



# British Association of Perinatal Medicine

## Therapeutic Hypothermia for Neonatal Encephalopathy

### A BAPM Framework for Practice For Consultation

Consultation period 22 June – 22 August 2020

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Throughout this document (\*) – represents consensus view

## Executive summary

Therapeutic hypothermia with intracorporeal temperature monitoring (TH) for moderate to severe neonatal encephalopathy (NE) is effective in improving outcomes and shows clear cost benefit.

TH should be instigated in infants who have evidence suggesting significant perinatal hypoxia – ischaemia and significant neonatal encephalopathy on clinical examination. Additional use of amplitude integrated electroencephalogram (aEEG) is strongly encouraged; because confirmation of abnormality would confirm treatment eligibility.

The decision to undertake TH should be prompt and made by a practitioner who is competent in the assessments necessary to establish whether or not a baby meets the criteria for TH. If there is uncertainty, early discussion with the local cooling centre is recommended.

Neonatal encephalopathy evolves with time. Therefore, babies who meet any of the criteria for significant perinatal hypoxia but on initial neurological examination are normal, should be reviewed several times in the first 6 hours of life by a trained practitioner who is competent in neonatal neurological examination.

Early open and honest communication by senior members of the neonatal team with the parents is essential. There should be no barriers to parents visiting and caring for their baby. TH is an intensive care activity and ongoing TH treatment should only be undertaken in appropriate neonatal intensive care units (NICUs).

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.

Neonatal networks should facilitate the provision of equipment and training on the recognition of NE and instigation of TH. They should undertake regular network wide audit and benchmarking activity.

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## Introduction

This Framework for Practice aims to expand and update the previous BAPM Position Statement on Therapeutic Hypothermia (TH) for Neonatal Encephalopathy (NE) (2010) in the light of newer research and evolving clinical practice in the UK. The investigation, management and treatment of NE is a very important area of practice with potential lifelong implications for babies and families. Reduction in neonatal brain injury is a key national objective and a number of strategies have been implemented to support this (1) (2) (3) . The role of this working group was to develop a Framework for Practice which can be used as a basis for network and local guidelines.

Perinatal asphyxia severe enough to cause neonatal hypoxic-ischaemic encephalopathy (HIE) occurs in approximately 1/1000 – 3.5/1000 births in the UK (3) (4). Without TH the risk of death or severe handicap in survivors of moderate or severe HIE is approximately 25 and 75% respectively, and children with and without motor impairments have lower cognitive scores on long term follow-up, poorer scholastic attainment in independent National Attainment Tests, and often need educational support. Perinatal hypoxia-ischaemia thus creates a major burden for the individual, the family and for society.

Until the publication of trials of TH beginning in 2005, no specific treatment for HIE was available. Systematic review has since confirmed that 72 hours of cooling to a core temperature of 33-34°C started within six hours of birth reduces death and disability at 18 months of age and improves a range of neurodevelopmental outcomes in survivors (5).

Therapeutic hypothermia with intracorporeal temperature monitoring is declared to be a standard of care in the NHS (6). Since the previous position statement long-term follow up has now assessed neurodevelopmental outcome, health related quality of life and economic costs, confirming a persistent beneficial effect (7) (8) (9). With current practice of TH, mortality due to HIE has reduced from 25% in the clinical trials to 9% and disability from 20% to around 16% with a reduction in the rate of cerebral palsy, although some of this improvement may be due to the use of hypothermic therapy in some infants with less severe brain injury (10)(11). However, not all children benefit from treatment and some level of intellectual impairment may remain even in the absence of cerebral palsy (12).

There have been more recent studies of longer, deeper or later hypothermic therapies, and also the value of MRI and MRS as prognostic tools. There is also evidence that some less severe cases of HIE are now receiving treatment. The aim of this updated framework is to provide recommendations and guidance.

**Of note:** (a) therapeutic hypothermia without intracorporeal temperature monitoring is not recommended by NICE; and (b) moderate to severe encephalopathy remains the only evidence proven indication for therapeutic hypothermia in the newborn period in 2020; other indications are essentially experimental.

This framework therefore focusses on TH with intracorporeal temperature monitoring and its indications.

## Case selection – eligibility

This framework suggests that TH treatment is instigated in babies who meet the criteria outlined in the TOBY study. This involves meeting three criteria: At least one 'A' criterion indicating significant perinatal hypoxia-ischaemia, fulfil 'B' criterion representing the presence of significant neonatal encephalopathy, and at least one 'C' criterion showing seizures or abnormal background activity on amplitude integrated electroencephalography (aEEG) . (13)

**A.** Infants >36 completed weeks gestation admitted to the NICU with at least one of the following:

- Apgar score of <5 at 10 minutes after birth
- Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth (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

Infants that meet criterion A will be assessed for whether they meet the neurological abnormality entry criteria (B) by trained personnel:

**B.** Moderate to severe encephalopathy, consisting of 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

Infants that meet criteria A & B will be assessed by aEEG (read by trained personnel):

**C.** At least 30 minutes duration of amplitude integrated EEG recording that shows abnormal background aEEG activity or seizures. (see notes below) There must be one of the following:

- normal background with some seizure activity
- moderately abnormal activity
- suppressed activity
- continuous seizure activity

## Notes on the practical application of TOBY criteria

The term “continued need for resuscitation including mask or endotracheal ventilation” does not include infants who are receiving PEEP or CPAP alone.

Neonatal encephalopathy evolves with time. Therefore, infants who meet at least one A criterion but on initial examination are neurologically normal should be reviewed several times in the first 6 hours of life by a trained practitioner who is competent in neonatal neurological examination. (\*)

It is also recognised that aEEG may not be available in all circumstances, and failure to obtain aEEG should not prevent or delay treatment if there is evidence from A and B criteria.

The decision to undertake TH should be prompt and made by a practitioner who is competent in the above assessments and their interpretation. It should always be discussed with a consultant and with the baby’s parents unless this is not physically possible. There should be early discussion with a network NICU and, where appropriate, network transport services. Management must involve continuous rectal temperature monitoring and is best delivered using a servo controlled total body cooling mattress or jacket. (\*)

## Therapeutic Hypothermia for Neonatal Encephalopathy

### A BAPM Framework for Practice

There is a tension between evidence that the benefit of TH is increased the earlier that it is initiated (14), and the concept that it would be better not to cool infants whose later review would suggest that TH was not indicated, or that the initiation of TH might distract attention from the important task of stabilisation. This uncertainty, combined with variation in skill-mix and staffing between networks might lead to a small variation in local guidelines and practice based on this framework. (\*)

aEEG (or cerebral function monitoring, CFM) is a very helpful tool for obtaining evidence of cerebral depression and in the ongoing management of these infants, including prognostication and recognition of seizures (15). Using it as part of assessing eligibility may reduce the number of babies cooled unnecessarily. It may be clear after only 10 min of monitoring that the criterion C has been met. However initiation of cooling in infants who are clearly neurologically abnormal should not be delayed awaiting aEEG data. Practitioners should be trained in the use and interpretation of aEEG which should be coordinated at network level. The aEEG should be used to monitor cerebral depression and seizure activity throughout the cooling process and until the end of rewarming. (\*)

Clinical seizures should only be treated if there is electrical correlation on aEEG. If aEEG is not available, then there should be a discussion with a network NICU consultant prior to treatment as antiepileptic treatment can affect neurological examination and aEEG and may therefore impair decision- making about eligibility for TH. (\*)

Hyperthermia is associated with increased brain injury in animal models of hypoxia- ischaemia (16) and in infants who were not cooled for HIE (17). It therefore must be avoided in all infants while they are being assessed for or undergoing TH.

Infants starting any form of TH, including switching the resuscitaire heater off, should have their temperature continuously monitored ideally using an intracorporeal (e.g. rectal) temperature probe. Cooling should only be considered once cardiorespiratory stability has been achieved including heart rate and oxygen saturation. (\*)

If infants are maintained with passive hypothermia (removal of external heat sources and clothing) while full assessment is undertaken, they must be continuously monitored with rectal temperature, and prevented from cooling below 33.5 C using a servo-controlled system if necessary. Alternatively, if the aim is normothermia but that requires an incubator then continuous rectal temperature should be used to prevent overheating. (\*)

At sites where there is no on site paediatric services, such as stand-alone midwifery led units and home confinement, it is recommended that staff are trained in the importance of identifying infants who might benefit from TH. However TH should not be initiated in these settings and infants should be transferred along the normal referral pathway for sick infants. This transfer should be undertaken as an emergency so that treatment can be started within 6 hours. There should be a focus of maintaining normothermia, avoiding hyperthermia, maintaining airway breathing, oxygenation with pulse- oximetry monitoring and regular clinical observations including axillary temperature and blood glucose assessment. Network transfer services need to take account of local hospital capabilities and individual patient needs when assessing transport response times. All transport services should be able to provide active servo-controlled cooling treatment in both the referring unit and during transportation. (\*)

Clinicians should seek to make an early, accurate diagnosis of encephalopathic infants recognising that the differential diagnosis of infants presenting with encephalopathy is wide.

### **Parent / carer communication**

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.

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 well-being of siblings and the wider family.

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 (18).

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. (\*)  
All parents whose child has died following intrapartum hypoxia-ischaemia should be offered a post mortem examination.

## Infants who fall outside of current criteria

### Infants identified between 6 and 24 hours

There is only modest evidence that initiating therapeutic hypothermia in infants diagnosed with presumed hypoxic-ischaemic encephalopathy between 6 and 24 hours might be of benefit (19). The only clinical trial examining this question failed to complete, and an interim analysis of the data did not reach conventional levels of statistical significance. Every effort should be made to identify and diagnose infants as soon as possible, but in rare cases where this does not happen within 6 hours, in the absence of evidence of harm or other available treatments, clinicians may decide to administer hypothermia in this context.

Cooling for longer periods (120 hours) or lower temperatures (32°C) does not improve outcomes and evidence indicates that such a strategy is associated with higher mortality (20).

### Infants less than 36 weeks gestation

There is currently no randomised controlled trial evidence to support the use of TH in infants less than 36 weeks. Many cooling centres have offered TH to selected infants from 33-35 weeks and have published non controlled case series (21) in which the possibility of higher risk of complications including hyperglycaemia, death and brain injury exists (22). TH for these infants should only be undertaken after careful consideration including seeking a second opinion from an experienced consultant and detailed discussion with the parents including explaining the risks of TH which may be increased in such late preterm infants, and the limitations of the evidence suggesting benefit. The basis and outcome of these discussions should be clearly documented. There is an ongoing trial of TH in preterm infants in the US with initial results expected in 2022.

### Sudden Unexpected Postnatal Collapse (SUPC)

There is currently no randomised controlled trial evidence to support the use of TH in infants who have signs of moderate or severe encephalopathy following a postnatal collapse, and given the rarity of this condition high-quality trial data is unlikely to become available. However, many animal models of neonatal hypoxic-ischaemic encephalopathy that demonstrate the effectiveness of TH involve a postnatal insult. Moreover a cohort study indicated that the outcomes of infants cooled following postnatal collapse are similar to that of infants cooled for presumed HIE, providing circumstantial evidence that TH might be of benefit (21). As the underlying conditions leading to SUPC are varied, including conditions in which TH may carry adverse risks, it is recommended that every effort is taken to understand any underlying reasons for collapse preferably before TH is initiated. It is recommended that decision-making involves a second senior person, and that the decision is taken in conjunction with the parents with an explanation of the potential risks and benefits.

### Mild neonatal encephalopathy

There is no clear agreed definition of mild neonatal encephalopathy, which is commonly based on one or two identified features in a standardised neurological test as well as features suggesting perinatal hypoxia-ischaemia. There is some evidence that there may be increased neurological morbidity in this group of patients (23). However in the absence of any evidence of benefit, TH for the treatment of mild HIE is not recommended outside clinical trials (24).

## Investigations

Consider other diagnoses that can present with signs that overlap with HIE and investigate appropriately.

All infants undergoing TH should have a cranial ultrasound within 12 hours to exclude some other causes of encephalopathy other than intrapartum hypoxia-ischaemia. (\*) Cranial ultrasound is less sensitive than MRI for the detection of small or subtle problems (e.g. focal arterial infarction).

## MRI and MRS

There is strong evidence that magnetic resonance imaging (MRI) and spectroscopy (MRS) are reliable predictors of neurological outcomes in infants treated with therapeutic hypothermia, and provide parents and follow-on services with information to help plan ongoing care (25)(26)(27)(28). The use and interpretation of both MRI and MRS requires specialist equipment and skills, and NICU units undertaking TH should ensure access to appropriate facilities and expertise.

All infants undergoing TH should have a MRI scan undertaken between 5 and 15 days, preferably between 5 and 7 days of birth. This would best be performed in the treating NICU and should be reported by a consultant radiologist with expertise in neonatal brain MRI interpretation (29). 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 (27)(28).

### **Network and transport implications**

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. This should be coordinated at Network level (\*).

Ongoing care of the cooled infant is an intensive care activity and should only be undertaken in NICUs (29). Commencing TH and/or neurophysiological assessment with aEEG, in a SCU or LNU, must not delay transfer.

Infants in whom TH has been initiated should be transferred to the appropriate NICU by an established transport service with ongoing servo controlled cooling, ongoing intensive care monitoring including rectal temperature and aEEG monitoring. These uplift transfers should be prioritised according to clinical need and follow local and national transport service guidance regarding timeliness of transfer (30).

Network NICUs should explore the electronic networking of aEEG monitors to allow remote review and the use of telemedicine to support decision-making in referring units (\*). Networks should have network wide clear pathways of care, informed by guidelines based on this framework (\*).

Networks should monitor, audit and benchmark the incidence of TH, using consistent definitions, and investigate trends or outlier status which are unexpected (\*).

## **Nursing Care**

All nursing staff involved in the care of infants and their families receiving TH should have received additional training regarding the equipment required and the implications of this treatment. This should be supported by networks to encourage supportive working across services within a region.

Additional documentation and resources should be available including checklists and troubleshooting for LNU and SCU services to support teams in initiating safe and effective TH care, where the incidence of cases is low, and cases are transferred to NICUs for ongoing treatment.

Support of the family during this time is crucial with consistent open and honest communication. Offering family integrated care where possible should be encouraged.

## 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 (31). In general MRI and 1H MRS are most valuable where prognosis is uncertain (28).

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 (27).

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 (32).

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 included in Appendix 1.

### Reorientation of care

Given the nature of severe neonatal encephalopathy and associated multi-organ pathology there will be some infants for whom the reorientation of care to a palliative pathway is appropriate (33).

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 (34).

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 confused by drug effects.

### Follow-up

All infants undergoing therapeutic hypothermia must be offered a standardised neurodevelopmental assessment such as the Griffiths, Mullen or Bayley assessments at two years of age. (\*)

Babies in high and medium risk groups should have early assessments with experienced medical and/or Paediatric Allied Health Practitioners. This should be aimed at early detection of developmental problems with early intervention, in order to optimise outcomes. (\*)

## Governance

There should be timely multidisciplinary and multispecialty review, following standardised Trust risk management procedures, of the perinatal care 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.

There should be peer review of all cases that are assessed for possible TH, including clinical details, aEEG and neuroimaging where available. There should be multidisciplinary review of all infants who have undergone TH to assess opportunities for prevention of NE, appropriateness of TH and timeliness of its initiation. This process should include mechanisms for dissemination of learning. (\*) Electronic aEEG files, as well as MRI scans should be stored in compliance with the Data Protection Act, in ways that can be easily retrieved if later case review is needed. (\*)

There should be regular audit against standards identified in guidelines created from this framework.

There should be annual review and benchmarking, using consistent criteria and definitions, of TH and NE cases across network units. It is recommended that a consistent definition of hypoxic-ischaemic encephalopathy is used for diagnostic, treatment, documentation and audit purposes, whether or not a baby has received therapeutic hypothermia, not least because it is distressing for parents if the term is included in a discharge summary without valid indication. Inconsistent definition or application of definition may account for some of the variation seen in audits.

There should be formal logs of training and competence in the key skills of standardised neurological examination and its interpretation, and in aEEG interpretation. (\*)

There should be clear, contemporaneous and complete documentation of decision making and management of cases where TH has been considered and initiated or not initiated including regular review of neurology and aEEG in the patient record. This should include documentation of discussions with parents. Given the proven benefit of TH and its safety, formal written parental consent is not considered necessary, but it is important that parents are as fully informed as possible and their views taken into account. (\*)

## Future research

The management of neonatal encephalopathy is an area of active research particularly investigating adjuncts to improve outcomes further.

It is strongly recommended that clinical teams seek to enrol infants into such multicentre randomised controlled trials as they arise. (\*)

Units are encouraged to undertake or contribute to research into other aspects of the management of NE patients, including evaluation of baby wellbeing and parent experience.

## Appendix 1. Magnetic Resonance Imaging and Spectroscopy

### Preparation

- Appropriate clinical supervision with monitoring of vital signs is mandatory during imaging.
- The majority of infants can be successfully imaged following a feed or whilst sedated for ventilation.
- A complete metal check must be made just before transporting the baby into the magnet room with particular attention to specific neonatal items such as arterial lines with terminal electrodes, electronic name tags and metal poppers on clothes.

### Magnetic Resonance Imaging

- Timing of imaging: In general aim to image between 5 and 15 days after birth. Magnetic Resonance Imaging (MRI) within the first few days may give information to plan management but be prepared to repeat if a day 1 or 2 scan is normal in an infant with clinical signs of encephalopathy. Imaging during the second week provides maximum information about the pattern of injury and the clinical outcome.
- Diffusion imaging may detect abnormalities earlier than conventional MRI.
- Severe acute injury, for example placental abruption, is usually associated with abnormalities in the basal ganglia–thalamic (BGT) region and the posterior limb of the internal capsule (PLIC). There may be additional lesions in white matter and the brain stem in severe cases. Associated hippocampal lesions are best seen during the second week.
- Marked white matter and cortical changes may suggest a more chronic and possibly repetitive injury.
- Early diffusion weighted imaging should detect white matter infarction and is particularly useful for neonatal stroke.
- The nature of the abnormal outcome can be initially determined by the extent of basal ganglia–thalami injury. In the absence of lesions within the basal ganglia and thalami the site and extent of white matter injury is important.

### Magnetic Resonance Spectroscopy

- Peak area ratio of (Lac)/(NAA) acquired from proton Magnetic Resonance Spectroscopy (MRS) between 5-15 days after birth is a good indicator of the severity of deep grey matter injury and accurately predicts neurodevelopmental outcome at 18-24 months.

### Field Strength

1.5 and 3.0T MRI are both appropriate and validated for clinical imaging. 3.0T is best for MRS.

### Pulse Sequences

The neonatal brain has a higher water content (92–95%) than the adult brain (82–85%) and so T1 and T2 values are greater. This means that echo times (TE), repetition times (TR) and inversion times (TI) have to be increased. The following are suggested pulse sequences that have been widely used in clinical practice and trials:

#### 1.5T pulse sequences

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Sequence name	Sequence type	TR (ms)	TI (ms)	TE (ms)	Slice thickness (mm)	Orientation
T2 weighted	Fast Spin Echo	3500	-	208	4	Transverse
T1 weighted	Conventional Spin echo	600	-	4.6	4	Sagittal
T1 weighted	Inversion Recovery Fast spin echo	7857	1	49	4	Transverse

**3T pulse sequences**

Sequence name	Sequence type	TR (ms)	TI (ms)	TE (ms)	Acquired Resolution (mm <sup>3</sup> )	Orientation
T2 weighted	Multi-slice fast spin echo	15715	-	160	1.15x1.18x2.0	Transverse
T1 weighted	MP-RAGE	17	1465	4.6	0.82x0.97x1.0	Sagittal
DT-MRI (b-value 750 s/mm <sup>2</sup> )	Spin echo EPI	7857	-	49	2.0x2.03x2.0	Transverse
MRS (~6 mins)	PRESS	2288	-	288	15x15x15	Acquire in thalamus

**How useful is MRI/MRS in assigning prognosis?**

This summary gives broad guidance on the prognostic value of different MRI and MRS modalities but clinicians are advised to consult these and other original publications before considering using the data in clinical practice as patient selection, field-strength, acquisition parameters, data dichotomisation etc. can affect clinical implementation.

**1. T1 and T2 weighted MRI**

The TOBY Trial provided data on prognostic values for MRI in both cooled and uncooled infants. Major MRI abnormalities were defined as moderate or severe basal ganglia or thalamic lesions, severe white matter lesions, or an abnormal posterior limb of the internal capsule (Rutherford et al 2010):

	<b>Cooled</b>	<b>Non-cooled</b>
<b>Sensitivity</b>	0.88 (0.79–0.97)	0.94 (0.88–1.0)
<b>Specificity</b>	0.82 (0.72–0.92)	0.68 (0.56–0.80)
<b>Positive predictive value</b>	0.76 (0.65–0.87)	0.74 (0.63–0.85)
<b>Negative predictive value</b>	0.91 (0.83–0.99)	0.92 (0.85–0.99)

In the Marble multicentre study prognostic values were slightly lower, and may reflect use outside a therapeutic trial setting (Lally et al 2019):

Abnormality	Sensitivity	Specificity
Basal Ganglia and Thalami	0.71 (0.52-0.86)	0.88 (0.82-0.93)
PLIC	0.71 (0.52-0.86)	0.87 (0.81-0.91)

## 2. Diffusion MRI

The Marble multicentre study reported that measurements of fractional anisotropy had:

Sensitivity of 0.75 (0.19-0.99) and Specificity of 0.98 (0.91-1.0) (Lally et al 2019). Single centre studies report comparable results for fractional anisotropy, for example Mitra et al 2019 report Sensitivity of 0.45 and Specificity of 0.94. Diffusion MRI thus adds relatively little to T1 and T2 weighted imaging.

## 3. Proton MRS

MRS is not as widely used as MRI but has good prognostic power. The Marble and TobyXe multicentre studies report proton spectroscopy measurements of the Lactate/ n-acetyl Aspartate ratio as:

	Sensitivity	Specificity
Marble (Lally et al 2019)	0.87 (0.70-0.98)	0.90 (0.84-0.94)
TobyXe (Azzopardi et al 2019)	0.64 (0.35-0.87)	1.0 (0.92-1.00)

### Optimizing MRS

Higher prognostic values have been observed using software such as Tarquin in accordance with Medical Device Regulations. By including threonine (Thr) and N-acetylaspartylglutamate (NaaG) in the fitting function, this can improve the analysis of the spectrum in the regions close to Lactate (Lac) and N-acetylaspartate (NAA) respectively. The acquisition of the MRS is straightforward, taking around 6 mins. (Mitra et al 2019)

	Sensitivity	Specificity
Motor outcome	1.0 (0.83 – 1.0)	0.97 (0.85 – 0.99)
Cognitive outcome	0.90 (0.67 – 0.99)	0.97 (0.84 – 0.99)
Language outcome	0.81 (0.58 – 0.95)	0.97 (0.83 – 0.99)

Absolute quantitation of N-acetylaspartate concentration is also reported to have higher prognostic value, with a Sensitivity of 1.0 (0.74-1.0) and Specificity of 0.97 (0.90-1.0), but this requires longer acquisition times and specialist facilities. (Lally et al 2019).

### References and further information

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## Appendix 2. General care

All infants undergoing TH should have physiological parameters including intra-arterial blood pressure continuously monitored (wherever possible) along the lines of standard neonatal intensive care principles. Ongoing intensive care should take place in a neonatal intensive care unit NICU, which may involve an intensive care transport.

### Airway and respiratory

- Aim for normal blood gas values and saturations- avoid hypocarbia /hyperoxia – correct blood gas for patient temperature.
- Intubation and ventilation should be considered to maintain
- adequate gas exchange depending on the respiratory drive, need
- for sedation and the ventilatory status
- Ensure regular repositioning and suction if secretions increase
- Watch for stridor in extubated and non-ventilated patients

### Cardiovascular

- Achieve central venous and arterial access
- Bradycardia 80-100bpm is normal
- Rise in heart rate may be due to 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

- Initial maintenance fluids at 40-60 ml/kg/d
- Watch for SIADH and avoid severe hyponatraemia
- Avoid hypoglycaemia maintaining glucose  $\geq 2.6$ mmol/L
- Avoid fluid overload during oliguria and avoid hypovolaemia once diuresis starts
- Watch for accumulation of nephrotoxic drugs e.g. gentamicin

### Gastrointestinal and liver

- Consider trophic breast milk if there is no ongoing organ dysfunction or poor perfusion
- Give colostrum as mouth care where available in all
- Beware accumulation of drugs metabolised by liver: e.g. morphine, midazolam, phenobarbital
- Coagulopathy is physiological in TH but only active bleeding needs treatment. Be alert for any evidence of intracranial bleeding particularly in babies where there may have been head trauma at birth and consider correcting coagulation accordingly.
- Give vitamin 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 rise with TH and may not be a sensitive marker of infection. (35)

### Seizures

- Consider treating seizures which are confirmed with aEEG, particularly if they are associated with physiological disturbance, are prolonged (>3 minutes) or frequent

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(>3 per hour).

- Detection of seizures is an indication for urgent review of blood sodium, glucose, calcium and magnesium.
- Use intravenous phenobarbital as first line treatment in babies undergoing TH, in a dose of 20 mg/kg given over 20 minutes. Repeat in a dose of 10-20 mg/kg to a maximum of 40 mg/kg if seizures continue. Note that in babies who are not ventilated respiratory depression can occur at these high doses
- In babies who do not respond to phenobarbital consider phenytoin IV 20 mg/kg over 30 minutes. Levetiracetam 20mg/kg IV over 15 minutes with repeat doses to a maximum of 40 mg/kg, or midazolam 150 micrograms/kg over 5 minutes followed by a continuous infusion of 60 micrograms/kg/hour (max 300 microgram/kg/h) being aware that midazolam levels will accumulate. Lidocaine has also been shown to be effective but dosing should be modified in TH (35).
- While 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.

#### Sedation

- Babies who are cooled should be closely assessed for pain and distress which should be treated with opiate medication if present.
- There is preclinical evidence that distress increases brain injury in the context of neonatal encephalopathy (36) (37). This needs to be weighed against concerns that analgesic agents are themselves potentially neurotoxic
- Analgesia should be used for procedures such as intubation which are likely to cause pain and distress

#### Rewarming

- Monitor for hypotension, apnoea and seizures including continuing aEEG
- Re-warming can be delayed or slowed where seizures emerge
- Maintain normothermia after re-warming with paracetamol and environmental measures where required

### Appendix 3. Neurological examination

The framework recommends that the repeated neonatal neurological examination is based on a modified Sarnat scoring system. Implementation of this will require training and assessment which should be coordinated at network level, and has been achieved in other health settings(38).

If repeated examination within the 6 hours after birth suggests deterioration to stage 2 or 3, apply aEEG if not already in place and cool if meet criterion C.

This neurological assessment should be repeated and documented at regular intervals as infants go through their pathway of care. (\*)

Domain	Stage1	Stage2	Stage3
Seizures	None	Common focal or multifocal seizures	Uncommon (excluding decerebration) Or frequent seizures
Level of consciousness	Normal hyper alert	Lethargic Decreased activity in an infant who is aroused and responsive Can be irritable to external stimuli	Stuperose/ 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 only one position	Distal flexion, complete extension or frog – legged position	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 extension of limbs followed by flexion	Suck: weak  Moro: incomplete	suck: completely absent Moro: completely absent
Autonomic system	Pupil – normal size Reactive to light Heart rate normal >100 Respirations - normal	Pupils – constricted <3mm but react to light Heart rate: bradycardia (<100 variable up to 120) Respirations: periodic irregular breathing effort	Pupils: fixed dilated, skew gaze not reactive to light Heart rate: variable inconsistent rate, irregular, may be bradycardic Respirations: completely apnoeic requiring positive pressure ventilation

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