Hypoxic Ischaemic Encephalopathy (HIE)- Full Clinical Neonatal Guideline – Joint Derby and Burton

Reference no.: NIC NE 01/ Jul 22/v005

1. Introduction

The aim of this guideline is to outline the initial management of neonates born at the UHDB who are eligible for therapeutic cooling under the TOBY criteria for hypoxic ischaemic encephalopathy. The scope of this guideline is to look at the initial treatment only, as babies requiring cooling must be transferred for management at the Network's Tertiary Centre.

Burton neonatal unit does not have access to aEEG/CFAM and does not offer active cooling. All babies will require transfer to a cooling centre, therefore early discussions with a tertiary centre or the transport team is essential.

Hypoxic ishcaemic encephalopathy (HIE) is a neurological syndrome in babies who have been exposed to prolonged low blood and oxygen delivery to the brain antenatally or during birth. The hypoxic ischaemic event results in the death of neuronal cells in 2 phases. The first phase is as a direct result of the reduction in oxygen and high energy substrates. The second phase occurs as a result of reperfusion after six hours of the insult.
The syndrome comprises of abnormalities in levels of consciousness, tone, primitive reflexes, autonomic function and even seizures. The syndrome has different levels of severity and is graded as mild, moderate or severe.
Therapeutic hypothermia provides neuroprotective effects in those babies suffering from moderate to severe HIE. The aim of the treatment is to reduce the core temperature of the neonate and thus reduce neuronal cell death. It is performed on infants of gestational age 36 weeks and above and of less than 6 hours of age.

2. Main body of Guidelines

Inclusion Criteria

The UK Cooling TOBY Register sets out criteria for the consideration of treatment with cooling. This criteria focuses of two elements, the first focuses upon the risk factors for developing hypoxic ischaemia followed by clinical findings that suggest moderate or severe encephalopathy. There must be evidence for both of these elements in order for therapeutic cooling to be considered.

The criteria below will outline the framework and algorithm for treating suspected HIE.

2.1 Risk factors of hypoxic ischaemia (Criteria A):

Used to identify infants who may develop encephalopathy and who may benefit from neuroprotective hypothermia.

Infants must be **≥ 36 weeks' gestation** (if between 34 and 36 weeks discuss with Centre) **AND within 6 hours of birth** **AND** they **must have at least one of the following:**

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

If at least one of the above is present then move on to Criteria B:

2.2 Definition of moderate or severe encephalopathy (Criteria B):

If one of the conditions of Criteria A is met then the following criteria will identify those neonates who may clinically have moderate or severe encephalopathy.

Altered state of consciousness (lethargy, stupor or coma) and at least **ONE** of the following:

1. Abnormal tone (focal or general hypotonia or flaccid) **AND**
2. Abnormal primitive reflexes (weak or absent suck or Moro response)

OR

3. The presence of clinical seizures

If Criteria A and B are met, the infant should be assessed for **Criteria C** by amplitude-integrated electroencephalography (aEEG/CFM) if available (read by a trained personnel)

2.3 Definition of moderate or severe encephalopathy (Criteria C):

At least 30 minutes duration of:

- **Abnormal aEEG/CFM background voltage***
- **Seizures (either clinical or electrical)**

→ **INITIATE ACTIVE COOLING (33.5 deg C)**

*Abnormal aEEG criteria are **at least one** of the following at any time during the first six hours after birth:

1. Normal background voltage with electrical seizure activity
2. Moderately abnormal voltage (upper margin of trace >10µV and lower margin trace of <5µV)
3. Suppressed activity (upper margin of trace <10µV and lower margin of trace <5µV)
4. Continuous seizure activity

3. Management of Encephalopathy

The following sections of the guideline will now address the practicalities of management when using the above framework

3.1 Resuscitation at Birth (in labour ward/theatre)

- Resuscitation should be as per the Newborn Life Support (NLS) Guidelines set by the Resuscitation Council. Once the patient has been resuscitated and stabilised, the possibility of HIE should then be considered through the use of the criteria outlined above.
- Once HIE is suspected and cardiorespiratory stability is achieved, maintain normothermia whilst assessing for moderate/severe HIE. Rectal temperature monitoring should be initiated as soon as able, and before any colling is commenced.
- Record the weight of the placenta, examination of the placenta for signs of infection or abnormalities
- Request Cord gases.

3.2 Therapeutic cooling - Initial Temperature Management on NICU (Burton Only)

- Once HIE is suspected, **cooling should be considered only once cardiorespiratory stability has been achieved, including heart rate and oxygenation**. A baseline core temperature should be taken before commencing cooling on arrival to the neonatal unit. Maintain normothermia whilst undergoing assessment for moderate/severe HIE.
- Babies who meet criteria A&B, when they arrive in neonatal unit should have the central temperature monitored. Ensure temperature doesn't drop below 33.5°C. It is also essential to avoid hyperthermia.
- To achieve cooling, consider not actively warming the child, not having the overhead heater on, not having a hat on the head and turning off the heat in and nursed undressed in an open incubator.

3.3 Supportive Measures Post Resuscitation

Proper supportive measures are essential in the management of the encephalopathic neonate. Areas to address are: airway and ventilation, circulation, fluids, neurology and sepsis.

Airway and ventilation:

- If ongoing airway protection or ventilator support is needed intubation and ventilation is indicated.
- Maintain O2 sat > 93 - 98%
- Frequent blood gases should be performed to maintain pCO2 between 5-7 kPa and a pO2 between 8-12 kPa.
- Spontaneously breathing acidotic babies will drive their own respiration and achieve low pCO2. If babies are paralysed and ventilated, aim for pCO2 6 – 7.5 kPa (when analysed at 37°C, when you are hypothermic the true value is actually lower by a factor of 0.83)
- If patient is ventilated, ensure adequate analgesia using a morphine infusion:
    - Loading dose 50 - 100micrograms/kg and follow on infusion of 10-40 micrograms/kg/hr. Babies who are being cooled but not ventilated often require morphine as cooling is an unpleasant experience.

Circulation:

- if there are concerns regarding blood pressure, invasive blood pressure monitoring should be established and blood pressure maintained ideally at an MABP >40 mmHg. This will allow for adequate perfusion of the kidneys and brain.
- To maintain BP, If volume depleted, give 10ml/kg fluid bolus (if no improvement repeat once)
- If no improvement, commence inotropes (discuss with tertiary centre/Centre). Please refer to the Cardiovascular Monitoring and Management of Neonatal Hypotension guideline (NIC RC 06):
    - 1st line: Dobutamine
    - 2nd line: Adrenaline
    - 3rd line: Hydrocortisone
    - Consider cardiac echocardiography to look for Pulmonary hypertension/function.

Fluids & Electrolytes:

- Additional considerations include fluid restriction to 40ml/kg/day, but maintain glucose within normal range (3 – 8mmol/L)
- These neonates are at risk of developing renal impairment (acute tubular necrosis), therefore a strict fluid balance should be kept, consider urethral catheterization if needed It is important to avoid fluid overload during oliguria and hypovolaemia once diuresis start
- Watch for SIADH and avoid severe hyponatraemia
- Maintain Magnesium levels - this should be in the high normal range around 1.0 mmol/L. If it is low, consider giving 100mg/kg by slow iv infusion (over 10 mins)

Neurology:

- Once cardiorespiratory status is stable, a careful neurological examination should be performed and recorded using the neonatal encephalopathy chart (Appendix 1)
- Look for pupillary reaction and measure head circumference. Assess grade of encephalopathy using a modified Sarnat score (table 1)

3.4 Antibiotics

Start antibiotics in line with antibiotic guidelines. Consider Gentamicin levels (pre and post) before the second dose if there is suspicion of renal failure.

3.5 Blood Investigations

On Admission: FBC,CRP, Blood cultures, Clotting, Glucose, Blood group & DCT and blood gas. Regular monitoring of blood gases, Blood Glucose is required.
At 12 hours: UE, LFT, Calcium, Magnesium and regular monitoring every 12-24hourly.
If suspicion of metabolic condition: perform metabolic screen.
If Meningitis is suspected: perform Lumbar puncture when stable.

3.6 Management of seizures:

- If baby has clinical seizures, ideally should have correlating aEEG – as antiepileptic medication can affect neurological examination and may therefore impair decision making.
- Consider treating seizures which are confirmed with aEEG, particularly if they are associated with physiological disturbance, are prolonged (>3 minutes) or frequent (>3 per hour).
- Please refer to the neonatal seizure guideline (NIC NE03)
- Detection of seizures is an indication for urgent review of blood sodium, glucose, calcium and magnesium. Whilst seizures are common in HIE, unremitting seizure activity should

lead to urgent consideration of other causes of epileptic encephalopathy, including consideration of a trial of pyridoxine

- If no clinical seizures, but has seizure activity in aEEG, discuss with consultant on call regarding the management.

4 Infants with risk factors but *without* Encephalopathy

A Neonate may be born with risk factors under Criteria A but not may not be encaphalopathic immediately after birth. Therefore, it is critical that the patient should have repeated careful neurological examination, preferably from a middle grade doctor or above.

All babies with a ***pH <7.00 in the first hour*** or ***Apgar score <5 at 5 minutes*** or ***first hour lactate >8mmol/L*** must have documented regular reviews (1-2 hourly) for the first 6 hours of life. Please use the Neonatal encephalopathy chart below. Observations to be done in line with NEWTT2.

5 Imaging

- Consider formal EEG at 5 - 7 days and repeat at a later date if the background was abnormal and the baby's neurology has not improved.
- Perform an early cranial ultrasound scan looking for features of cerebral odema (slit like ventricles), congenital abnormalities, bleeding or infarction. Repeat formal cranial ultrasound by radiologist, when appropriate.
- A CT scan or MRI may be indicated in the first 24 hours if there is concern about significant intracranial bleeding or profound herniation.
- An MRI should be performed for prognostic purposes - usually during the first week – discuss with neuroradiologist.

6 Prognosis

The prognosis depends on the cause of encephalopathy, many of the studies reporting outcome having concentrated on post hypoxic ischaemic encephalopathy. Generally, babies with moderate encephalopathy with seizures of short duration, whose neurology and feeding rapidly normalise within first week, will have good outcomes. Outcome is difficult to predict with certainty.

Outcome based on grade of encephalopathy has consistent findings.

Grade of Encephalopathy	Mild	Moderate	Severe
Death	<1%	5%	80%
Severe handicap	<1%	24%	20%
No sequelae	100%	71%	0

An Apgar score of 0-3 at 10 minutes is associated with an 18% risk of death in the first year and a 5% risk of Cerebral palsy. An Apgar score of ≤5 at 10 minutes has a sensitivity (43%) and specificity (95%) of poor outcome. Abnormalities of the posterior limb of the internal capsule (PLIC) on MRI after day 4 are associated with poor outcome following moderate or severe H.I.E.

7 Follow up

All babies identified with encephalopathy will be followed up regularly in outpatient clinics for neurodevelopment monitoring until 2 years of age.

8 Special Circumstances and Situations (Derby NICU only)

Generally, all the babies who are having therapeutic hypothermia should be transferred to tertiary care centers.

But if:

If there are no beds within the region, or if transport cannot move the baby and the baby fulfils the following criteria, then consider cooling locally at Derby NICU after liaison with the Tertiary consultant and transport consultant.

Criteria:

a) Moderately abnormal aEEG/HIE grade 2
b) Minimal ventilatory support or Spontaneously breathing
c) Not needing inotropic support
d) If severe HIE and grade 3 and baby unlikely to survive, to keep baby close to parents

If the baby is to be cooled in Derby, the following measures ***must*** be taken overnight:

a) Consultant to attend the night handover
b) Night middle grade to attend the baby at least twice in the shift. This is to review the baby clinically and aEEG/CFAM and document within the notes
c) If the middle grade is extremely busy and unable to physically attend the baby, they are to inform the on call neonatal consultant

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19. Neonatal encephalopathy chart - adapted from the Nottingham University Hospitals NHS trust guideline "Management of Neonatal Encephalopathy at NUH", Guideline ID number: 3100

10 Documentation Controls

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Appendix 1

NEONATAL ENCEPHALOPATHY CHART (Adapted from NUH)

Please affix patient label	Gestation:
Patient Name:	Time of Birth:
Date of birth:	Cord gases: • Venous
NHS/Hosp. Number:	• Arterial:

A criteria	Hypoxia / ischaemia (HI) (any from below)	Values	
	Resuscitation ≥ 10 min	Y/N	NA
	Apgar ≤5 at 10 min	Y/N	
	Early acidosis (pH<7.00 and or BE≥-16) cord or from baby ≤1hr	Y/N	

B Criteria *Diagnosis of encephalopathy*								
		Temperature(°C)		°C	°C	°C	°C	°C
Categories (See reverse for definitions)		Rating (Moderate Severe)	Date Time	Date Time	Date Time	Date Time	Date Time	Date Time
1. Level of consciousness (Response to pain/noxious stim)		Normal						
		Hyperalert						
		Quiet/Lethargic						
		Stuporose or coma						
2. Muscle tone		Normal						
		Increased						
		Hypotonia (focal or general)						
		Flaccid						
3. Primitive reflexes (either Suck or Moro or palmar grasp)	Suck	Normal						
		Weak or poor						
		Weak or bites						
	or	**Absent**						
	Moro	Normal						
		Strong/low threshold						
		Incomplete						
		Absent						
Seizures (clinical):			Y/N	Y/N	Y/N	Y/N	Y/N	Y/N

C Criteria	**aEEG change (any of the below):**
	normal background with some *seizure* activity, *moderately* abnormal activity, *suppressed* activity, continuous seizure activity

Sarnat severity (see reverse for how to classify)									
	4.Spontaneous Activity		Normal						
			Increased						
			Decreased						
			No activity						
	5. Posture		Normal						
			Mild distal flexion						
			Strong distal flexion						
			Decerebration						
	6.Autonomic function (either)	Pupils	Normal						
			Dilated *and reactive*						
			Constricted						
			Deviated, dilated and *un-reactive*	B					
		Breathing	Normal						
			Hyperventilation						
			Periodic breathing						
			Apnoea						
	Sarnat grade (see over):(Mild-I, Mod-II, Sev-III								
	Signature or Initial								

Diagnosis of NE

Definitions of level of consciousness

- **Hyper-alert:** Vigilant, has a stare, jitteriness, high pitched cry, exaggerated response to minimal stimuli, inconsolable.
- **Lethargic**: Not unconscious but having decreased alertness and decreased responsiveness such that a noxious stimulus response can still be provoked eg. responsive to light, sound and a leg squeeze.
- **Stuporose or Coma**: Unresponsive to all stimuli including noxious stimuli.

NE is **diagnosed** when a baby is lethargic or stuporose/comatose in addition to abnormalities of muscle tone AND primitive reflexes.

- If performing the **Moro reflex is impractical** then palmar grasp reflex is a suitable alternative.
- The NE diagnosis matrix (domains 1-3) can be used in those with obvious NE or those with HI risk factors.

Classification using modified Sarnat system

The purpose of **classification** is for accurate description and recording of NE. The grading matrix (domains 4-6) should be used when a diagnosis of NE has been made (above).

Encephalopathy is graded moderate or severe based on the number of moderate or severe ratings in at **least 3 of the 6 categories** of the modified Sarnat classification system.

- **≥3 of 6 categories rated as moderate or severe**: Review number of categories rated as moderate or severe.
    - If number rated as severe > moderate then grade as: Severe NE.
    - If number rated as moderate> severe then grade as: Moderate NE.
    - If equal numbers rate as moderate and severe AND level of consciousness rated as severe then grade as Severe NE, else grade as Moderate.
- **≤2 categories rated as moderate or severe** and seizures present since the last examination grade as Moderate NE else grade as mild/none.

Appendix 2

PARENT INFORMATION LEAFLET - COOLING

Treatment of babies who have perinatal asphyxia (shortage of oxygen around the time of and before birth).

We know that your baby has been very unwell. Your doctor will already have spoken to you about what has happened to your baby and discussed the treatment needed. You have been given this leaflet because your baby has been born with perinatal asphyxia and is being offered cooling treatment, and this information will help you to understand more about what this means.

What is perinatal asphyxia?

We do not always know what causes perinatal asphyxia but we do know that lack of oxygen to the baby's brain can lead to brain injury. This injury may be severe and some babies will not survive. If a baby with perinatal asphyxia does survive, there is a chance that the baby will be disabled. Disability can be severe or it can be very mild but some degree of disability occurs in about half of all babies born with perinatal asphyxia.

The only standard treatment we have for perinatal asphyxia is intensive care treatment. There are no specific treatments that definitely help this condition. However, researchers continually try to find ways to improve the health of babies such as yours.

There has been much research over recent years into the use of cooling as a possible treatment that could limit the amount of brain injury caused by perinatal asphyxia.

What is cooling?

Cooling means, a baby is cooled from the normal body temperature of 37°C (98.6°F) down to a temperature of 33.5°C (92.3°F). The baby is kept cool for about three days (72 hours). Cooling is started as early as possible after birth, and after 72 hours of cooling the baby's temperature is slowly returned to normal.

How might cooling help?

There have been several studies that have looked at the effect of cooling after perinatal asphyxia. These include studies in animals, studies in adults and also studies in babies born with perinatal asphyxia. The three main reported studies of cooling for newborn babies with perinatal asphyxia have suggested that cooling can be beneficial.

The largest was the TOBY Study which recruited 325 babies and was funded by the Medical Research Council. The results were published in the New England Journal of Medicine in October 2009 showing that cooling can be beneficial for some babies with perinatal asphyxia. However, there may be side effects from cooling that we do not yet know about, so all cooled babies are always carefully observed and monitored.

A safe treatment that will help some babies

NICE (National Institute for Health and Clinical Excellence) published new guidance on cooling in May 2010. NICE had reviewed evidence from 8 studies and considered the expert opinions of specialist clinical advisers before agreeing to support the use of cooling as a routine treatment option for babies born with a brain injury caused by a shortage of oxygen. NICE guidance encourages clinicians to enter the details of each cooled baby into the UK TOBY Cooling Register which will contribute to the long term evidence about the safety and efficacy of cooling

How will my baby be treated with cooling?
Your baby will receive standard intensive care and in addition your baby will be cooled. This means that your baby will be nursed on a special cooling mattress that cools the whole body to the desired temperature. The mattress is filled with fluid that can be cooled or warmed. You will still be able to touch your baby just as you would if they were not being cooled.

We will aim to cool your baby for three days (72 hours). After this time the cooling will be stopped and your baby's temperature will slowly return to normal whilst still being carefully observed and controlled.
Your baby's temperature will be measured closely to make sure that this stays at around 33.5°C (92.3°F). It is important to know exactly what your baby's temperature is during cooling and re-warming, and we usually do this by measuring the temperature from a small probe placed in the baby's bottom (which measures rectal temperature).

What are the possible side effects of cooling?
From studies which have been performed in animals or adults and from the existing studies of newborn babies we know that cooling may lead to problems with blood pressure control, abnormal heart rhythm, bleeding and clotting problems, and chemical and sugar imbalances in the blood. Skin problems have also been reported. The doctors and nurses looking after your baby are aware of this and your baby will be closely monitored for signs of these unusual complications. Your baby's doctors can decide to stop the cooling early if they consider this to be best for your baby.

What happens now?
Thank you for reading this information leaflet. If you wish to discuss anything about the treatment your baby is receiving please speak to the doctor or nurse in the neonatal unit.