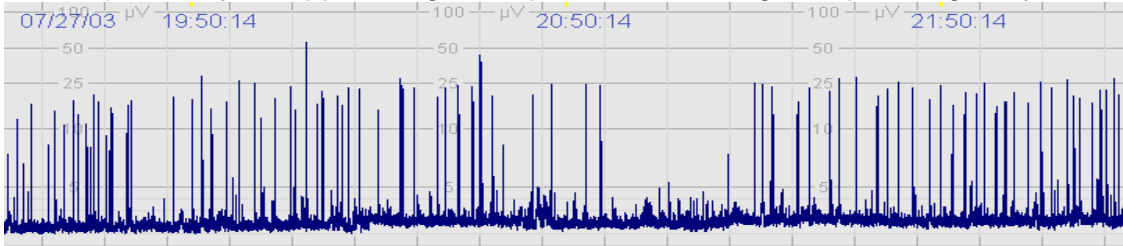
Moderately abnormal CFM:

No sleep wave cycle, upper margin $>10\mu$ volts, lower margin $<5\mu$ volts



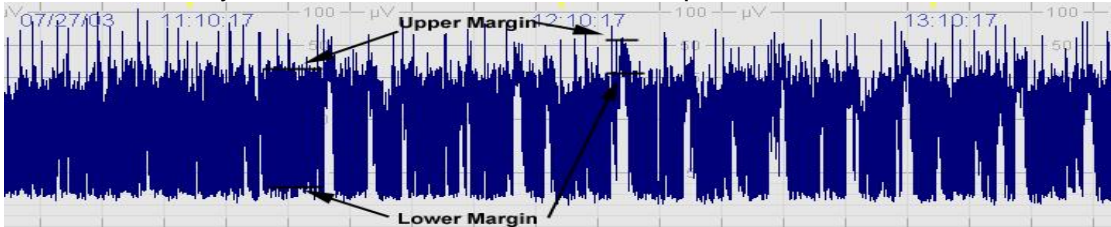
Severely abnormal CFM:

No sleep wave cycle, upper margin < 10 μ volts, lower margin < 5 μ volts, greatly reduced variability



Seizures:

Increased activity, causes CFM to narrow and rise up



8. Complications of cooling

Complications of therapeutic hypothermia are infrequent and symptoms may also be related to the effects of the original asphyxial insult on all systems.

Adverse effects which are transient and reversible with warming include ¹³

- sinus bradycardia
- hypotension requiring inotropic treatment
- increased oxygen requirement
- thrombocytopenia and coagulopathy
- fat necrosis

However, no clinically significant complications related to treatment with cooling in asphyxiated infants have been reported to date. ^{14,15,16}

9. Prognosis

Good prognostic features

Stage I encephalopathy

Absence of fits in first 24 hours

Resolution of fits, off anticonvulsants, by 7 days

Ability to suck and feed by 7 days

Poor prognostic features

Stage II/III encephalopathy

Encephalopathy >5 days

Unreactive or discontinuous EEG

Ultrasound evidence of thalamic or extensive parenchymal involvement

Prognosis by stage of encephalopathy

Early onset neonatal encephalopathy is the best single predictor of long-term outcome

Quick recovery is associated with a better outcome

Stage 1 (Mild)

Wide-eyed, hyper-alert, irritable, weak suck, normal tone. No seizures, normal EEG. Resolves in 24 - 48 hrs. Normal neurologic outcome in greater than 90% of cases. ¹⁷

Stage 2 (Moderate)

Lethargy, little spontaneous movement, hypotonia. Brisk reflexes, sustained clonus, weak or absent suck. Small pupils, doll's eye movements present, apnoeas. Clinical or electrophysiological seizures. Should resolve within 5 days. Majority normal on follow-up. Risk of abnormality higher if prolonged encephalopathy. Incidence of poor outcomes ranges from 30 - 60%.¹⁷

Stage 3 (Severe)

Coma, flaccidity, diminished or absent reflexes, usually require assisted ventilation. Absent doll's eye movements, absent gag reflex. Poorly reactive or absent pupillary light reflex. Most die. Severe neurological abnormality in survivors.¹⁷

Prognosis by electroencephalogram abnormality

Background EEG abnormalities, detected in the first few days of life after HIE can provide prognostic information even in babies treated with hypothermia. Grade of abnormality predicts the rate of death or severe handicap.¹⁸

At 6 hours of age a moderately abnormal CFM gives a PPV for disability of 0.23, and a severely abnormal CFM a PPV of 0.55.¹⁹

Failure of improvement of the CFM to moderately abnormal/normal by 48 hours of age suggests a 90% chance of death or severe disability.²⁰

Prognosis by MRI findings

MRI is an established investigation in the evaluation of neonates with suspected hypoxic-ischaemic encephalopathy (HIE). However, its role as a predictor of neurodevelopmental outcome remains complex.

Grade 1 (mild) MR changes

Normal outcome²¹

Grade 3 (severe) changes

Death or severe disability

If a baby is in a poor prognostic group consider early (<5days) MRI to aid decision making. Palliative care and referral to local hospice should be offered to babies who are dying or where life sustaining treatments are being withdrawn due to poor prognosis.

10. Follow up

Perform magnetic resonance imaging (MRI) brain scan with the timing according to local guidelines. 5-14 days is recommended.

Ensure regular neurodevelopmental follow up after discharge

It is a National Neonatal Audit Programme (NNAP) requirement that all babies who have received therapeutic hypothermia as treatment for HIE, should be followed up for long term neurodevelopmental assessment at 2 years

If the baby dies, the value of a post mortem should be discussed with parents. Organ and heart valve donation should also be considered in these cases. The family should be offered bereavement support and referral to the local children's hospice.

11. Theory and Evidence for Therapeutic Hypothermia

Neonatal encephalopathy has an incidence of approximately 3/1000 births, with hypoxic-ischaemic encephalopathy (HIE) occurring in approximately 1.5-2/1000²²

A word to use with caution: asphyxia is a term which is often used in the wrong context, and when used incorrectly may have serious medico-legal consequences. Be careful not to mislabel an infant with low Apgar scores at birth and who requires resuscitation, but has no other problems, as 'asphyxiated'. It is recommended that the terms 'perinatal asphyxia', 'birth asphyxia' and 'HIE' not be used until or unless there is some available evidence specific to the asphyxial origin for the neurological illness in the baby. "Poor condition at birth" can be used

Hypoxic-ischaemic insult occurring around the time of birth may result in neonatal encephalopathy. Affected infants may present with a need for resuscitation at birth, neurological depression, seizures and cerebral function monitoring abnormalities. The risk of death or neurodevelopmental abnormalities increases with the severity of the encephalopathy.

Evidence:

Results of 11 randomised controlled trials, including the UK total body cooling trial (TOBY) confirm that 72 hours of cooling to a core temperature of 33-34 °C started within six hours of birth reduces death and disability at 18 months of age and improves a range of neurodevelopmental outcomes in survivors^{23,24,25,26}

A Cochrane review concluded “Therapeutic hypothermia resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age (typical RR 0.75 (95% CI 0.68 to 0.83); typical RD -0.15, 95% CI -0.20 to -0.10); number needed to treat for an additional beneficial outcome (NNTB) 7 (95% CI 5 to 10) (8 studies, 1344 infants). Cooling also resulted in statistically significant reductions in mortality (typical RR 0.75 (95% CI 0.64 to 0.88), typical RD -0.09 (95% CI -0.13 to -0.04); NNTB 11 (95% CI 8 to 25) (11 studies, 1468 infants) and a reduction in neurodevelopmental disability in survivors (typical RR 0.77 (95% CI 0.63 to 0.94), typical RD -0.13 (95% CI -0.19 to -0.07); NNTB 8 (95% CI 5 to 14) (8 studies, 917 infants).”²⁵

NICE and BAPM support the use of this treatment in selected neonates with HIE.^{1, 27}

No single factor predicts outcome (death or disability) with absolute certainty. Apgar score alone is a poor predictor of outcome. Apgar scores at 10 minutes provide useful prognostic data before other evaluations are available for infants with HIE. Death or moderate/severe disability is common but not uniform with Apgar scores < 3; caution is needed before adopting a specific time interval to guide duration of resuscitation.²⁸

In a large series of infants, an Apgar score of 0-3 at 20 minutes was associated with death within one year in 59% of infants and cerebral palsy in 57% of the survivors.

Actions of hypothermia

Hypothermia appears to have multiple effects at a cellular level following cerebral injury. Hypothermia reduces vasogenic oedema, haemorrhage and neutrophil infiltration after trauma. In addition mild hypothermia may reduce the activation of the cytokine and coagulation cascades through increased activation of suppressor signalling pathways, and by inhibiting release of platelet activating factor.

Experimental studies show that following hypoxic-ischaemic injury, mild induced hypothermia – a reduction of body temperature by 3-4°C – preserves cerebral energy metabolism, reduces cerebral tissue injury and improves neurological function. Randomised trials in full term and near full term newborns suggest that treatment with mild hypothermia is safe and may improve survival without disabilities up to 18 months of age, but long term efficacy and safety are yet to be established.

12. References

1. NICE Interventional Procedure Guidance 347. Therapeutic Hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury. May 2010
2. Rao R, Trivedi s, Vesoulis Z, Liao SM, Smyser CD, Mathur AM. Safety and short-term outcomes of therapeutic hypothermia in preterm neonates 34-35 weeks gestational age with hypoxic-ischemic encephalopathy. *J Pediatr* 2017;183:37-42
3. Laptok AR. Therapeutic Hypothermia for preterm infants with hypoxic-ischemic encephalopathy: how do we move forward? *J Pediatr* 2017;183:8-9
4. Herrera TI, Edwards L, Malcolm WF, Smith PB, Fisher KA, Pizoli C et al. Outcomes of preterm infants treated with hypothermia for hypoxic-ischemic encephalopathy. *Early Hum Dev* 2018;125:1-7
5. Manja V, Kirpalana H, Lakshminrusimha S. Factors influencing decision-making: delayed hypothermia in late preterm infants with hypoxic-ischaemic encephalopathy. *Early Hum Dev* 2018; <https://doi.org/10.1016/j.earlhumdev.2018.10.006>
6. Smit E, Liu X. Cooling neonates who do not fulfil the standard cooling criteria-short and long-term outcomes. *Acta Paediatrica* 2014, 104; 138-145
7. Thoresen M. Who should we cool after perinatal asphyxia? *Seminars in Fetal and Neonatal Medicine*.2015; 20:66-71
8. Saliba E. Should we extend the indications for therapeutic hypothermia? *Acta Paediatrica* 2014 104: 114
9. Austin T, Shanmugalingam S, Clarke P. To cool or not to cool? Hypothermia treatment outside trial criteria. *Arch Dis Child Fetal Neonatal Ed* 2013, 98; F451-453
10. Guidelines for the investigation of newborn infants who suffer a sudden an unexpected postnatal collapse in the first week of life. Recommendations from a professional group on sudden unexpected postnatal collapse. March 2011
11. Balamurugan Thyagarajan. Minimal enteral nutrition during neonatal hypothermia treatment for perinatal hypoxic-ischaemic encephalopathy is safe and feasible. *Acta Paediatrica* 2015 Feb;104(2):146-51
12. Zanelli S, Stanley D, Kaufman D. Hypoxic-ischaemic encephalopathy. *eMedicine* 2008 [Available from: <http://emedicine.medscape.com/article/973501-overview>
13. Jacobs S, Hunt R, Tarnow-Mordi W, Inder T, Davis P. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2007 (4):CD003311.
14. Gunn AJ, Gluckman PD, Gunn TR. Selective head cooling in newborn infants after perinatal asphyxia: a safety study. *Pediatrics* 1998;102 (4 Pt 1):885-92.
15. Thoresen M, Whitelaw A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. *Pediatrics* 2000;106 (1 Pt 1):92-9
16. Azzopardi D, Robertson NJ, Cowan FM, Rutherford MA, Rampling M, Edwards AD. Pilot study of treatment with whole body hypothermia for neonatal encephalopathy. *Pediatrics* 2000;106:684-94.
17. Murray DM, Boylan GB, Ryan CA, Connolly S. Early EEG findings in hypoxic-ischemic encephalopathy predict outcomes at 2 years. *Pediatrics* 2009.
18. Perlman JM, Risser R. Can asphyxiated infants at risk for neonatal seizures be rapidly identified by current high-risk markers? *Pediatrics* 1996;97(4):456-62.
19. Predictive value of the amplitude integrated EEG in infants with hypoxic ischaemic encephalopathy: data from a randomised trial of therapeutic hypothermia. Azzopardi D, et al. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F80–F82.
20. Thorensen M. Effect of hypothermia on amplitude integrated Electroencephalogram in Infants with Asphyxia *Paediatrics* 2010; 126:e130
21. Jyoti R, O'Neil R, Hurrion E. Predicting outcome in term neonates with hypoxic-ischaemic encephalopathy using simplified MR criteria. *Pediatr Radiol* 2006; 36(1):38-42
22. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. *Early Hum Dev* 2010;86(6):329-38

23. Gluckman PD, Wyatt JS, Azzopardi D et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005;365(9460):663-670.
24. Shankaran S, Laptook AR, Ehrenkranz RA et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005;353(15):1574-1584.
25. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy *CochraneDatabase of SystematicReviews* 2013, Issue 1. Art.No.:CD003311. DOI: 10.1002/14651858.CD003311 .pub3
26. Azzopardi D, Strohm B, Edwards AD et al. Moderate hypothermia to treat perinatal asphyxia encephalopathy. *N Engl J Med* 2009;361:1349-58.
27. British Association of Perinatal Medicine. Position Statement on Therapeutic Cooling for Neonatal Encephalopathy. July 2010
28. Abbot R, Laptook, Seetha Shankaran, Namasivayam Ambalavanan et al. Prediction of Early Childhood Outcome of Term Infants using Apgar Scores at 10 Minutes following Hypoxic-Ischemic Encephalopathy. [Pediatrics Dec 2009; 124\(6\): 1619.](#)

13. Appendices

Appendix A - Bliss parent information leaflet: <https://shop.bliss.org.uk/en/products/parent-resources/hie-a-guide-for-parents>

Appendix B - PEEPS leaflet: <http://www.peeps-hie.org/>

Appendix C – Active Cooling Daily Assessment 1, Daily Assessment 2, Daily Assessment 3

Appendix D – Assessment prior to Active Cooling

Active cooling: daily assessment 1

Up to 24 hours of age

Date and time:

Age (hours):

Gestation:

Weight:

OFC:

Name:
DOB:
Hosp number:
NHS number:

Organ Involvement

| | | | |
|-----------------------|--------------|-----------------------|--------------|
| Cardiovascular | No inotropes | Inotropes | |
| Renal | Normal | Oliguria (<1ml/kg/hr) | Anuria |
| Hepatic | Normal | Deranged LFTs | Coagulopathy |

Neurological Assessment – Thompson Score

| | | | | |
|----------------------------|--------|------------------|----------------|--------------|
| Tone | Normal | Hypotonic | Hypertonic | Flaccid |
| Conscious Level | Normal | Hyper-alert | Lethargic | Comatose |
| Seizures | None | <3 per day | >2 per day | |
| Posture | Normal | Fisting/Cycling | Distal Flexion | Decerebrate |
| Moro | Normal | Partial | Absent | |
| Grasp | Normal | Partial | Absent | |
| Suck | Normal | Partial | Absent | |
| Respiratory Support | Normal | Hyperventilation | Brief Apnoea | Apnoeic/IPPV |
| Fontanelle | Normal | Full | Tense | |

| | | | |
|-----------------|--------|---------------------|-------------------|
| aEEG/EEG | Normal | Moderately abnormal | Severely abnormal |
| Comments | | | |

Anticonvulsants and sedatives given

| | |
|-------------|----------------------------|
| Name | Date and time given |
| | |
| | |
| | |

Signature:

Name:

Grade:

Active cooling: daily assessment 2

24 to 48 hours of age

| |
|--------------|
| Name: |
| DOB: |
| Hosp number: |
| NHS number: |

Date and time:

Age (Hours):

Organ Involvement

| | | | |
|-----------------------|--------------|-----------------------|--------------|
| Cardiovascular | No inotropes | Inotropes | |
| Renal | Normal | Oliguria (<1ml/kg/hr) | Anuria |
| Hepatic | Normal | Deranged LFTs | Coagulopathy |

Neurological Assessment – Thompson Score

| | | | | |
|----------------------------|--------|------------------|-----------------------|--------------|
| Tone | Normal | Hypertonic | Hypotonic | Flaccid |
| Conscious Level | Normal | Hyperalert | Lethargic | Comatose |
| Seizures | None | <3 per day | >2 per day | |
| Posture | Normal | Fisting/cycling | Strong distal flexion | Decerebrate |
| Moro | Normal | Partial | Absent | |
| Grasp | Normal | Poor | Absent | |
| Suck | Normal | Poor | Absent/bites | |
| Respiratory Support | Normal | Hyperventilation | Brief apnoea | Apnoeic/IPPV |
| Fontanelle | Normal | Full, not tense | Tense | |

| | | | |
|-----------------|--------|---------------------|-------------------|
| aEEG/EEG | Normal | Moderately abnormal | Severely abnormal |
| Comments | | | |

Anticonvulsants and sedatives given

| | |
|-------------|----------------------------|
| Name | Date and time given |
| | |
| | |
| | |

Signature:

Name:

Grade:

Active cooling: daily assessment 3

48 to 72 hours of age

Date and Time:

Age (Hours):

Name:
DOB:
Hosp number:
NHS number:

Organ involvement

| | | | |
|-----------------------|--------------|-----------------------|--------------|
| Cardiovascular | No inotropes | Inotropes | |
| Renal | Normal | Oliguria (<1ml/kg/hr) | Anuria |
| Hepatic | Normal | Deranged LFTs | Coagulopathy |

Neurological assessment – Thompson score

| | | | | |
|----------------------------|--------|------------------|-----------------------|--------------|
| Tone | Normal | Hypertonic | Hypotonic | Flaccid |
| Conscious Level | Normal | Hyperalert | Lethargic | Comatose |
| Seizures | None | <3 per day | >2 per day | |
| Posture | Normal | Fisting/cycling | Strong distal flexion | Decerebrate |
| Moro | Normal | Partial | Absent | |
| Grasp | Normal | Poor | Absent | |
| Suck | Normal | Partial | Absent/bites | |
| Respiratory Support | Normal | Hyperventilation | Brief apnoea | Apnoeic/IPPV |
| Fontanelle | Normal | Full not tense | Tense | |

| | | | |
|-----------------|--------|---------------------|-------------------|
| aEEG/EEG | Normal | Moderately abnormal | Severely abnormal |
| Comments | | | |

Anticonvulsants and sedatives given

| | |
|-------------|----------------------------|
| Name | Date and time given |
| | |
| | |
| | |

Signature:

Name:

Grade:

Appendix D

Assessment prior to active cooling

Date and Time of Birth:

Gestation: Weight: OFC:

Apgar score at 10 minutes:

Continued need for resuscitation at 10 minutes of age: Yes/No

Gases: Cord arterial Cord venous Admission gas

pH:

BE:

Lactate:

Does the infant meet any exclusion criteria (see reverse page): Yes/No

Cooling treatment criteria

| |
|--------------|
| Name: |
| DOB: |
| Hosp number: |
| NHS number: |

| | | Date: | | Date: | | Date: | |
|----------------------------------|--|--------|-------|--------|-------|--------|-------|
| | | Time: | | Time: | | Time: | |
| Pupils | Size, reactivity | Left | Right | Left | Right | Left | Right |
| | | | | | | | |
| Tone | Normal, hyper/hypo, flaccid | | | | | | |
| Conscious Level | Normal, hyper-alert, lethargic, comatose | | | | | | |
| Seizures | Yes/no | | | | | | |
| Posture | Normal, fisting, distal flexion, decerebrate | | | | | | |
| Moro reflex | Normal, partial, absent | | | | | | |
| Grasp reflex | Normal, poor, absent | | | | | | |
| Suck | Normal, poor, absent | | | | | | |
| Respiratory support | Normal, hyperventilation, apnoea, IPPV | | | | | | |
| Fontanelle | Normal, full, tense | | | | | | |
| aEEG (if available) | See descriptions on reverse page | | | | | | |
| Decision to actively cool | For treatment criteria – see reverse | Yes/No | | Yes/No | | Yes/No | |
| Reason for decision | | | | | | | |
| Name Signature Grade | | | | | | | |

A. Infants \geq 36 completed weeks gestation admitted to the neonatal unit with at least one of the following:

- Apgar score of ≤ 5 at 10 minutes after birth
- Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth
- Acidosis within 60 minutes of birth (defined as any occurrence of umbilical cord, arterial or capillary pH < 7.00)
- Base Deficit ≥ 16 mmol/L in umbilical cord or any blood sample (arterial, venous or capillary) within 60 minutes of birth

Infants that meet criteria A should be assessed for whether they meet the neurological abnormality entry criteria (B):

B. seizures or moderate to severe encephalopathy, consisting of:

- Altered state of consciousness (reduced response to stimulation or absent response to stimulation) and
- Abnormal tone (focal or general hypotonia, or flaccid) and
- Abnormal primitive reflexes (weak or absent suck or Moro response).

Exclusions for cooling

Do not start cooling infants if:

- Is likely to require surgery during first three days after birth
- Has other major congenital abnormalities indicative of poor long term outcome
- Is felt to be dying
- Has a significant intracranial bleed

Decision to cool infants of 34-35+6 weeks should be made by 2 consultants.

aEEG (CFM) patterns

Continuous normal voltage (lower > 5 mv, upper > 10 mv with sleep wake cycling)

Discontinuous normal voltage (lower < 5 mv, upper > 10 mv)

Continuous low voltage (lower < 5 mv and Upper < 10 mv)

Burst suppression (background 0 to 2mv with bursts > 25 mv)

Flat/isoelectric (all activity < 5 mv)

Seizures