Kent Surrey and Sussex Neonatal Operational Delivery Network

Management of Hypoxic Ischemic Encephalopathy	
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Content

1. Introduction / background:

Neonatal Encephalopathy (NE) is a clinically defined syndrome of disturbed neurological function in the earliest days of life in an infant born at or beyond 35 weeks of gestation, manifested by difficulty initiating and maintaining respiration, depression of tone and reflexes, sub normal level of consciousness and often seizures. There are many potential causes of neonatal encephalopathy, the commonest of which is a Hypoxic-ischaemic Encephalopathy (HIE).

The incidence of Neonatal HIE is approximately 1-3.5/1000 live birth in UK. (1). HIE is caused by a decrease in the oxygen supply to the infants brain close to the time of birth or early neonatal period. This can result in significant Mortality and Morbidity including long term neurodisability. Therapeutic Hypothermia (cooling) therapy is the only approved treatment which aims to cool the brain to 33.5 degrees for 72 hours to reduce the effect of secondary injury following the hypoxic insult. Studies have shown that with cooling, the Mortality due to HIE has reduced from 25% to 9 % and disability rates from 20% to 16%.

2. Aim of Guideline:

The Aim of the guideline is to ensure that appropriate evidence based care is provided for babies presenting with Hypoxic ischemic Encephalopathy in the south east coast ODN Region. All the units in the region are equipped to provide active cooling and along with the dedicated transport team the cooling treatment should be initiated early and continued.

3. Eligibility for Therapeutic Hypothermia (TH): Flowchart

	Criteria for cooling	Criteria met
Gestational Age	≥36 weeks gestation: Start Cooling if criteria met	
Age	Infant <6 hours of age, Start Cooling if criteria met	
Criteria A Evidence of Hypoxic Ischemia.	One of the criteria to be met ➢ Apgar score ≤ 5 at 10 minutes after birth ➢ Continued need for mask or ET ventilation at 10 minutes after birth ➢ Acidosis defined as Ph. ≤ 7.00 Base deficit ≥16mmol/l ****continued need for mask or ET ventilation at 10 minutes does not include infants receiving PEEP or CPAP alone***	
Criteria B Evidence of Encephalopathy	Moderate to Severe Encephalopathy on NICHD Assessment.	
Criteria C Infants satisfying Criteria A and B Assessed on aEEG	Infants meeting Criteria A and B will need to be commenced on aEEG for at least 30 minutes and assessed by trained clinician for abnormal a EEG background or seizures showing one of the following features. ➢ Normal Background with some seizure activity ➢ Moderately abnormal activity ➢ Suppressed activity ➢ Continuous seizure activity ***Infants should satisfy Criteria A and B and supported with aEEG findings. Please note that inability to perform aEEG should not delay initiation of cooling***	

4. Grading of Hypoxic Ischemic Encephalopathy:

The Severity of Hypoxic Ischemic Encephalopathy is determined by clinical examination using the NICHD tool.

NICHD		Domains			
Categories		Normal	MILD	MODERATE	SEVERE
1. Level of Consciousness		Alert, responsive to stimuli (state dependent)	Hyperalert, staring, jittery, high pitched cry, exaggerated response to minimal stimuli, inconsolable	Lethargy	Stupor/ comatose
2. Spontaneous Activity		Normal, changes position when awake	Normal, or decreased, with or without periods of excessive activity	Decreased	No activity
3. Posture		Predominantly flexed when quiet	Mild flexion of distal joints (fingers, wrists)	Strong distal flexion, complete extension	Intermittent decerebration
4. Tone		Strong flexor tone in all extremities	Normal or slightly increased peripheral tone	Hypotonia or hypertonia	Flaccid or rigid
5. Reflexes	Suck	Strong, easy to elicit	Weak, poor	Weak or has bite	Absent
	Moro	Complete	Partial response, low threshold to elicit	Incomplete	Absent
6. Autonomic	Pupils	Normal [Dark 2.5-4.5mm, Light 1.5 – 2.5mm]	Mydriasis	Constricted	Deviated, non-reactive, dilated
	Heart rate	Normal (100 to 160 bpm)	Tachycardia >160/min	Bradycardia <100/min	Variable
	Resp. rate	Regular respirations	Hyperventilation >60/min	Periodic breathing	Apnoea / ventilated
NICHD Scoring – 6 categories with 9 clinical aspects in 4 domains (normal, mild, moderate, severe). Evaluate all 9 aspects. Circle worst domain in each of the categories. If two or more categories are not normal (in any domain of HIE) then neonate has at least mild HIE. If ≥3/6 categories are moderate or severe, then neonate has moderate or severe HIE. If an equal number in mod/severe, then Category 1 (LoC) dictates grade. Note if confirmed evidence of seizure activity, classifies as at least moderate HIE.					
Total in each domain: (max 6)					
Level of HIE (circle):		Normal	Mild	Moderate	Severe
Seizure activity:		No		Yes	

CFM	Recording: Yes/No	Normal/Abnormal	Lower limit (mV):	Upper Limit (mV):	Sleep-wake cycling? Yes /No

5. Therapeutic hypothermia

Therapeutic Hypothermia(TH) involves cooling core temperature to 33-34c with intracorporeal temperature monitoring started within 6 hours of life and continued for 72 hours. This reduces death and disability at 18 months of age and improves neurodevelopmental outcome in survivors of moderate to severe encephalopathy (2). TH is now a standard of care for in the NHS (3) and should be started without delay and the babies will need to be cared at level 3 unit to provide an optimal intensive care support to manage the HIE.

Criteria for cooling.

The decision to cool should be made promptly by the clinician once in babies ≥ to 36+0 weeks and satisfy the three Criteria as below.

Criteria A At least one of the following (Indicating significant perinatal Hypoxia)

- Apgar score of ≤5 at 10 minutes after birth
- Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth* (see notes below)
- Acidosis defined as any occurrence of:
  pH ≤7.00
  Base deficit ≥16mmol/l in any cord or baby gas sample within 60 minutes of birth

*_**continued need for resuscitation does not include infants who are receiving PEEP or CPAP alone**_.

Criteria B: Babies meting criteria A should be assessed for signs of moderate to severe Encephalopathy using the NICHD tool or with the following

- Altered state of consciousness (Lethargy, Stupor or coma)

  And at least one of the following

- Hypotonia
- Abnormal reflexes including Oculomotor or pupillary abnormalities
- Absent or weak suck
- Clinical Seizures

Criteria C: (aEEG Criteria)

Infants meeting Criteria A and B will need to be commenced on aEEG for at least 30 minutes and assessed by trained clinician for abnormal a EEG background or seizures showing one of the following features.

- Normal background with seizure activity
- Moderately abnormal activity
- Suppressed activity
- Continuous seizure activity.

*Please note that cooling should started and not be delayed due to inability to obtain aEEG if the infant meets Criteria A and B

Exclusion Criteria:

1. Severely moribund child where survival is unlikely and decision to redirect care.

2. Outside the cooling criteria: Discuss the cases with the NICU Consultant.

3. Neonates needing surgery in the first 72 hours: this will need to be discussed with the surgical team and decision made weighing the risk factors against the benefits of cooling.

6. Clinical Conundrum: Cooling outside Trial Criteria:

The above treatment criteria is based on the available clinical evidence and recommendations. There are certain clinical situations where cooling therapy might be indicated and this may have to be discussed with the NICU consultant on an individual case by case basis

I. **Gestational age:** 34+0 weeks to 35+6 weeks: There are currently no RCT evidence to support cooling in infant less than 36 weeks. TH should only be commenced after careful consideration of the benefits versus side effects with a detailed discussions with the family.

II. **Mild HIE:** Current evidence and studies do not support the use of Therapeutic hypothermia in mild HIE. Cases presenting with Mild HIE need to monitored closely in the first 6 hours with repeated neurological assessment as the HIE can progress to moderate or severe.

III. **Postnatal Collapse:** Infants presenting with a postnatal collapse in the hospital and meeting criteria for cooling need to be considered for TH and discussed with the NICU team. (4)

IV. **Infants more than 6 hours old**: Cooling may be considered for infants between 6 and 24 hours after the insult but the benefit is likely to be small.(5)

V. **Neonatal Stroke**: can benefit from cooling if the Diagnosis is made within 6 hours of birth.

7. Clinical management of HIE:

a. **Ventilation:** Note that most infants with HIE needing ventilation would have a normal lungs without the need for high ventilatory support.

- Avoid Hyperoxia (PaO2 7-10 Kpa) and hypocarbia (5-7kpa).
- Blood gases should be preferably from an arterial sample.
- Baby's core temperature has to be entered in the gas machine.
- Routine sedation with Morphine not recommended.

b. **Cardiovascular System**: Impaired cardiac contractility is common in HIE

- Perfusion to be assessed using BP along with Cap Refill, Lactate and urine output.
- Consider Early ECHO and Inotropes to support cardiac output.
- ECG abnormalities Bradycardia (<100, prolonged QT), Tachyarrhythmia common during cooling.
- Risk of tachyarrhythmia and Hypotension during rewarming

c. **Fluids**: Fluid restriction to 40mls/kg/day.

- Consider additional fluids only if h/o hypovolemia.
- Consider higher concentration dextrose to maintain normoglycemia.
- Monitor urine output and consider catheterisation.
- Nephrotoxic drugs cause worsening of renal function.
- Consider fluid bolus during rewarming or if excessive diuresis.
- Feeds to remain trophic until rewarming. 20mls/kg of

d. Seizures: Clinical seizures in HIE are difficult to treat and manage

- Commence CFAM without delay.
- Treat seizures if
    - prolonged seizures (>3mins) ,
    - frequent seizures >3 in an hour
    - associated with cardiorespiratory compromise
- Monitor anticonvulsant levels

e. Multi-organ Involvement

- Monitor and treat deranged liver functions, clotting, bone marrow suppression and renal impairment.

f. Infection: commence on first line antibiotics

- Gentamicin level pre second dose and hold.
- Consider Lumbar puncture depending on clinical stability.

g. Rewarming:

- Cooling is completed at 72 hours after reaching the temperature of 33.5c.
- Rewarming should be gradual and not more than 0.5c/hour until Normothermia (37c) is reached.
- Monitor for Seizures, hypotension and cardiac arrhythmia during the rewarming phase.
- CFAM should be continued until rewarming is completed.

Clinical prompts

Resp	Does baby require active respiratory support? Ventilation for apnoea may require low pressures and very slow rates Blood gases from cool peripheries can be misleading	Avoid hypocapnoea
CVS	Does baby require inotropic support? Blood may be needed to replace acute loss, but babies are often pale and vasoconstricted. Early consideration of inotropes is advised.	Saline may not be the best choice for volume
Fluids	Usually restrict to 40ml/kg/day, 10% dextrose	Watch for hypoglycaemia
Sepsis	Sepsis rare but CRP rise common Get clear history of sepsis risk, take 1ml blood for cultures	Consider renal function when prescribing antibiotics
Neuro	Document encephalopathy & seizures	Discuss anticonvulsant treatment with regional NICU
Placenta	Ensure placenta is not discarded	Send placenta for microbiology and histology
Comfort	e.g. morphine infusion 5 micrograms/kg/hr	Avoid distress from cooling
Parents	Explain reason for transfer: for neurointensive care and further investigations	Document all discussions, manage expectations

*****Time = Brain SEN ODN project Dr Peter Reynolds.(6)*

Complications:

1. Cooled neonates have a high risk of developing arrhythmias during rewarming.
2. Hypotension can occur during rewarming.
3. Sub cutaneous fat necrosis is a well-known complication of hypothermia.
4. Monitor for late hypercalcemia secondary to subcutaneous fat necrosis.

8. Imaging:

All infants undergoing TH should have Cranial Ultrasound scan within 24 hours to exclude other causes of encephalopathy.

MRI and MR Spectroscopy are a good predictors of neurological outcome in babies who are cooled for HIE. MRI brain and MRS Lactate/N acetyl Aspartate (LAC/NAA) of the basal ganglia and thalamus MRS needs to be performed for all babies who undergo TH between Days 5 and 15 after birth. MRS is an accurate predictor of outcomes. (7)

9. Follow up

All babies who required TH need to be followed up regularly until the age of two for monitoring neurodevelopmental progress. They will need to be assessed at two years of age with a standardised neurodevelopmental assessment tool such as Bayley or Griffiths.

10. Scope of Guideline Framework

The guideline applies to all Neonatal Units covered by Kent Surrey and Sussex Neonatal ODN. This includes the following hospitals:

Kent, Surrey and Sussex	
Medway Hospital NHSFT	-Medway Maritime Hospital, Gillingham
East Kent Hospitals University NHSFT	- William Harvey Hospital, Ashford -Queen Elizabeth the Queen Mother, Margate
Ashford and St Peter's NHSFT	-St Peter's Hospital, Chertsey
University Hospitals Sussex	-Royal Sussex County Hospital, Brighton -Princess Royal Hospital, Haywards Heath - Worthing Hospital
Frimley Health NHSFT	-Frimley Park Hospital
Surrey and Sussex Healthcare NHST	- East Surrey Hospital, Redhill
Maidstone and Tunbridge Wells NHST	- Tunbridge Wells Hospital, Pembury
Dartford and Gravesham NHST	- Darent Valley Hospital, Dartford
East Sussex Healthcare NHST	- Conquest Hospital, Hastings
Royal Surrey NHSFT Guildford	- Royal Surrey County Hospital,

11. Auditable Standards

- Infants identified as eligible should have access to therapeutic hypothermia
- Infants should reach target temperature (33-34˚C) within 6hrs of life
- Infants should not be overcooled (below 33˚C)
- Infants undergo MRI at 5-14 days of age, with image acquisition and reporting informed by current professional guidance.
- Infants should undergo standardised neurodevelopmental follow up to the age of 2y

12. References

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2. Azzopardi D, Strohm B, Marlow N, Brocklehurst P, Deierl A, Eddama O, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. New England Journal of Medicine. 2014;371(2):140-9.

3. NICE. Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury Interventional procedures guidance [IPG347] 2010 [Available from: https://www.nice.org.uk/guidance/ipg347.

4. Time = Brain Project: https://www.networks.nhs.uk/nhs-networks/south-east-coast-neonatal-network/time-brain/documents/background-evidence-for-time-brain

5. Neuroprotection Care Pathway for Infants with Hypoxic Ischemic Encephalopathy , The Scottish Cooling Group, 2nd Edition, December 2020. https://www.clinicalguidelines.scot.nhs.uk/media/2889/neuroprotection-care-pathway-for-infants-with-hie.pdf

6. Time = Brain Project: https://www.networks.nhs.uk/nhs-networks/south-east-coast-neonatal-network/time-brain/documents/clinical-prompts-for-cooled-babies

7. Montaldo P, Lally PJ, Oliveira V, Swamy R, Mendoza J, Atreja G, et al. Therapeutic hypothermia initiated within 6 h of birth is associated with reduced brain injury on MR biomarkers in mild hypoxic-ischaemic encephalopathy: a non-randomised cohort study. Arch Dis Child Fetal Neonatal Ed. 2019;104:F515–F20.

Version Control:

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