HIE (Hypoxic Ischaemic Encephalopathy)

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The North West Neonatal Network (NWNODN) consists of 3 locality neonatal networks, Cheshire and Merseyside (CM) Lancashire and South Cumbria (LSC) and Greater Manchester (GM). This document has agreed by locality Clinical Effective Groups (CEG) and can be adapted for local use. **Please acknowledge source if this document is adapted for local use.**	

HYPOXIC ISCHAEMIC ENCEPHALOPATHY (HIE)

A hypoxic-ischaemic insult occurring in the perinatal period may result in an encephalopathic state characterised by the need for resuscitation at birth, neurological depression, seizures and electroencephalographic abnormalities. There is a risk of death or neurodevelopmental abnormalities with moderate/severe encephalopathy.

Indications for commencing total body hypothermia (cooling treatment) (adapted from (1, 9)):

1. **≥ 34+0 weeks gestational age**

2. **Evidence of intrapartum hypoxic ischaemia (list A)**
   a. Apgar ≤ 5 at 10 minutes
   or
   b. Need for resuscitation at 10 minutes after birth including face mask ventilation
   or
   c. Acidosis within 60 minutes of birth (defined as any occurrence of blood pH <7.00) or base deficit ≥ 16 mmol/L in any cord blood sample or blood sample within 60 minutes of birth

3. **Evidence of encephalopathy (list B)**
   a. Altered state of consciousness (reduced or no response to stimulation, need for respiratory support because of diminished respiratory drive)
   or
   b. Abnormal tone (focal or general hypotonia, or flaccid)
   or
   c. Abnormal primitive reflexes (weak or absent suck or Moro response)
   or
   d. seizures
   or
   e. An abnormal aEEG/CFM recording for a continuous period of at least 30min

Note: If criteria A and B are met, active cooling with the Tecotherm Neo apparatus should be started as soon as possible. Passive cooling should be done if active cooling is not immediately available

CFM: Cerebral Function Monitor (CFM) is not an essential criterion for cooling to be commenced. It is a useful bedside tool to augment neurological monitoring and should be commenced as soon as possible once the cooling apparatus is in place. Refer to local guidelines about commencing and interpretation of CFM. (see appendix 2)

In all infants receiving total body hypothermia the CFM trace and clinical neurological status (the grading system below can be used for clinical assessment) should be documented in the case record daily.

Following points are useful while making a diagnosis of HIE

- History of a sentinel event such as abruption or uterine rupture
- History of fetal /intrapartum distress or acidosis
- Low Apgar scores and/or delayed onset of respiration, resuscitation required
- Symptoms or signs of encephalopathy. A characteristic feature of many cases of HIE is an *evolving* encephalopathy – babies get worse and then get better
- Signs of multi-organ involvement usually occurs in association with a moderate to severe encephalopathy
- Exclusion of other likely causes of encephalopathy

HIE - Grading of severity (adapted from Sarnat and Sarnat)

Grade 1 (mild)	**Grade 2 (moderate)**	**Grade 3 (severe)**
Irritable, hyper alert	Lethargic	Comatose
Mild hypotonia	Marked abnormality of tone	Severe hypotonia
Poor sucking	Tube feeding required	Failure to maintain self-ventilation
No seizures	Seizures	Prolonged or intractable seizures

Cooling Therapy

In infants with moderate and severe HIE, induced hypothermia (cooling) to a rectal temperature of 33-34 C improves survival and neurological outcomes to 18 months of age (combined outcome of survival without disability at 18 months RR (1.53 (1.22 – 1.93), number needed to treat 8)) (2). In the UK, infants who receive hypothermia treatment follow the total body hypothermia (TOBY) guidelines as set out in the TOBY handbook (https://www.npeu.ox.ac.uk/toby/protocol).

When to cool

Cooling should be started as soon as possible after resuscitation is completed. Current evidence suggests that cooling is unlikely to be beneficial if started more than six to eight hours after birth.

Infant's ≥34+0 weeks who require resuscitation at birth and show early signs of encephalopathy (need for ventilation, abnormal tone) should initially receive passive cooling (see appendix 1) until they can be assessed for criteria in List A and List B. (3)

Infants who are ≥34+0 weeks gestation and fulfil criteria in list A (as above) but do not initially demonstrate any features of encephalopathy should be admitted to the neonatal unit for a period of observation (minimum 12 hours).

They do not need passive cooling but should have a neurological examination documented at admission and again at 4-6 hours of life. All these cases should be discussed with the consultant on admission. The decision to commence or not commence active cooling in an infant (≥34+0 weeks) who meets at least one of the criteria in List A should always be made only after discussion with the on-call consultant and the decision and reason to cool or not to cool MUST be clearly documented in the records.

Cooling should also be considered in the following circumstances. Currently as there is no strong evidence that cooling is beneficial in these circumstances, all these cases should be discussed with a consultant before active cooling is commenced.

1. Babies **≥**34+0 weeks gestation who needed resuscitation for 'post-natal collapse' in the first 72 hours of life

2. Babies **≥**34+0 weeks gestation who fulfil criteria in List A **and** demonstrate evidence of encephalopathy (list B) between 6-12 hours after birth

When is cooling not appropriate?

Initiating and/or continuing Cooling treatment **may not be** appropriate in certain circumstances. The final decision in these cases (below) should be made by a consultant on a case by case basis.

- Confirmed major congenital or chromosomal abnormalities or syndromes with long term poor prognosis. Infants with suspected Trisomy 21 should not be excluded from hypothermia treatment.
- Any conditions requiring immediate surgery.
- Moribund infants with severe HIE not responding to resuscitation or intensive care.

How to Cool?

Refer to local cooling guidelines

Supportive Management

Respiratory Support: Ventilate if poor respiratory effort, frequent apnoea, pCO2 >60mmHg or 8kPa or signs of pulmonary hypertension. If transferring a baby for cooling therapy intubation to secure the airway during transfer may be necessary.

The aim during ventilation is to maintain a normal pH, pO2 (60 – 90mmHg or 8-12 kPa) and pCO2 (35 - 50 mmHg or 5-6.6 kPa). Avoid hyperventilation and alkalosis. Infants can be extubated whilst being cooled if their respiratory drive is sufficient.

Cardiovascular Support: Most cooled infants will have a resting heart rate of approximately 100 bpm. Intra-arterial access is required to continually monitor systemic blood pressure. Hypotension is usually secondary to myocardial compromise from hypoxic-ischaemic damage rather than hypovolaemia. For management of hypotension please refer to hypotension guidelines.

Seizure management: Seizure management is described in the guideline "Neonatal Seizures". Seizures evident on CFM monitoring *without* clinical seizure activity may need treatment as there is some evidence that continuous electrographic seizures (for >15min per hour) is associated with worse outcomes on neuro-imaging.(8) These cases should be discussed with the consultant prior to commencing anti-seizure medication . Cooling may affect the metabolism of several drugs, including anticonvulsants and sedatives, and toxic drug levels may occur even with normal doses. (4)

Analgesia/Sedation: Cooling therapy is potentially distressing. Stress may have adverse effects in asphyxiated infants and may influence the therapeutic effect of hypothermia. (4) All ventilated infants receiving cooling treatment should be commenced on morphine Non-ventilated infants who appear distressed will also require sedative therapy with either morphine or chloral hydrate. Respiratory function must be monitored in these babies.

Fluid Therapy: Infants should initially be commenced on 60ml/kg/day with this being reviewed daily on the consultant ward round. Fluid balance must be assessed on at least a 12 hourly basis and adjusted according to blood glucose measurement, serum sodium levels, daily weights and urine output. Regular blood glucose monitoring (at least 4 hourly in the first 24 hours) should be performed.

Anti cerebral oedema therapy: Infants should **not** be treated with steroids (other than for treatment of hypotension), or mannitol.(4)

Nutrition: Asphyxiated infants are at increased risk of NEC, aspiration secondary to pharyngeal incoordination and transient milk intolerance due to reduced small intestinal motility. Minimal enteral feeds or comfort feeds using breast milk via naso/orogastric tube may be commenced in infants receiving cooling therapy. Enteral feeding can be cautiously introduced once the initial biochemical and metabolic disturbance are corrected, bowel sounds are present and the gastric aspirates are minimal (4) **The decision to commence enteral feeding is made by the consultant.**

Infection A full septic screen including LP should be considered and antibiotics commenced as meningitis may have similar presenting features and infection can be the underlying aetiological factor for HIE. Whilst there is little published evidence, CRP can be elevated in HIE without infection and must be interpreted with caution. (5)

Intravascular access: A UAC and double lumen UVC should be inserted in all infants who undergo cooling therapy. Once cooled it becomes difficult to insert peripheral lines and capillary blood gas analysis becomes unreliable. Intra-arterial access is required to monitor systemic blood pressure.

Coagulopathy: Disseminated intravascular coagulation can occur in HIE and therefore clotting studies must be performed on day one in all babies. If normal no further samples will be required. If abnormal treat and repeat until normalised.

Parent Communication
This is one of the most important aspects of management. It is often difficult to give the parents an accurate prognosis early on, and this should be made clear to them.

Do not give opinions on the obstetric or midwifery management, but refer the parents to their obstetrician or midwife.

Parents should be counselled within the first 24 hours after admission by the consultant. A clear summary of the discussion should be documented in the health care record.
BLISS parent information leaflet on HIE should be offered to all parents.

Neuroimaging

CrUSS: A cranial ultrasound scan should be performed on all infants with HIE within the first 24hours after admission.
MRI:
MRI scans can provide information regarding the diagnosis, timing and nature of the insult and prognosis. The timing of MRI scanning is important as abnormal features may not be evident if performed too early (before day 5) or too late (after day 21).[6] Interpretation of the MRI may take up to 2 days and the parents should be informed of this prior to the scan. Once the results of the MRI scan are available they should be discussed with the parents by a consultant.

Babies who are transferred from an LNU to a NICU for therapeutic hypothermia can be transferred back to the respective LNU 24 hours after rewarming. MRI brain scans can be performed at the local LNU if facilities are available and back transfers should not be delayed solely for performing MRI scans at Alderhey or Arrowe Park hospitals.

For babies at Liverpool Women's Hospital:

Once the infant is rewarmed to normal temperature, an MRI scan should be performed as soon as the infant is stable for transfer to Alder Hey children's hospital. We aim to perform the MRI between day 5 and day 14.
To request an MRI scan, discuss the case with the radiologist and fax a letter to the radiology department at Alder Hey Children's hospital. Please arrange transfer by contacting CMNNTS.

For babies at Arrowe Park Hospital:

Once the infant is rewarmed to normal temperature, an MRI brain scan should be performed by our Radiology Department between day 5 and day 10. The scan should be requested on our Millenium Cerner system,

Follow up

All infants who receive cooling treatment will receive a 6-8 week clinic appointment at the responsible neonatal unit. Babies will continue to be reviewed until at least 2 years. The referral letter for babies being followed up at local neonatal units will include the following statement

> "This baby has been subject to Total Body Cooling therapy. Infants should be followed up regularly with a neurological examination and psychomotor assessment to be carried out at approximately 2 years of age. We would appreciate being copied into any correspondence regarding this infant."

References

1. UK TOBY Cooling Register Clinician's Handbook**.** Version 4, May 2010

2. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. Azzopardi D et al. BMJ. 2010 Feb 9;340:c363

3. UK Toby Cooling Register Clinician's handbook. Ver 4 May 2010. https://www.npeu.ox.ac.uk/toby/protocol

4. TOBY study protocol. https://www.npeu.ox.ac.uk/toby/protocol

5. Whole body hypothermia and oxidative stress in babies with hypoxic-ischemic brain injury. Perrone S, et al. Pediatr Neurol. 2010 Oct;43(4):236-40.

6. Martinez-Biarge M, et al, Outcomes after central grey matter injury in term perinatal hypoxic-ischaemic encephalopathy, Early Hum Dev (2010). doi:10.1016/j.earlhumdev.2010.08.013

7. Moderate Hypothermia to Treat Perinatal Asphyxial Encephalopathy; Azzopardi D et al. N Engl J Med, 2009; 361:1349-1358.

8. Shah DK, Wusthoff CJ, Clarke P, et al.Arch Dis Child Fetal Neonatal Ed 2014;99:F219–F224.

9. Smit E, Liu X, Jary S, Cowan F, Thoresen M. Cooling neonates who do not fulfil the standard cooling criteria–short-and long-term outcomes. Acta paediatrica. 2015 Feb 1;104(2):138-45.

Appendix 1 - Passive cooling guide adapted from TOBY handbook

Any baby receiving passive cooling should have rectal temperature monitoring.

Target rectal temperature is 33^{0}C to 34^{0}C

Decision made to commence passive cooling

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Commence continuous rectal temperature monitoring (measure axillary temperature every 15 min if rectal temperature monitoring not available)

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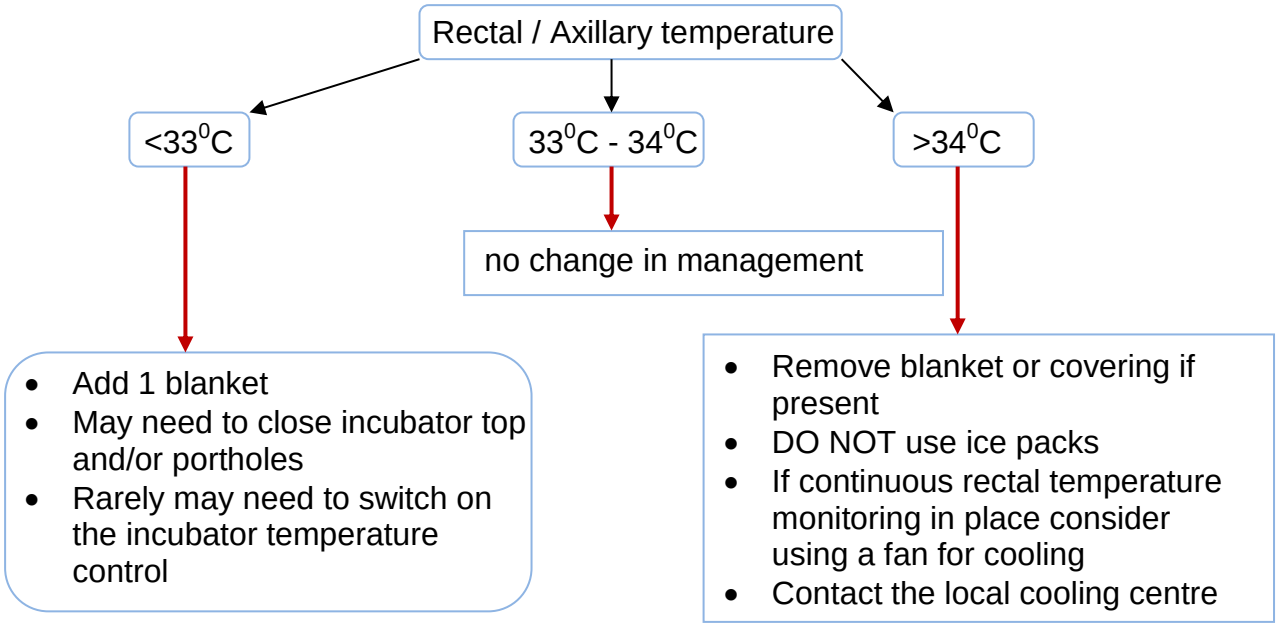
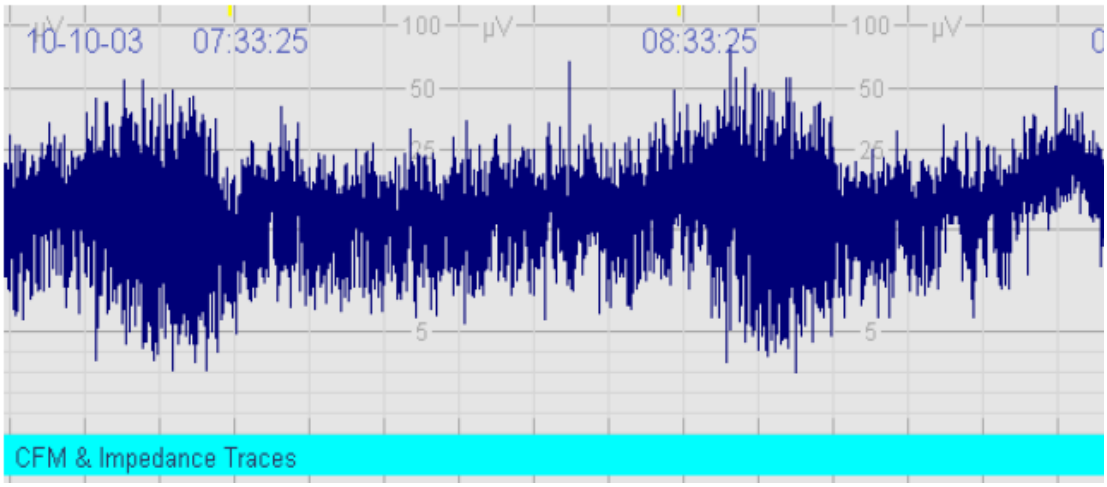
Document initial temperature
Turn off incubator
Open portholes of the incubator OR open the incubator/thermal cot top
Document rectal/axillary temperature every 15 minutes



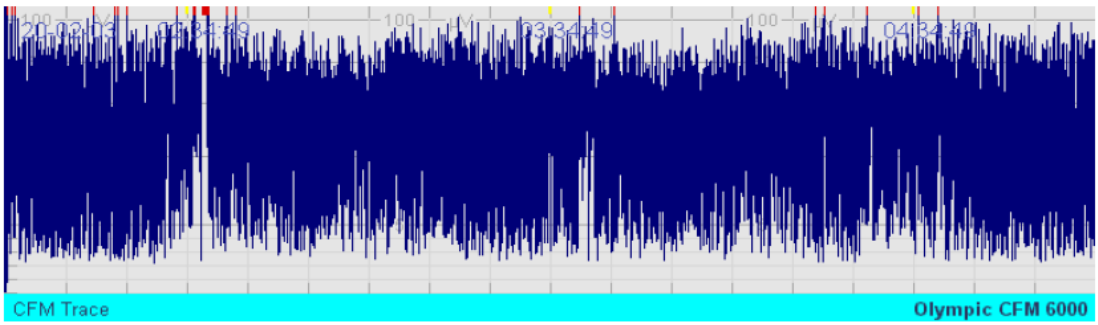
- Continue monitoring rectal / axillary temperature every 15 minutes and document clearly.
- Contact local cooling centre as needed for advice.

Appendix 2 - CFM / aEEG guide

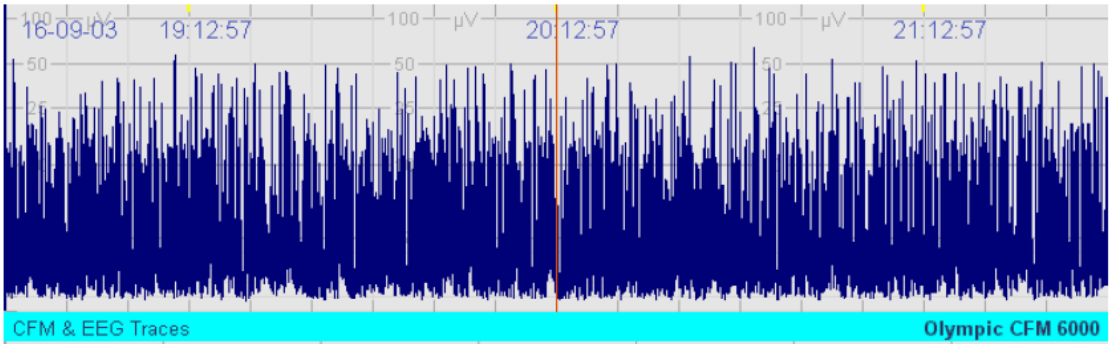
1. Normal trace - upper margin is >10 microvolts and lower margin of trace is >5 microvolts



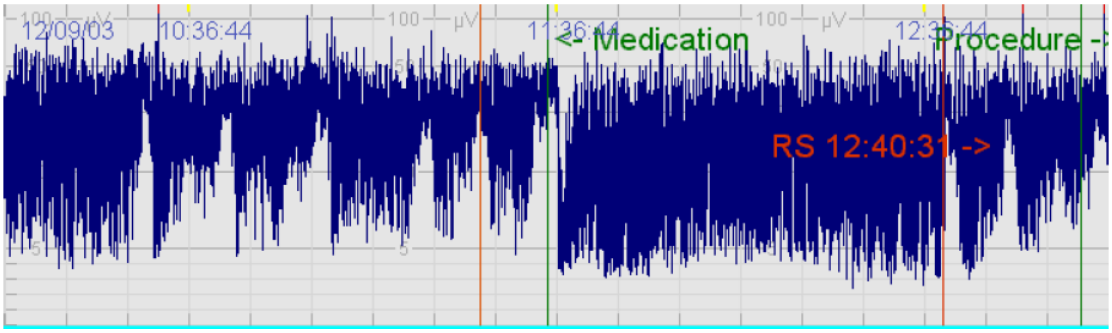
2. Moderately abnormal trace - upper margin is >10 microvolts and lower margin of trace is <5 microvolts

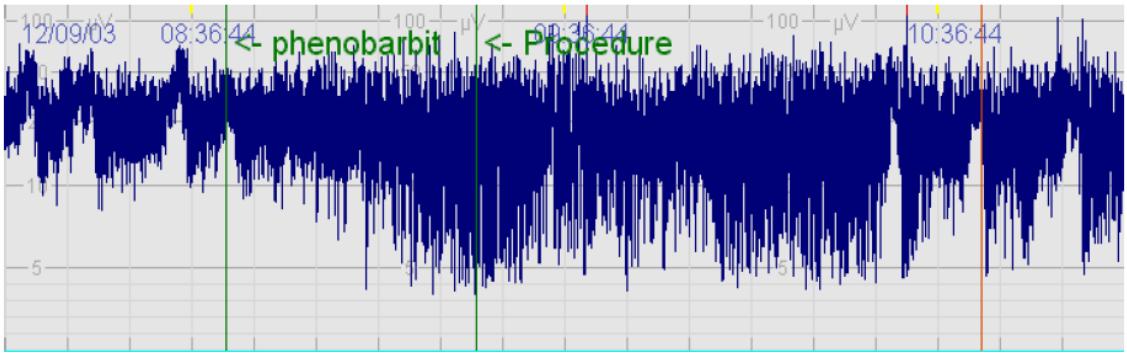


3. Severely abnormal trace - upper margin is <10 microvolts and / or a burst suppression pattern is seen as shown below. Do not include the spikes while assessing the upper margin.



4. Example CFM traces showing seizures (sudden rise in baseline)





For more detailed review of CFM tracing and examples of CFM traces to identify seizures refer to
http://www.neoweb.org.uk/CFM/CFM6000+manual.pdf