Neuroprotection Care Pathway for Infants with Hypoxic-Ischaemic Encephalopathy

The Scottish Cooling Group

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Disclaimer

These guidelines have been prepared to promote and facilitate standardisation and consistency of practice using a multidisciplinary approach. Information within is current at time of publication.

The Scottish Cooling Group does not accept liability to any person for loss or damage incurred as a result of reliance upon the material contained in this guideline.

Clinical material offered in this guideline does not replace or remove clinical judgement, or the professional care and duty necessary for each specific patient case. Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This guideline does not address all elements of standard practice and assumes that individual clinicians are responsible to:

- Discuss care with parents in an environment that is culturally appropriate and which enables respectful confidential discussion, including the use of interpreter services where necessary
- Provide care within scope of practice, meet all legislative requirements and maintain standards of professional conduct
- Apply standard and additional precautions as necessary when delivering care
- Document all care in accordance with mandatory and local requirements

Document Properties

Policy	**Care Pathway for Infants with Hypoxic Ischaemic Encephalopathy (HIE)**
Document Purpose	For use in Scottish Maternity and Neonatal units and by the Scottish Neonatal Transport Team
Authors	See Appendix 7
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Circulation List	Network Lead Cooling Centre Leads LNU and SCU Leads Transport Leads Community Midwifery Units
Description	National guideline for the assessment and treatment of HIE
Superseded Docs	All current local, regional and transport guidelines for the management of HIE
Timing	With Immediate Effect
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1. Neuroprotection Care Pathway for Infants with Hypoxic-Ischaemic Encephalopathy

1.1 Purpose of pathway

This pathway has been designed to inform the diagnosis, referral, transport and management of infants with moderate and severe hypoxic-ischaemic encephalopathy who are born and/or treated in Scotland.

This pathway has been devised to ensure safe, timely and high quality care is available to all infants who may be eligible for therapeutic hypothermia (TH). Guidelines have been developed largely in accordance with the BAPM Framework for Practice for Therapeutic Hypothermia (https://www.bapm.org/resources/237-therapeutic-hypothermia-for-neonatal-encephalopathy).

The pathway gives guidance in the following areas:

1. Diagnosis and management of HIE
2. Referral and transport of infants with HIE
3. Ongoing management of infants with HIE undergoing therapeutic hypothermia

1.2 Audit standards

Audit standards for clinical practice and for Cooling Centres are detailed in Appendix 1.

2. Location of care

Cooling can be initiated in any hospital setting where rectal temperature monitoring can be carried out. All units (bar Community Midwifery Units, see below) should have servo-controlled cooling equipment to induce hypothermia rapidly where required, whether the baby is in a cooling centre or in a referring unit. It is recommended that units use cerebral function monitoring to optimise decision-making for cooling. Infants who are eligible for ongoing cooling should be transferred to a Cooling Centre (BAPM 2020) that has facilities for providing neuro-intensive care, prognostic expertise and counselling to parents of brain injured infants. Infants in whom TH has been initiated should be transferred to the appropriate NICU by ScotSTAR with ongoing servo-controlled cooling, and intensive care monitoring including rectal temperature. These uplift transfers should be prioritised according to clinical need and follow local and national transport service guidance regarding timeliness of transfer.

Community Midwifery Units should resuscitate and stabilise and call ScotSTAR to arrange transport of the baby. Normothermia (36.5-37.4C) should be maintained and hyperthermia should be avoided.

3. Principles of assessment

Refer to Therapeutic Cooling Decision Aid and Pre-Cooling Documentation Aid.

It is a national recommendation that All Special Care Units (SCUs), Local Neonatal Units (LNUs) and NICUs should be able to assess infants and instigate TH using aEEG and servo controlled cooling equipment as outlined above. Staff in all units should be trained and competent in the neurological assessment of infants, as well as in aEEG monitoring and interpretation (BAPM 2020).

Cooling is <u>not</u> appropriate if:

- There are other abnormalities indicative of poor long term outcome eg trisomy 18.
- The infant appears 'moribund' and is dying despite intensive care efforts.

Cooling may be appropriate if:
The infant falls outside of the set criteria. Please see Appendix 2 and contact the Cooling Centre for further advice.

Infants who are likely to require early surgery should be discussed with the Cooling Centre **and** Surgery at an early stage. Cooling may still be feasible during surgery or the surgery may be delayed to accommodate neuroprotective interventions.

4. Principles of care during and after Therapeutic Hypothermia

4.1 General principles
Refer to Management Aids for Referring Centres, Cooling Centres and Transport Teams.
Expanded management guidance is provided in Appendix 3.

4.2 Complications associated with cooling
Cooling infants to 33-34°C in an intensive care environment can be done safely.

Subcutaneous fat necrosis (SCFN) is a recognised complication of total body cooling. This condition can lead to pain, scarring, and hypercalcaemia that may present after discharge. It may be subtle and occur in any area of the body containing subcutaneous fat and is not restricted to body areas in contact with cooling mats. It is recommended that the infant's skin is closely observed for the development of SCFN both during neonatal stay and after discharge by parents. If it develops, weekly calcium levels should be monitored at least until clinical resolution of SCFN occurs, and in some instances for up to 6 months. Parents should be alerted to the symptoms of hypercalcaemia whether or not SCFN is diagnosed during stay and this information is in the National Parent Information Leaflet (Appendix 4)

4.3 Prognostication
An assessment should be made of the likely prognosis into high, moderate and low risk of significant neurodevelopmental impairment, based on the baby's neonatal condition, the evolution of neurological examination, aEEG, MRI and, where available, MRS. If there is overwhelming clinical evidence of very poor prognosis before day 5, an MRI may not be required to support clinical judgement when counselling parents. However MRI obtained during TH has a sensitivity of 100% (95% CI 84% to 100%) to identify the presence and extent of later brain injury. In general MRI and 1H MRS are most valuable where prognosis is uncertain. Where MRI and 1H MRS are used for prognostication, clinicians should be aware of the confidence limits around point estimates of predictive values, and efforts made to translate uncertainties in appropriate ways for parents.

Prognosis should be discussed with parents in a timely manner before discharge from the NICU and summarised in a written communication to parents and other health professionals in the referring unit and primary care. Where the result and interpretation of the MR investigations are not available at the time of transfer, specific arrangements should be made to communicate this information to parents and referral teams in a timely manner.

Suggested MR sequences and the prognostic values of MRI and MRS after hypothermia are found in the BAPM Framework for Practice: Fetal and Neonatal Brain Magnetic Resonance Imaging: Clincial Indications, Acquisitions and Reporting 2016 (https://www.bapm.org/resources/33-fetal-neonatal-brain-magnetic-resonance-imaging-clinical-indications-acquisitions-and-reporting)

4.4 Withdrawal of intensive support

In some cases, it may also be apparent soon after delivery that the prognosis of a baby is so poor that ongoing intensive care is likely to be futile. In these circumstances the baby should not be cooled and it is usually inappropriate to separate the mother and baby by transferring to a Cooling Centre. These cases should be discussed with the neonatal Transport Team and Cooling Centre.

In infants in whom it is possible to deliver TH with physiological stability, it is recommended that such consideration be delayed for 48 hours to assess any recovery before considering reorientation of care. Consideration should be given to the drugs that have been administered and appropriate tests should be undertaken to ensure that the assessment of prognosis has not been modified by drug effects.

If a decision is made to withdraw intensive support during cooling, cooling should be discontinued and, if time allows, the baby re-warmed before intensive care is withdrawn.

Palliative care teams including those from a local children's hospice may be very beneficial to both the infant and their family. The ScotSTAR neonatal transport team can provide transport of an infant planned for palliative care to a hospice or a unit closer to the infant's home. In the event that the infant has died before the hospice team was contacted, the hospice may still be able to offer help and support to the family.

When any baby dies, the parents should be counselled by a Consultant about the value of post mortem examination. The possibility of organ donation should be explored with the local Donor Transplant Coordinator and discussed with the parents.

5. Parents

Early open and honest communication by senior members of the neonatal team with parents is an essential part of neonatal care, and there should be no barriers to this. The decision to treat with cooling should be explained to the parents and the Parent Information Leaflet should be provided (Appendix 4).

There should also be no barriers to parents being with and caring for their baby, aiming for a culture of minimal separation. This will involve timely transfer of mothers after birth. Mothers should be encouraged and supported to express breast milk.

Sensitive and open communication needs to be repeated throughout the patient pathway, with parental care being integrated with the clinical care. The clinical team should be responsive to parents concerns and questions, and to the wellbeing of siblings and the wider family. Parents should be signposted towards support organisations (Appendix 5).

There should be timely multidisciplinary and multispecialty review of the perinatal care of the mother and baby of any infant who undergoes TH with a particular focus on avoidable factors. This should be discussed with parents in a timely open and honest way, meeting standards of GMC/NMC duty of candour. All parents whose baby has undergone TH should be offered follow up to reflect on antenatal, intrapartum and neonatal care, and the opportunity to ask questions within the review process.

Therapeutic Cooling Decision Aid

Resuscitation of baby with suspected asphyxia (NLS)

Admit to NNU where required, for ongoing care and assessment
(If not admitted, assess need for NEWS, ongoing neurological assessment and glucose monitoring)

Prompt stabilisation of airway, breathing and circulation

Maintain normothermia Avoid hyperthermia	Achieve peripheral access	Update parents

Assess for cooling **promptly once stabilised**

Assess Criteria A and B

Criterion A

Evidence of intrapartum asphyxia, ANY of the following features:

- Apgar score of ≤ 5, 10 mins after birth ☐
- Ongoing need for endotracheal or mask ventilation,10 mins after birth ☐
- pH <7.00 in cord or baby sample within 60 mins of birth ☐
- Base Deficit ≥ 16 mmol/L in cord or baby sample within 60 mins of birth ☐

Criterion B

Moderate or severe encephalopathy (see Neuro Exam table), including ALL of below:

- Altered consciousness (reduced or absent response to stimulation) ☐
- Abnormal primitive reflexes (weak or absent suck or Moro response) ☐
- Abnormal tone (hypotonia, flaccid) ☐

Or Altered consciousness + seizures alone ☐

A- Yes	**A- Yes**	**A- No**
B-Yes	**B- No HIE, mild HIE or improving**	**B -Yes**
Neurology severely abnormal or not normalising over first hour: **Start CFM where available** **Start cooling**	Reassess B *often, up to 6*h Consider starting CFM Consider early discussion with cooling centre Maintain normothermia	Consider other causes of encephalopathy* Gather information Consider value of CFM/USS Do not cool without discussion with cooling centre
Aim to reach target temperature by 2-4h but **always within 6h**	If encephalopathy progresses within the first 6h: **Start CFM where available** **Start cooling**	* Includes infection, drugs, neuromuscular/ metabolic conditions, stroke, intracranial trauma, structural anomalies etc

The decision to start cooling (active or passive) should **only** be made by a Consultant or Senior Associate Specialist

Document:

- ☐ the timing and features of all assessments including CFM where used
- ☐ the rationale for initiating or withholding cooling
- ☐ the names and seniority of those involved in decision-making
- ☐ discussions with parents

Neurological Examination (based on Modified Sarnat scoring system)

Domain	Stage 1 (Mild)	Stage 2 (Moderate)	Stage 3 (Severe)
Seizures	None	Common focal or multifocal seizures	Uncommon or frequent refractory seizures
Level of consciousness	Normal Hyperalert	Lethargic or decreased activity in an infant who may be responsive Can be irritable	Stuporose/ comatose Not able to rouse and unresponsive to external stimuli
Spontaneous activity when awake or aroused	Active Vigorous does not stay in one position	Less than active Not vigorous	No activity whatsoever
Posture	Moving around and does not maintain one position	Distal flexion, complete extension or frog-legged	Decerebrate with or without stimulation (all extremities extended)
Tone	Normal – resists passive motion Hypertonic, jittery	Hypotonic or floppy, either focal or general	Completely flaccid like a rag doll
Primitive reflexes	Suck: vigorously sucks finger or ET tube Moro: normal	Suck: weak Moro: incomplete	Suck: completely absent Moro: completely absent
Autonomic system	Pupils: normal, reactive Heart rate: normal >100 Respirations - normal	Pupils: constricted, reactive Heart rate: bradycardia Respirations: periodic irregular breathing effort	Pupils: fixed dilated, skew gaze, not reactive to light Heart rate: variable may be bradycardic Respirations: completely apnoeic

CFM Criteria for Cooling

CFM should be applied and interpreted by personnel who are trained in its use. This skill includes but is not restricted to:

- Ensuring accurate placement of electrodes
- Ensuring correct machine set up, including appropriate scales and speed
- Accurate interpretation of both aEEG and raw EEG
- Ability to identify artefacts
- Ability to identify normal and abnormal patterns, and accurately diagnose seizures

There must be at least one of the following criteria (based on TOBY criteria) present:

- Moderately abnormal activity (upper margin of aEEG >10μV and lower margin <5μV)
- Suppressed activity (upper margin of aEEG <10μV and lower margin of aEEG <5μV)
- Continuous seizure activity as confirmed on both aEEG and raw EEG (rare before 6 hours of age)

Pre-Cooling Documentation Aid (0-6h)

Name				Apgar at 10 mins		
Hospital Number				IPPV at 10 mins (not CPAP/PEEP alone)		
Date and time of birth				Worst pH in cord or in first hr		
Gestation				Worst BE in cord or in first hr		
Date and time of assessment (Frequent assessment including at around 5.5h)						
Temperature of baby						
Sedative drugs						
Level of consciousness (alert, lethargic, comatose)						
Spontaneous activity (normal, reduced, absent)						
Respiratory effort (normal, irregular, absent)						
Tone (normal, hypertonia, mild/moderate hypotonia, flaccid hypotonia)						
Moro reflex (normal, weak, absent)						
Suck reflex (normal, weak, absent)						
Gag reflex (normal, weak, absent)						
Doll's eye reflex (normal, weak, absent)						
Clinical Seizures						
CFM: electrical seizures						
CFM: upper limit (uV) lower limit (uV)						
Discussed with cooling centre						
Decision, for example: A. Continue normothermia & assess frequently B. Not eligible: no further assessments necessary C. Further investigations required D. Start cooling						
Assessor name and grade						

Therapeutic Cooling Management Aid - Referring Centres

In clear cut cases, contact SCOTSTAR on emergency 03333 990 222 and cooling centre will be invited to join call after iinitial discussion with transport team

Where there is uncertainty, contact Cooling Centre directly to discuss initiation of cooling

Contact transport team through SCOTSTAR

Update parents

Start sedation

General management

Aim	Actions
Airway and breathing Avoid hyper/hypoxia Avoid hypocarbia <4.5kPa	Saturation monitoring Assess and support respiration Regular blood gases
Circulation Avoid hypotension <45mmHg	Assess perfusion and BP Secure central access Measure BE and lactate Assess for volume/ inotropes
Metabolism Avoid hypoglycaemia <2.5mmol/l	Measure sugar regularly Start iv fluids at 60ml/kg/d
Infection Treat promptly	Take blood cultures Start first line antibiotics for congenital sepsis Give vitamin K
Neurology Assess and document	Document full examination Ensure sufficient sedation Consider CFM if available Discuss with cooling centre **prior to** treatment of seizures
Information Gather key data	Baseline FBC, G&S, coagulation Urinalysis Placental histology Full maternal Hx

Temperature managment

Ensure rectal monitoring

Passive cooling	**Servocontrol** cooling
Aim for core temperature of 34C +/- 0.5C within 6h of birth and 1h of decision	Aim for core temperature of 33.5C +/- 0.5C within 6h of birth and 1h of decision
Nurse naked, uncovered on open cot or nonheated incubator, open portholes Record temp every 15mins	Nurse naked on open cot or a nonheated incubator Record temp every 15 mins
If temp 33.5-34.5C, maintain this temperature and record every 15 mins	Maintain temperature at 33.5C and record every 15 mins
Temp >34.5C: remove any blanket, move to open cot if in incubator **Temp<33.5C:** put hat on baby, add 1 blanket or put heater to lowest setting Consider seeking advice from Cooling Centre	

Do not use ice/cool packs or fans as they can lower temperature too quickly and by too much

Prepare the discharge letter:

- ☐ Details of maternal history, labour, delivery, cord pH, resuscitation, time to heart rate >100, first gasp
- ☐ Blood test results and timing of drugs and their dosages
- ☐ Examination of the baby including head circumference, details of neurological examination
- ☐ Time of cooling decision and time to reach target temperature of 33-34C
- ☐ The results of any imaging specifically cranial ultrasound and the position of central lines
- ☐ Details of discussions with parents and whether the Parent Information Leaflet has been given

Therapeutic Cooling Management Aid - Cooling Centres

Parents	•Inform of intention to commence TH and give Parent Information Leaflet •Joint obstetric and neonatal debrief soon after birth •Daily consultant update •Support lactation if intention to breastfeed and cuddles if can be done safely •Ensure prognostic assessment is undertaken and dw parents prior to discharge
Temperature	•Site rectal probes •Load with morphine, ensure adequate sedation for optimal neuroprotection •Start servocooling within 6h, ideally 4h and always within 1 hour of decision •Aim to reach 33.5C within 30 min of initiation and to continue cooling for 72h
Monitoring and Investigations	•Continuous HR, O2 saturation and invasive BP monitoring •Regular blood gas and glucose analysis •Fluid balance 6 hourly •Other investigations as indicated (see proforma in full pathway and below) •Monitor for subcutaneous fat necrosis throughout stay
Airway and Respiratory	•Aim for normal blood gas values and saturations- avoid hypocarbia /hyperoxia •Intubation is not always required •Ensure regular repositioning and suction if secretions increase •Watch for stridor in extubated and nonventilated patients
Cardiovascular	•Achieve central venous and arterial access •Bradycardia 80-100bpm is normal •Rise in HR may be distress, hypovolaemia, hypotension, seizures or inotropes •Aim for BP >45mmHg and treat hypotension according to local guidelines •Avoid excessive fluid boluses and consider inotropes early
Fluids and electrolytes	•Catherisation recommended in assessing urinary output •Initial maintenance fluids at 40-60ml/kg/d •Avoid hypoglycaemia maintaining glucose ≥ 2.5mmol/l •Avoid fluid overload during oliguria, and hypovolaemia once diuresis starts •Watch for accumulation of nephrotoxic drugs eg gentamicin
Gastrointestinal and liver	•Consider trophic breast milk if no ongoing organ dysfunction or poor perfusion •Give colustrum as mouthcare where available in all •Beware accumulation of drugs metabolised by liver: morphine, phenobarb •Coagulopathy is physiological. Only active bleeding needs treatment. Give vit K.
Infection	•Take blood cultures and give antibiotics within one hour of birth •Consider lumbar puncture •Physiological drop in white cell count and platelets is common in TH •C-reactive protein rises with TH and may not be a sensitive marker of infection
Neurology	•Continuous CFM. Consider EEG where CFM has not normalised by rewarming •Perform neurological examination every 12 hours (see Neuro Exam Table) •Treat symptomatic seizures or burden of ≥10 min/hr with ref to local guidance •Ensure electrolyte dustrubances/hypoglycaemia are ideintified and treated •MRI 5-7d (up to 14d) +/- MRS 5-10d reported according to BAPM standards
Rewarming	•Monitor for hypotension, apnoea and seizures including continuing CFM •Re-warming can be delayed or slowed where seizures emerge •Maintain normothermia after re-warming with paracetamol and environmental measures where required
Discharge	•Discharge letter to parents, GP, Obstetrician, HV +/-referring unit including parent expectations and prognosis, and vigilance for subcutaneous fat necrosis •Ensure plan for 2 year standardised neurodevelopmental follow up •Signpost parents to support groups where relevant

Therapeutic Cooling Management Aid - Transport Teams

Assessment & stabilisation of airway, breathing and circulation

Assess need for any immediate stabilisation or further assessment prior to cooling

Assessment of current cooling situation

Not currently cooled | Cooled (active or passive)

Not for cooling

Is transfer to the cooling centre still indicated?

If yes:
Aim normothermia
(36.5C +/- 0.5)
Aim transfer to cooling centre within 6hrs from birth
Consider rectal probes
Consider CFM

Pre-cooling assessment

Use Therapeutic Cooling Decision Aid

Active cooling for transport

Servo-controlled cooling unless flight or equipment malfunction (if so use gel packs)

The decision to start cooling should only be made by a Consultant or Senior Associate Specialist

Check transfer documents complete:

- ☐ Details of maternal history, labour, delivery, cord pH, resuscitation, time to heart rate >100, first gasp
- ☐ Blood test results and timing of drugs and their dosages
- ☐ Examination of the baby including head circumference, details of neurological examination
- ☐ Time of cooling decision and time to target temperature
- ☐ The results of any imaging specifically cranial ultrasound and the position of central lines
- ☐ Details of discussions with parents and whether the Parent Information Leaflet has been given

Stability not achievable

Cooling is not appropriate for infants who are deteriorating despite maximal efforts

Separation from parents by transfer is to be avoided

For Consultant level discussion regarding direction and location of ongoing care

General management

Aim

Airway and breathing
Avoid hyper/hypoxia
Avoid hypocarbia <2.5kPa

Circulation
Avoid hypotension
<45mmHg

Metabolism
Avoid hypoglycaemia

Infection
Treat promptly

Neurology
Assess & document

Actions

Saturation monitoring
Assess and support respiration
Ensure blood gas stable pre-transfer
ET CO2 on transfer if ventilated

Assess perfusion and BP
Central lines*
Measure BE and lactate
Assess for volume/ inotropes

Ensure sugar ≥ 2.5mmol/l pre-transfer
IV fluids at maximum 60ml/kg/d

Ensure blood cultures taken and appropriate antibiotics started

Document full examination
Ensure sufficient sedation for comfort/stress relief
Consider CFM application
Discuss with cooling centre prior to seizure management or paralysis (seizures are rare <6hr & medication will impair assessment of neurology & CFM on arrival)

Temperature management

Ensure rectal monitoring

Aim for core temperature of 33.5C +/- 0.5C within 30 minutes

Nurse naked in a nonheated incubator
Start servocooling
Record temp every 15 mins

Maintain temperature at 33.5C and record temperature every 15 mins

*If journey short & HR 80-100, lactate & other measures of perfusion normal, arterial access can be delayed until reaching cooling centre

Appendix 1. Audit standards

1.1 Audit Standards for Clinical Practice

- 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

1.2 Audit Standards for Cooling Centres

- Within Cooling Centres, therapeutic hypothermia should be undertaken according to nationally developed guidelines and pathways.
- Cooling Centres should ensure there is an established pathway within networks for referral of infants and that frontline staff are trained to identify infants who are eligible for therapeutic hypothermia.
- Therapeutic hypothermia should only be undertaken in centres which are experienced in the care of severely ill neonates and which are supported by a multidisciplinary team experienced in neonatal electrophysiology and neuroimaging. Care of such infants should be directed by clinicians experienced in the diagnosis and prognosis of perinatal brain injury.
- There will be a named Lead Neonatologist and Lead Nurse in each Cooling Centre who has expertise in cooling and who remains abreast of professional recommendations and current literature.
- Cooling Centres should ensure that all in-house staff undergo training in the process and its effects.
- Cooling Centres should ensure that all infants undergoing cooling have access to a standardised developmental assessment at two years of age.
- Cooling Centres will ensure that all relevant professionals receive information on discharge about cooled infants, specifically with regard to parental communication about prognosis and the need for regular follow up.
- Cooling Centres should collect data on process and outcomes and be encouraged to share nationally.
- Individuals from Cooling Centres should contribute at least annually to teaching on National Hypothermia Training days.
- Cooling Centres should engage in annual meetings and other communications of the Scottish Cooling Group and be responsible for dissemination of information where appropriate through their network.

Appendix 2. Cooling in Special Circumstances

Cooling Outside Trial Criteria

There are some clinical circumstances where it may be appropriate to offer cooling despite the lack of clinical evidence in the form of randomised controlled trials. These include:

- Infants <36 weeks gestation
- Infants > 6 hours old
- Infants with mild encephalopathy
- Infants with congenital anomalies
- Infants presenting as sudden unexpected postnatal collapse
- Infants presenting with neonatal stroke

In all the above cases, the patient should be discussed with the Cooling Centre BEFORE passive or active cooling is started.

2.1 Infants <36 weeks gestation

Infants between 34+0 and 35+6 can be considered for cooling if the infant fits all criteria.

2.2 Infants >6 hours old

Infants between 6 and 24 hours of age may be considered for cooling; however beyond 6 hours of age the benefit from hypothermia is likely to be small.

2.3 Infants presenting with mild encephalopathy

Infants presenting with mild encephalopathy should not currently be considered for cooling. It is however important to ensure that an infant with mild HIE does not develop signs of a more moderate encephalopathy over the first 6 hours of life. Repeated neurological examination is required during this time to assess potential eligibility for cooling. CFM may be helpful.

2.4 Infants with congenital anomalies

Cooling should be considered on a case by case basis depending on the underlying anomaly. The following should be considered:

- Is the condition life-limiting? I.e. would cooling improve the long term outcome?
- Would cooling impact on the anomaly? E.g. cooling may compromise blood flow to the gut in an infant with gastroschisis.
- Would the condition make it harder to assess neurological examination? E.g. a baby with Down's syndrome may be hypotonic as a result of the condition (this does not mean that such a baby should not be cooled, just careful neurological assessment is necessary).

2.5 Infants presenting with sudden unexpected postnatal collapse

Infants presenting with in-hospital postnatal collapse can be considered for cooling. The following should be considered:

- Is there an underlying condition which may be worsened by cooling? E.g. structural cardiac abnormality, intracranial bleeding

2.6 Infants presenting with neonatal stroke

Infants presenting with neonatal stroke could be considered for cooling if the diagnosis is made within 6 hours of birth.

Other Clinical Situations

2.7 The infant whose clinical condition normalises *within* 6 hours of birth

Careful neurological assessment is essential to demonstrate that such an infant does not meet criteria based on neurological examination. If cooling has been commenced it would be reasonable to slowly rewarm the infant if neurological examination and CFM are both normal. These infants should be carefully observed over the next 24 hours.

2.8 The infant whose clinical condition normalises *after* 6 hours of birth

Infants whose are already being cooled but the clinical condition normalises after 6 hours should continue cooling for 72 hours.

2.9 The infant who develops 'rebound' seizures during or following re-warming

Where re-warming is associated with seizures, the process can be slowed or paused until seizure control is achieved. There is no clinical evidence that prolonging cooling to 96 hours improves neurodevelopmental outcome.

Appendix 3. Ongoing management of the cooled infant with HIE

3.1 Monitoring and investigations

1. Double continuous rectal temperature monitoring with alarm limits set within 1°C of the target rectal temperature. Insert rectal probes to 6cm and secure firmly. One rectal probe is to allow the machine to servo-control and the other is connected to monitoring for continuous recording and alarming when out of the target range. Both should be checked for correct placement every hour and placement recorded. If the servocontrol probe is displaced, the cooling machine may start to rewarm the baby to the target temperature, although an alarm will also be activated in the case of a sudden change in temperature.
2. Continuous heart rate, oxygen saturation and invasive BP monitoring.
3. Regular blood gas and glucose analysis to assess metabolic acidosis, adequacy of ventilation and glucose requirements. Temperature-corrected values should be analysed.
4. Fluid balance 6 hourly- measure urine volume by catheter until urine output is normal. Urinalysis in the first 24 hrs following birth.
5. FBC, daily urea and electrolytes, including Ca and Mg at an appropriate frequency for clinical condition. Initial coagulation screen on day of admission and as clinically indicated thereafter.
6. CFM should be continued throughout cooling and re-warming, particularly as non-clinical seizures may occur on re-warming.
7. Neurological examination and encephalopathy score- every 12-24 hours for the first 4 days of life.
8. Cranial ultrasound scan within 12 hours to exclude other causes of encephalopathy, and as clinically indicated thereafter
9. All infants undergoing TH should have a MRI scan undertaken between 5 and 15 days, preferably between 5 and 7 days of birth.
10. Where possible, Proton (1H) MRS Lactate/N acetyl aspartate (Lac/NAA) of the basal ganglia and thalamus should be performed with the MRI at 5-10 days after birth. This is the most accurate predictor of outcome in babies who have undergone TH.
11. Anticonvulsant and aminoglycoside levels as required- there may be delayed metabolism during hypothermia and doses may need to be adjusted on the basis of these results (Appendix 6).

3.2 Ventilation

Cooling does not have any direct effect on respiratory function. Persistent pulmonary hypertension of the newborn or meconium aspiration may coexist with HIE and should be treated with the necessary ventilatory support, including HFOV and nitric oxide if necessary.

- Most babies will require ventilation. A hat should not be used to fixate the ETT.
- Some babies will be able to be extubated halfway through cooling but may require noninvasive support due to sedation and respiratory pathology.
- Ventilator gases should be warmed and humidified in the normal way, according to unit policy.
- Avoid hyperoxaemia and hypocarbia as these are associated with poor outcome. Note that blood gas analysis which does not correct for temperature will overestimate PCO2 and PO2. Hypothermia will reduce respiratory rate as metabolism is reduced. If ventilated it is easy to overventilate as CO_2 production is reduced. Hypocarbia may induce seizures.

- More frequent suction and regular re-positioning might be necessary as secretions become more abundant as cooling duration continues. Decisions about whether to use saline during suction should be made on an individual basis.
- Stridor has been reported in the context of hypothermia with or without preceding intubation. Apnoea is more common particularly if sedation has accumulated or if there are seizures. Both are transient although may require temporary escalation of ventilatory support.

3.3 Positioning and skin care

- Vary the position 6 hourly during care – flat – slightly uptilted – supine, right or left side to avoid pressure sores
- Do not turn the head only but keep nose in body midline to avoid impairment of cerebral blood flow or return.
- Cyanosis of the hands and feet (but not of the central oral mucous membranes) is common initially but settles with time.
- Subcutaneous fat necrosis, is a recognised complication of therapeutic hypothermia in asphyxiated infants. Monitor skin for red painful nodules, and if diagnosed, ensure a plan for regular monitoring of calcium levels over coming weeks.

3.4 Cardiovascular Support

Cardiovascular instability is frequent and manifest as hypotension, metabolic acidosis and pulmonary hypertension. Although some of the pathologic mechanisms associated with asphyxia involve a loss of volume (usually blood), hypovolaemia is not consistently associated with asphyxia initially and in the face of poor myocardial function, volume replacement may worsen cardiac function and inotropic support should be considered early. Cardiovascular support should be directed at improving cardiac contractility and systemic perfusion.

- Use clinical guidelines and assess cardiac function clinically (BP, heart rate) and/or by echocardiogram when choosing volume or drug.
- Electrocardiography and biochemical markers, such as troponin levels, may help in the assessment of myocardial dysfunction.
- Refer to local guidance for management of hypotension.
- Later in cooling infants can become hypovolemic as water is displaced to the interstitial tissue and because hypothermia can induce diuresis. This is particularly common where fluids have been restricted in the prior days and where renal function is not impaired. Volume replacement may be appropriate in this instance.
- During the rewarming process, a rise in body temperature may cause hypotension by inducing peripheral vasodilatation. If hypovolaemia is suspected an initial bolus of 10-20ml/kg of normal saline should be given and repeated if necessary.
- Bradycardia (<100bpm) is normal during cooling as is a prolonged QT interval. It is important to maintain the temperature above 33°C as there is a risk of ventricular fibrillation at lower temperatures. Arrhythmias that may occur during cooling usually resolve with re-warming.
- If there is a rise in heart rate the infant may be distressed, in pain or it may be a sign of sepsis. Consider increasing sedation if pain or distress are suspected.

3.5 Fluid and electrolyte management

Renal function is commonly impaired after asphyxia and weight, creatinine, electrolytes and urine output will guide fluid management. However, be aware that hypothermic patients may need more volume due to redistribution of fluid to the tissue. Although babies may suffer acute renal failure due to the HI insult, cold induces diuresis, and this is often seen after renal function resumes towards the end of cooling. As such babies often need more volume at this stage.

- Babies may require catheterisation to assess urine output accurately.
- Maintenance fluids should start at 40-60 ml/kg/day and fluid balance assessed 6 hourly, with increments in fluids when urine output is adequate.
- Maintain electrolytes in the normal range, including calcium and magnesium levels.
- If there is renal failure, maintenance fluid may be dropped to 30ml/kg/day plus any measured losses
- Ensure blood glucose is kept in the normal range which in the fluid restricted infant may require infusion of higher dextrose concentration (>10%) through central venous access.
- Care must be taken regarding the potential accumulation of nephrotoxic drugs such as aminoglycosides in the event of renal impairment. Consider withholding aminoglycosides until the blood level is known, or change to a non-nephrotoxic alternative such as a cephalosporin (Appendix 6).

3.6 Gastrointestinal

Commencing enteral feeds in infants during therapeutic hypothermia should be considered on an individualised basis taking into account the overall clinical status. Enteral feeds should not be given in infants with significant multisystem derangement where gut perfusion may be compromised. Consideration of parenteral nutrition should be given in view of the initial catabolic state, although where there is significant electrolyte, fluid and glucose imbalance this may be complex.

Early trophic feeding may be beneficial and can be started during cooling but the evidence is limited in this population group. Feed intolerance is common even after re-warming as gut circulation may have been compromised and sedation may slow gut motility. There is an increased risk for necrotising enterocolitis and breast milk is preferable to formula milk. Advice and support for mothers regarding expressing breast milk should be provided early in the course of the infant's management appreciating the impact of acute stress on milk production.

Any baby in whom there are concerns with swallow or suck following rewarming should be assessed by a Speech and Language Therapist for suitability for oral feeding. For other babies with intact gag and suck reflex, oral feeds can be introduced by either breast or bottle.

3.7 Impaired synthetic liver function/consumptive coagulopathy

If a baby starts hypothermia treatment with normal clotting, a 3.5°C reduction in temperature will affect coagulation only moderately (~30% prolongation) and function should remain within normal limits. A reduction in the production of clotting factors and platelets is seen with hypothermia resulting in prolonged coagulation, this is physiological. In the absence of bleeding, mild derangement of coagulation can be tolerated without treatment.

It is likely that hypothermia has a significantly adverse effect on clotting if the patient starts out with abnormal coagulation. Be aggressive in checking coagulation and treating deranged clotting when there is a suspicion of bleeding, for example from cord or on cranial USS.

Any drug metabolised by the liver has prolonged metabolism in hypothermia especially morphine and phenobarbitone. Avoid continuous infusions of paralytic agents or anticonvulsants where possible, using boluses as an alternative (Appendix 6).

3.8 Infection

Perinatal infection often co-exists with HIE. All babies should have a septic screen and be commenced on antibiotics (as per local policy) as soon as possible after birth. It is important to consider viral infections such as herpes simplex, and meningitis.

Note that renal impairment may affect aminoglycoside clearance and that it is advisable to be cautious about toxicity if urine output is low (Appendix 6).

Note that it is normal to observe a fall in white cell and platelet counts during cooling, as well as a rise in CRP.

Hypothermia is not associated with an increased risk of infection in newborn infants. However ventilated babies do need regular ET suction to clear secretions and regular positioning to avoid skin breakdown. The presence of central venous and arterial lines increases the risk of bloodstream infection.

3.9 Neurology

3.9.1. Seizures

Clinical seizures following HIE can be difficult to diagnose and treat. Many seizures are subclinical and only a quarter of suspected seizures have an electrical correlate. On the other hand two thirds of electrographic seizures do not have overt clinical signs. True seizures secondary to hypoxia-ischaemia are uncommon in the first 6 hours of life and the treatment of presumed seizures within the first 6 hours will alter the neurological examination and may impair robust decision-making about the suitability of a child for therapeutic hypothermia. Other abnormalities of neurological behaviour such as tremulousness, cycling, paddling movements and oromotor dyskinesia are very common and do not require anticonvulsant treatment. As such it is recommended that treatment of seizures only occurs following confirmation on CFM.

All infants undergoing cooling should have continuous CFM monitoring as subclinical seizures are common and may be the only evidence of abnormal electrical activity if the baby is muscle relaxed, or even following anticonvulsant therapy. Symptomatic seizures or where the total electrical seizure (aEEG/EEG) burden within 1 hour is 10 minutes or longer should be treated with anticonvulsants. Seizures may re-emerge on re-warming and CFM monitoring is advised until normothermia is reached. If seizures occur during re-warming, hypothermia to 33.5°C can be re-induced for a further 24 hours and a slower rate of re-warming commenced (<0.5°C/hour).

For treatment of seizures, refer to local guidelines on seizure management.

Ensure that ventilation and cardiovascular status are stable and monitored before giving anticonvulsant therapy. Anticonvulsant therapy should be given intravenously to achieve a rapid onset of action and predictable blood levels. Drug levels are important when maintenance doses of these drugs are used. Slow elimination rates secondary to cooling, hepatic and/or renal injury may lead to drug accumulation and suppressed neurological activity on examination and background activity on CFM (Appendix 6).

Hypothermia may decrease the amplitude of seizures and seizure burden- possibly due to earlier detection and earlier treatment but does not affect background activity.

Note that Lidocaine should not be given if Phenytoin has already been given due to similar arrhythmogenic effects and that specific dosing schedules have been published for infants undergoing therapeutic hypothermia (Appendix 6). Other causes of intractable seizures in neonates should be considered, e.g. Pyridoxine deficiency and other inborn errors of metabolism.

3.9.2. Electroencephalography (EEG)

A formal EEG provides information on regional background cerebral activity and can detect some seizures and other abnormalities not seen using aEEG. However access to neurophysiology services both to perform and interpret the examination can be limited. The most useful prognostic information can be obtained once the infant has been rewarmed and off anticonvulsant medication.

EEG may also be important in the following circumstances:

- If needed clinically to confirm or exclude electrical seizures
- Where aEEG background has not returned to normal at end of cooling
- Continuing clinical concern about encephalopathy after the period of cooling

3.9.3. Cranial ultrasound Scans (CUSS)

Cranial ultrasound scans can provide vital information on infants with HIE. The diagnosis of HIE can be complicated, and other disease processes may present in a similar way such as neonatal stroke. For this reason, a cranial USS should be performed in any infant with suspected HIE, ideally prior to their transfer to a Cooling Centre. Refer to local guidance for image acquisition and interpretation.
Scans should be performed on admission and then daily for the first three days of life.

Possible USS Findings in HIE

- Early cerebral oedema – generalised increase in echogenicity, indistinct sulci and narrow ventricles, loss of normal tissue differentiation
- After 2-3 days of age, increased echogenicity of thalami and parenchymal echodensities
- Haemorrhage
- Relative increase of end-diastolic blood flow velocity compared to peak systolic blood flow velocity (Resistive Index <0.55) in anterior cerebral artery predicts poor outcome.

3.9.4. MRI

All infants undergoing TH should have an MRI scan undertaken between 5 and 15 days, preferably between 5 and 7 days of birth. This is best performed in the treating NICU and should be reported by a consultant radiologist with expertise in neonatal brain MRI interpretation. Where possible, Proton (1H) MRS Lactate/N acetyl aspartate (Lac/NAA) of the basal ganglia and thalamus should be performed with the MRI at 5-10 days after birth. This is the most accurate predictor of outcome in babies who have undergone TH.

3.9.5. Analgesic and sedative therapy

All babies should receive analgesia and sedation as being cold is stressful and unpleasant. There is some evidence that in the absence of sedation, hypothermia may not be neuroprotective A persistently high heart rate, shivering and facial grimacing may all indicate that a baby is experiencing discomfort and it is not unusual for babies to require an increase in

sedation dose. It is important to assess regularly whether the baby is irritable, shivering or has clonus. Shivering has been shown to reduce the neuroprotective effects of cooling and so sedation should be considered to minimise this. Sedation should not be withheld to avoid respiratory depression which can be easily supported with ventilatory adjuncts.

Sedation should be provided with morphine prior to inducing hypothermia and continuing thereafter. Consider whether infusion rate should be reduced after 24-48hours to lessen the risk of toxicity and accumulation as the metabolism of morphine is reduced during hypothermia (Appendix 6). At 48 hours, discontinuation of morphine should be considered. Morphine should be made up in 10% dextrose to avoid hypoglycaemia.

Chloral hydrate may also be given as an adjunct to morphine or as an alternative in non-ventilated babies. There is also a risk of over-sedation due to accumulation. Infants may need ventilatory support following sedation (Appendix 6).

Monitoring of pain and distress
Heart rate is a good proxy marker for adequate sedation. At 33.5°C, the average heart rate is around 80-100 bpm. The heart rate changes by 14 beats per minute per 1°C change in temperature over a wide range.

If HR is high (>120bpm) despite hypothermia, the reasons may include distress and/or pain, hypovolaemia, hypotension, inotrope use, seizures.

NB if the heart rate is lower than 80bpm, this suggests the baby may be overcooled and the position of the temperature probes should be checked immediately. It may also mean that the baby is overly sedated with morphine or anticonvulsants and the doses of these should be reduced.

Appendix 4. Parent Information Leaflet. Hypoxic Ischaemic Encephalopathy in the Newborn

Parent Information leaflet
Hypoxic Ischaemic Encephalopathy in the Newborn

Introduction
Having a baby affected by Hypoxic Ischaemic Encephalopathy is very stressful for families. The team looking after your baby will keep you up to date with your baby's condition and explain what is happening. This leaflet gives you some background information but will not be able to say what will happen with your baby in detail. The medical and nursing teams will answer any questions so please ask.

What is Hypoxic Ischaemic Encephalopathy?
This is a term that we use to describe the way a baby behaves (encephalopathy) caused by a lack of oxygen (hypoxic) and blood flow (ischaemic) to a baby's brain. It is known as HIE for short.

HIE can affect newborn behaviour in many ways. A baby may be floppy and less alert than normal. They may need help with their breathing and seizures (also known as fits) may occur. Other babies can be jumpy or restless and appear more alert then usual.

As well as the brain, other organs such as the kidneys, liver and heart can be affected by the lack of oxygen. These organs will also be monitored carefully.

Why has this happened?
In the womb, oxygen reaches your baby through the placenta (afterbirth) and umbilical cord. HIE can occur if there has been a major problem with this oxygen supply in the womb. This might happen if the placenta comes away from the wall of the womb or the umbilical cord becomes entangled. Often the problem is not clear at the time of birth. Sometimes there is more information from having the placenta examined by a specialist in the coming weeks. The team looking after your baby will keep you informed about this. It may also help to discuss your labour and delivery with your obstetrician.

What treatment will be required?
Babies with HIE are cared for in the Neonatal Intensive Care Unit. This allows close monitoring of heart, lung, kidney and brain function, and supporting these where needed. This may involve your baby being on a ventilator, having "lines" (thin tubes) into their umbilicus (belly button) and bladder, and being attached to a brain monitor.

Babies with HIE are often cooled for the first three days of life. This involves carefully lowering a baby's temperature from the normal temperature of 37ºC (98.6ºF) to a temperature of 33.5ºC (92.3ºF). A normal body temperature is 37ºC. Cooling is started as early as possible after birth. Pain relief will be given to prevent your baby feeling discomfort during cooling. At the end of the treatment the baby's temperature is slowly returned to normal. This period of cooling gives the brain a chance to recover from the injury. This is effective in some but not all babies. It has been shown to be a safe treatment with very few side effects. During the first few days you may not be able to hold your

baby because of the amount of monitoring equipment and the need to keep the body temperature very stable. You will still be able to touch and talk to your baby and take part in cares, such as nappy changing and washing. If you are planning to breast feed you can express your milk and this can be given to your baby once they are well enough to digest it.

Will my baby be OK?
This is the most important question for families and often the hardest to answer. We know that each baby is different and predicting how any one baby may get on can be difficult.

Some babies do go on to make a full recovery. Other babies may develop disability as they grow up, which can range from very mild to severe. Some babies show such severe injury after birth that they do not survive.

We understand that families want to know as much as they can, and as we gather information we will discuss this with you.

The information that we collect includes monitoring of your baby's behaviour and brain waves, and if and how both of these recover. An MRI scan is usually done in the second week of life but even a scan will not be able to give an accurate prediction. Any baby affected with HIE who has received cooling treatment will be seen regularly in clinic over the first two years of life, where we will monitor your baby's progress and make sure that any extra help required is available as soon as possible.

What happens afterwards?

Once the cooling is over, the lines and monitoring can be removed, and your baby will be nursed in a normal cot, depending on how well your baby is. Your baby will then need some time to learn to feed and continue recovery in hospital. Your baby will be discharged home when you and the staff think that your baby is ready. Once you are home you will be seen regularly by the team from your local hospital who will be able to answer any questions about your baby's progress.

Is there anything I should look out for?
Your baby's feeding and weight gain will be monitored as is usual with any newborn baby.

One rare complication of cooling that can occur is injury to the fat tissue in the skin. This causes red painful lumps in the skin in the first two months after cooling. These lumps will go away without lasting damage to the skin, but may result in high levels of calcium in the blood. High calcium levels can cause dehydration and sometimes injure the kidneys, so this will need correction.

The skin changes may not be seen straight away. Your baby may be more sleepy or floppy or restless. Your baby may not feed as well and lose weight or not gain weight as quickly as expected. There may be vomiting or constipation. If you are concerned that your baby may be affected by any of these problems you should contact the team that are caring for your baby.

Further information
If you wish to discuss anything about your baby's treatment, please speak to the doctor or nurse on the neonatal unit.

Appendix 5. Support for families

Organisation	Description
BeBop	A resource for parents about HIE, hypothermia and neuroprotection http://bebop.nhs.uk/families
Birth Trauma Association	Helping people who are finding it hard to cope with their childbirth experience www.birthtraumaassociation.org.uk
Bliss	For babies born too soon, too small, too sick –providing vital support and advice to families of premature and sick babies across the UK. Helpline: 0808 801 0322 www.bliss.org.uk
Child Bereavement Trust	They provide specialised support, information and training to all those affected when a baby or child dies, or when a child is bereaved. www.childbereavementuk.org
Newlife	Offers practical support for disabled children throughout the UK, cares for the carers, funds medical research, creates awareness and campaigns for change www.newlifecharity.co.uk
PEEPS-HIE	Provides peer support and equipment funding forfmaililes affected by HIE http://www.peeps-hie.org
SANDS	A stillbirth and neonatal death charity – supporting anyone affected by the death of a baby and promoting research to reduce the loss of babies' lives www.sands.org.uk
Scope	A charity that supports disabled people and their families through practical information and support, particularly at the time of diagnosis www.scope.org.uk
Together for Short Lives	Charity working to ensure that all children and young people, unlikely to live to reach adulthood, and their families get the best possible care and support whenever and wherever they need it www.togetherforshortlives.org.uk

Appendix 6. Effect of hypothermia on medications (modified from Neonatal Formulary 2019)

Neonatal units should follow their local guidance/monographs pertaining to specific drug dosages. The following table delineates the known or expected effects of hypothermia on medications and as such, neonatal units may wish to modify local guidance taking the following information into account.

Drug	Effect of Therapeutic Hypothermia (TH)	Suggested dose adjustments during hypothermia
Antibiotics		
Beta-lactams	Pharmacokinetics not studied. Unlikely that TH has any effect.	No adjustment necessary.
Gentamicin	Unclear as coexisting renal injury may be present. Hearing impairment is present in 10% of infants who have undergone TH. Newborn data suggests there may be a 25-33% reduction in clearance.	Consider decreasing dosing frequency to once every 36 hours. Measure levels and consider withholding dose until level is known if renal impairment is present.
Vancomycin	No data in infants. No effect in adults.	No adjustment necessary.
Sedatives		
Morphine	The affinity of morphine for the opioid receptors is reduced in hypothermia rendering it less effective, and secondly, clearance is reduced.	50 micrograms/kg loading dose followed by an infusion started at 10-20 micrograms/kg/hour, titrating rate to the response of the infant. If adequately sedated, the dose should be reduced after 24- 48 hours to lessen risk of accumulation and toxicity.
Fentanyl	Hypothermia can lead to a 25% increase in plasma fentanyl concentrations. There are insufficient data from hypothermic newborns to recommend any specific schedule; however, it would seem prudent to begin by halving the 'normothermic' dose.	Give loading dose of 5 microgram/kg and then infuse at 0.75microgram/kg/hour. Titrate according to the response of the infant. Consider reducing at 24- 48 hours to lessen the risk of accumulation and toxicity.
Chloral hydrate	No data. Metabolised by liver. Potential risk of accumulation with repeated doses.	Consider starting at lower recommended dose. Ensure monitoring and access to respiratory support in non-ventilated patients.

<table>
<tr><th>Drug</th><th>Effect of Hypothermia</th><th>Suggested dose adjustments during hypothermia</th></tr>
<tr><td colspan="3">Anticonvulsants</td></tr>
<tr><td>Phenobarbital</td><td>Reduced metabolism by liver enzymes in TH may prolong half life two fold. Suppresses EEG and indices of neurological examination.</td><td>Give loading dose of 20mg/kg, and if required a further loading dose of 10-20mg/kg. Avoid maintenance.</td></tr>
<tr><td>Phenytoin</td><td>Levels higher in adults during TH due to reduced liver enzyme activity.</td><td>Give loading dose of 20mg/kg and monitor levels. Avoid maintenance dosing.</td></tr>
<tr><td>Midazolam</td><td>Levels higher during TH due to reduced liver enzyme activity. In cooled adults, levels are 5 fold higher. Cleared quickly during re-warming.</td><td>Dosing not established in neonates. Ensure monitoring and access to respiratory support in non-ventilated patients.</td></tr>
<tr><td>Clonazepam</td><td>No data. It is likely that levels will be higher during TH due to reduced liver enzyme activity.</td><td>Dosing not established in neonates. Ensure monitoring and access to respiratory support in non-ventilated patients.</td></tr>
<tr><td>Lidocaine</td><td>Lidocaine is metabolised by liver enzymes and during hypothermia clearance is reduced by 24%. Main adverse effects relate to arrhythmias which have been reported in neonatal TH. A modified regimen has been suggested.</td><td>
<table>
<tr><th></th><th colspan="2">Loading phase</th><th>Maintenance phase #1</th><th>Maintenance phase #2</th></tr>
<tr><td>Duration</td><td>10m</td><td>3.5h</td><td>12h</td><td>12h</td></tr>
<tr><td>Wt 2-2.5kg</td><td rowspan="2">2.5mg/kg</td><td>6mg/kg/h</td><td>3mg/kg/h</td><td>1.5mg/kg/h</td></tr>
<tr><td>Wt≥2.5kg</td><td>7mg/kg/h</td><td>3.5mg/kg/h</td><td>1.75mg/kg/h</td></tr>
</table>
</td></tr>
<tr><td colspan="3">Topiramate and Levetiracetam are included in this monograph as they have been reported to be among the drugs more commonly used off-label in neonates with seizures; inclusion should not be taken to imply that these drugs are now recommended.</td></tr>
<tr><td>Topiramate</td><td>Very limited data from infants undergoing hypothermia suggest a slower absorption and elimination. Oral preparation only.</td><td>5 mg/kg on the first day and then a lower dose (3 mg/kg daily) for the next 2 days</td></tr>
<tr><td>Levetiracetam</td><td>Predominantly renal excretion of levetiracetam means that TH should not impact on dosing; excretion may be affected by renal impairment.</td><td>40mg/kg loading dose followed by 10mg/kg once daily.</td></tr>
</table>

Drug	Effect of Therapeutic Hypothermia (TH)	Suggested dose adjustments during hypothermia
Neuromuscular blockers		
Pancuronium	Primarily excreted by the kidneys, with some biliary excretion. Studies in hypothermic adults show an initial increased requirement during early stages of hypothermia and then, when hypothermia is established, increased plasma concentrations. No data in neonates.	No dose adjustment necessary. The baby may seem to require more frequent dosing initially but once hypothermic the duration of action may be longer.
Vecuronium	Primarily eliminated via liver metabolism. Risks of accumulation increase during hypothermia particularly with infusions.	No initial dose adjustment is necessary but titrate the dose after 6–12 hours according to the need. Avoid infusion if possible.
Inotropes		
Adrenaline	There is no evidence to suggest that a different dosing strategy for inotropic support is needed during neonatal therapeutic hypothermia.	No dose adjustment necessary. Titrate according to response
Dopamine	As above	No dose adjustment necessary. Titrate according to response
Dobutamine	As above	No dose adjustment necessary. Titrate according to response
Milrinone	Limited data. Largely excreted unchanged in urine and is not likely to be affected by cooling but renal impairment reduce clearance.	No dose adjustment thought to be necessary. Titrate according to response.

Appendix 7. Individuals and organisations involved in production and endorsement

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