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NEONATAL ENCEPHALOPATHY – BACKGROUND

Neonatal Encephalopathy (NE) is “a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, sub normal level of consciousness and often seizures”

Moderate or severe NE occurs in approximately 1.5 /1000 live births and usually affects the full term infant. The term Hypoxic Ischemic Encephalopathy (HIE) implies an antecedent and significant hypoxic-ischaemic insult. If it is not possible to document this then use the term NE and consider other causes (below).

We do not use the term “birth asphyxia” as it is unscientific, emotive and potentially inaccurate.

NE therefore includes those term infants with clinical seizures that are associated with cerebral function monitoring (CFM) and/or EEG abnormalities, and those infants with CFM / EEG abnormalities that are not associated with clinical seizures. The latter is called “electro-clinical dissociation”. Some infants may also have abnormal neurological symptoms without abnormal brain electrical activity. It is thus important to investigate in order to make the correct diagnosis.

Aetiology of NE and seizures

More Common:
Hypoxic-ischaemic encephalopathy (HIE) (50-60%)
Intracranial haemorrhage in term and preterm babies (11%)
Cerebral infarction / stroke (10%)
CNS structural abnormalities (6%)
Intracranial infections (2%)

Less Common:
Inborn error of metabolism
Electrolyte disturbances
Drug withdrawal
Trauma
Pyridoxine deficiency
Benign familial neonatal seizure syndromes
Progressive epileptic syndromes
Unknown/idiopathic (2-5%)

HIE in the term infant results from compromised oxygen and/or blood flow in the perinatal period resulting in depression at birth and ongoing encephalopathy. It may account for up to 30% of cases of cerebral palsy.

Infants with severe HIE are often very sick with multi-organ failure requiring intensive care. The standard of care is treatment with therapeutic hypothermia (“cooling”) to 33-34°C (rectal temperature) which improves neurological outcome. However, cooling is not performed in isolation and should be part of a package of neuro- and intensive- care that enables appropriate treatment, investigation and family counselling to be undertaken prior to long term follow-up being arranged for surviving infants.

Newborn babies are prone to seizures due to their immature central nervous system and the pronounced excitatory effects of GABA receptors. The prevalence of seizures is thus relatively high at 2 – 3 per 1000 term infants and 10-15 per 1000 preterm infants; data is from epidemiological studies relying on clinical diagnosis and may therefore be inaccurate.
Seizures represent the brain’s response to a wide variety of pathological insults. As such, they are often a manifestation of significant neurological disease, they are rarely idiopathic and they are a major predictor of adverse outcome in the newborn. In one study (Painter) babies with seizures were 3x more likely (16%) to develop cerebral palsy than were control babies (6%). Seizures are difficult to diagnose by clinical observation alone, and it is therefore important to use neurophysiological investigation (CFM / EEG) whenever seizures are detected clinically or suspected for other reasons.

Specifically, it is important to exclude metabolic disease, infection, drug exposure, nervous system malformation and neonatal stroke as possible causes of the encephalopathy. The requirement for investigation to exclude these possibilities will depend on the presentation, history and clinical features of the individual case.

Full-term infants who develop long-term neurological sequelae from perinatal asphyxia may not have low Apgar scores but will usually demonstrate neurological dysfunction within 48 hours.

**Ex-utero referrals**

The South East Coast Time=Brain project aims to ensure that servo-controlled cooling is available for all babies presenting with NE so that controlled and precise cooling can be carried out as soon as the decision to cool has been made, and that precise cooling continues throughout the baby’s cooling pathway. The Time=Brain care pathway paperwork should be completed for every baby undergoing cooling. We strongly encourage local teams to call the duty neonatal consultant to discuss the decision to cool a baby, especially if the indications are not clear, and this includes cases of in-hospital post-natal collapse with encephalopathy. Once the decision is made to cool and transfer the infant, the referring Paediatrician will commence active servo-controlled cooling and the aim is that babies should reach their target temperature within 3 hours of birth/hypoxic event.

Even if there is no cot at St. Peter’s, we will assist the local hospital by finding a cot for cooling elsewhere (via EBS) and the transport team can then facilitate this transfer.

We encourage all local Special Care Baby and Local Neonatal Units to cool early. Appendix 4 is a useful flow chart to guide passive cooling where servo-controlled cooling is not available. Overcooling is a risk as well as undercooling. All the SEC transport teams are equipped with servo controlled Tecotherm Neo cooling units.

This guideline describes the detail of history, examination and investigation required in these cases, as well as how and when to initiate therapeutic hypothermia and how to set up the aEEG recording on the Cerebral Function Monitor (CFM). There is also information on prognosis and help with talking to parents.

This guideline also contains some discussion points and thoughts. We encourage all our staff to express their ideas and consider audits and service improvements that could lead to even better care.

**Recognition of Encephalopathy**

Recognition that an infant is encephalopathic can be difficult, and this document describes how the use of clinical examination, clinical scoring and the use of aEEG, whilst useful, are not able to predict encephalopathy which can worsen over a number of hours post delivery. Any baby where there are concerns about poor condition at birth, intrapartum hypoxia, abnormalities of cord blood gases should be observed closely for emerging signs of encephalopathy during the first 24 hours. Network colleagues are encouraged to call the attending or duty consultant at St. Peter’s Hospital for advice if concerned.
HISTORY

Take a comprehensive history using as many sources as possible
1. Medical and Obstetric History
2. Current pregnancy
3. Labour
4. Delivery
5. Resuscitation

Detailed history including Family History

Maternal and paternal age
Maternal and paternal occupation
Maternal and paternal health
Consanguinity
Ethnic background
Parity [including fetal losses, infertility/subfertility and stillbirths]
Details of previous pregnancies
Health of other children (age, mode of delivery)
Familial illness/condition/unexpected death
History of neurological disease/CP/seizures/neonatal or infant deaths
History of thrombosis in family
History of any thyroid disease
Previous herpes infection
Travel abroad, before/during pregnancy

Pregnancy details

Blood results; including HIV, Herpes, Syphilis, Hepatitis, Blood group & Antibodies
LMP, EDD and certainty
Conception, natural or assisted
History of infertility
Maternal medication/drugs including homeopathic, herbal and recreational drugs
Antenatal care, from when, where?
Results of CVS/amniocentesis
Results of antenatal scans/why done
Placental site
Fetal position
Fetal movements, any changes
Chorionicity of twins/TTTS
Oligo/Polyhydramnios
Growth pattern
Diabetes Mellitus/gestational diabetes
Shock/Haemorrhage
Trauma / accidents / injury
Infection, bacterial, viral, where, when, treatment
Essential hypertension/PET
Rhesus incompatibility
Results of any CTG in pregnancy
Labour details

Antepartum:
- Gestational age
- Presentation
- CTG, pre/during labour

Intrapartum:
- Onset of labour: spontaneous/induced
- First symptoms and timing if spontaneous
- If induced, why, how, when
- Rupture of membranes
- Spontaneous/time
- Artificial, time/why
- Meconium – when first seen and description (we don’t use grading)
- Augmentation of labour, with what, when, how much
- Pain relief / epidural /GA, when, top up, any untoward effects
- Maternal pyrexia
- Chorioamnionitis or markers of potential sepsis (PROM, swabs, maternal CRP and FBC)
- Bleeding
- Acute intrapartum event: cord prolapse, ruptured uterus,
- Maternal hypotension, abruption, other.
- Fetal blood sampling
- Length of 1st and 2nd stage

Delivery details

- Time of delivery
- Vaginal OA/OP/Breech/malpresentation
- Forceps low lift out /high/rotational
- Ventouse
- CS Elective, indication
- CS semi-elective in labour, emergency pre or during labour, 1st or 2nd stage and reason

Resuscitation details

Evidence of:
- Intrapartum fetal distress (CTG, passage of meconium etc)
- Umbilical cord around the neck? loose or tight
- Shoulder dystocia
- Cord pH, base excess, lactate (if available) from both arterial and venous samples
- Apgar scores 1, 5 and 10 minute

Airway:
- Meconium below the cords
- Time to first gasp
- Onset of regular respirations

Breathing:
- Spontaneous or assisted
- Need for intubation and duration
- Maximum ventilatory requirement

Circulation:
- Onset of regular heart rate (document rate)
- Document oximetry saturations and pulse readings with times (timeline useful)
- Drugs/Fluids administered during resuscitation
Diagnosis of neonatal encephalopathy can be difficult, and the clinician must use all the information available to decide if cooling should be applied, as soon as possible. Cord and blood gases, Apgar scores and clinical examination, clinical scoring systems (Sarnat staging, Thompson scoring and Badgernet Scoring) and the aEEG will all be helpful, although there is no single test that can always guide the clinician, due to the “grey” areas around diagnosis and eligibility for cooling.

**Comprehensive notes are essential for clinical and medico-legal reasons**

**General Examination**

A complete physical examination is essential. This must include:

- Weight
- Head circumference
- Centiles to establish SGA / IUGR
- Sex
- Temperature on admission
- Dysmorphic features
- Meconium staining of skin
- Organomegaly
- Head size and shape
- Fontanelle
- Trauma
- Bruising or petechiae
- Limb movements and the presence of contractures/talipes
- Presence of seizures (see below)
- Muscle tone (may be increased, decreased, variable)
- Muscle reflexes (knee and biceps)
- Presence / Absence of ankle clonus
- Posture
- Responsiveness
- Primitive reflexes e.g. pupillary, gag, suck, grasp reflexes
- Pupil sizes
Modified Sarnat Classification

<table>
<thead>
<tr>
<th></th>
<th>Mild HIE (I)</th>
<th>Moderate HIE (II)</th>
<th>Severe HIE (III)</th>
</tr>
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<tr>
<td>Level of consciousness</td>
<td>Hyperalert</td>
<td>Lethargic</td>
<td>Stuporose</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
<td>Mild hypotonia</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Complex reflexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suck</td>
<td>Normal/Weak</td>
<td>Weak/Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>Strong</td>
<td>Weak/Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>Seizures</td>
<td>Absent</td>
<td>Common</td>
<td>Frequent/difficult to control</td>
</tr>
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</table>

- Sarnat staging should be assessed daily but is considered to be unreliable <24 hours from birth.
- Babies often don’t fit neatly into a Sarnat staging. It is common to use staging such as 1-2, or 2-3 as the prevailing clinical signs may not “fit”.
- Sedation and paralysis make this difficult to use and when assessing the child the type of medication, amount and time of last administration should be documented.
- Prognosis depends on the maximal worst grade (and can’t be used for this <day 3 if the grade is <3).
- Stage 1 good prognosis, recovers within 24 hours. Expect normal aEEG, no seizures and a good prognosis with normal outcome.
- Stage 2 abnormal and untreated 25% may develop cerebral palsy.
- Stage 3 severely abnormal, loss of reflexes leading to death or severe handicap.

Badgernet Score

The Badger system will bring up the HIE Data Form under Audit / Research and this must be completed for every baby who is cooled.

The severity of encephalopathy can be assessed using the HIE Score (below). The worst score is 13. This should be recorded daily, along with more detailed clinical examination. All fields should be completed using the highest scoring option if a lower score cannot be elicited on examination (e.g. if ventilated and sedated).

### Table 1 - HIE Score (Modified Thompson Encephalopathy Score, (Thompson CM))

<table>
<thead>
<tr>
<th>Sign</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alertness</td>
<td>Alert</td>
<td>Irritable</td>
<td>Poorly Responsive</td>
<td>Comatose</td>
<td></td>
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<tr>
<td>Tone</td>
<td>Normal</td>
<td>Hypertonia</td>
<td>Hypotonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Normal</td>
<td>Resp distress (Apnoea/needing O₂)</td>
<td>CPAP or mechanical ventilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflexes</td>
<td>Normal</td>
<td>Hyperreflexia</td>
<td>Hyporeflexia</td>
<td>Absent Reflexes</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>None</td>
<td>Suspected</td>
<td>Confirmed clinical Seizure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeding</td>
<td>Normal (Breast/bottle)</td>
<td>Tube/nil by Mouth</td>
<td></td>
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Neonatal Encephalopathy Guideline prepared by Dr. Peter Reynolds
Seizures

Seizures present in a variety of ways and may be difficult to detect, particularly in the preterm infant. It is useful to distinguish them into the categories below.

| Subtle (50-75%) | Orofacial - mouthing, chewing, lip smacking, blinking, staring  
Limb movements - pedalling, boxing  
Autonomic - unstable blood pressure, tachycardia, central apnoea |
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<tr>
<td>Clonic (30-40%)</td>
<td>Repetitive jerking that cannot be suppressed if limb is held still - focal or generalised</td>
</tr>
<tr>
<td>Tonic (2-23%)</td>
<td>Stiffening, sustained posturing of limbs or trunk or deviation of eyes - focal or generalised</td>
</tr>
<tr>
<td>Myoclonic (8-18%)</td>
<td>Usually in flexor muscle groups. Rapid isolated jerks - focal, multifocal or generalised</td>
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Differential diagnosis of seizures:

Jitteriness:
No associated eye movements or autonomic phenomena  
Does not involve the face  
Induced by stimulus or spontaneous  
Suppressed by handling

Benign neonatal sleep myoclonus:
Occurs during REM / active sleep  
Not stimulus sensitive

Severe gastro-oesophageal reflux
Back arching and trunk stiffening may be seen in infants with severe reflux, akin to Sandifer syndrome
INITIAL CLINICAL MANAGEMENT

The clinical management of infants with NE is a combination of supportive management and therapeutic hypothermia (where appropriate), dependent on the extent of organ compromise. Each baby’s management should be individualised, with close monitoring of cardiorespiratory status and early identification and treatment of multi-organ system complications. Regular neurological evaluations are important and good, thorough documentation is essential.

Resuscitation

Resuscitation should be carried out following the Newborn Life Support (NLS) guidelines. Resuscitation should be initiated using room air. The 2010 International Liaison Committee on Resuscitation (ILCOR) consensus statement recognised that term or near term infants with evolving moderate to severe hypoxic-ischaemic encephalopathy should have therapeutic hypothermia initiated. Thus if whilst resuscitating it is clear that a baby should be cooled (severe encephalopathy present at birth), then switch off the overhead radiant heater to commence passive cooling. Prompt initiation of cooling is beneficial.

Time=Brain: Indications for Therapeutic Hypothermia (Cooling)

The eligibility for cooling has broadened since the TOBY and other trials were published but the presence of moderate to severe encephalopathy remains an important component. Time=Brain is the regional cooling project with more details below (Page 13). More information and materials are also available at the Time=Brain website (St. Peter’s intranet site here).

Step 1
Identify babies AT RISK of neonatal encephalopathy

- Apgar score of ≤5 at 10 minutes after birth OR
- Ongoing need for resuscitation at 10 minutes after birth OR
- Severe acidosis (cord, arterial, venous or capillary) blood pH < 7.1 OR base excess ≥ -12 mmol/L within 60 minutes of birth
- In-hospital post-natal asphyxia event with resuscitation and acidosis (≤48 hours old)

Step 2
Clinical examination for signs of moderate to severe encephalopathy

- Altered consciousness (reduced or absent response to stimulation) AND
- Abnormal tone (focal or general hypotonia, flaccidity or hypertonia) AND
- Abnormal reflexes (weak or absent suck or Moro or gag) OR
- Seizures / Abnormal Movements

If baby meets criteria and is ≥ 35 weeks gestation and within 6 hours of birth, then servo-cooling should be started. We strongly encourage a discussion with the duty/on-call neonatal consultant especially for ex-utero transfer requests. All babies with postnatal collapse require careful evaluation of the history and examination findings, prior to a consultant-only decision to cool.

There are numerous circumstances where therapeutic hypothermia may also be appropriate, despite lower standards of evidence. These include:

- Infants 33-35 weeks gestation
- Infants > 6 hours old
- Infants with congenital anomalies
- Infants presenting with neonatal stroke
Any decision to cool babies in these criteria should be made by the Consultant Neonatologist on duty, and a record of that decision made in the notes. Parents should be informed about the treatment before it is started, involved in the decision to cool or not, and we must be open where the evidence is not particularly robust. These discussions MUST be documented in the notes. However it is not necessary to obtain written consent and it should be explained to the parents that it is not “experimental” nor part of a “trial or research study”.

**Infants with non-specific abnormal neurology immediately/soon after birth**

These are arguably one of the most difficult groups to assess. The aEEG can be extremely useful, but beware of suppressant medications.

Do not rely overly on cord blood gases which can be falsely reassuring. For example, in the presence of cord obstruction, a normal umbilical cord venous blood gas could conceal severe mixed umbilical arterial acidosis in an infant, and in extreme cases of acute obstruction both cord gases could be normal. 20% of paired arterial and venous samples were found, in one study, to be double venous samples. The review by Armstrong and Stenson provides more detailed explanation (see references).

Clinical depression or abnormal movements, concern about aEEG, depressed Apgar scores and a blood gas taken directly from the baby may lead the clinician to reasonably assume that there has been some perinatal event or poor fetal tolerance of the stresses of labour and delivery due to pre-existing illness.

Furthermore, HIE is dynamic and infants can worsen, so careful observation is necessary as signs of encephalopathy may develop.

A high blood lactate level should raise suspicion of a significant event and if the infant is not immediately cooled, close neurological observation is required. Whilst underlying illnesses, such as sepsis, need to be considered (and antibiotics commenced), **cooling of the infant during this continuing evaluation may be considered by the duty Neonatal Consultant.**

**Infants 34 - 35 weeks gestation with suspected NE**

Infants between 34+0 and 34+6 weighing more than 1.8kg should be considered for cooling if there are concerns about moderate or severe NE.

The main clinical trials included term and near term infants (36-37 weeks gestation) and many NICU have routinely cooled babies of 35+ weeks for several years. The mechanism of brain injury in infants 34-35 completed weeks gestation following a period of hypoxia-ischaemia is likely to be similar. A pilot study of moderate hypothermia (33.5°C-35.5°C) on preterm infants with necrotising enterocolitis showed no increase in mortality or morbidity. There is some evidence from the CoolCap trial that smaller infants benefitted less than larger infants, but the relationship between weight and gestational age was unclear (i.e. whether it was related to growth retardation). There is also data from the TOBY Register as to the safety of cooling infants <36 weeks and the Register indicates that the range of gestations being cooled are from 34-44 weeks.

**Therefore it is reasonable to consider infants between 34 and 35 weeks** for cooling although this is not in the Time=Brain protocol.

**Infants 33-34 weeks**

Some UK units (e.g. Addenbrooke’s in Cambridge) suggest that cooling can be offered safely to babies at 33+ weeks, and the pilot study of cooling for NEC indicated that cooling in moderately preterm babies appears to be safe. There is very limited evidence and we don’t currently recommend cooling less than 34 weeks gestation. There are some preterm studies planned which may help to inform this position in the future (e.g. Preemie Hypothermia for Neonatal Encephalopathy study (Clinical Trials Identifier NCT01793129))
Infants >6 hours old with suspected NE

Infants between 6 and 12 hours of age should be considered for cooling; however beyond 12 hours of age there is little evidence of benefit from hypothermia. The TOBY register indicates however that this practice is taking place in the UK, and therefore may be considered under specific circumstances and with consultant to consultant discussion.

Experimental studies tended to cool immediately after the hypoxic-ischaemic insult. For practical purposes the clinical trials had a 6 hour cut off. Although there was no significant difference in neurodevelopmental outcome between those cooled early and those cooled late there was a trend to favour those cooled earlier. There is a lack of benefit from delayed cooling. Training and education should be focussed on early identification of infants who may benefit from cooling, however it would be reasonable to offer cooling to infants between 6 and 12 hours of age. The NICHD is currently undertaking a RCT on therapeutic hypothermia in infants aged 6-24 hours of age. Parents must be aware of the limited evidence.

Infants with congenital anomalies with suspected NE

Cooling should be considered on a case by case basis depending on underlying anomaly. For obvious reasons this broad patient group was excluded from the clinical trials. When deciding whether an infant born with congenital anomalies who fit criteria A and B should be cooled the following should be considered:

- Is the condition life-limiting? i.e. would cooling actually alter the long term outcome?
- Would cooling impact on the anomaly? For example cooling may compromise blood flow to the gut in an infant with gastoschisis.
- Would the condition make it harder to assess criteria B? For example a baby with Down syndrome may be hypotonic as a result of the underlying condition (this does not mean that a baby with Down syndrome should not be cooled, but careful neurological assessment is necessary).

Infants presenting with postnatal collapse

Infants presenting with postnatal collapse in hospital in the first 48 hours should be considered for cooling. Although there is no clinical trial looking at hypothermia following postnatal collapse, these babies often have good evidence of hypoxic-ischaemic brain injury on neuroimaging and so it is likely that they could benefit from cooling. There are legitimate concerns as to whether cooling could make some conditions worse, particularly if initiated in a SCBU or LNU.

The recent publication of outcomes from Bristol (Smit et al) reported 10 babies with mean postnatal time of collapse 75 mins (range 15 min-32 hours). 6 infants collapsed whilst feeding or being held, 2 presented with seizures and 2 were found unresponsive in the cot. In two cases, an underlying diagnosis was found: hyperinsulinism and very long chain acyl-CoA dehydrogenase deficiency. None of the infants died and the outcomes/complications rate for the group as a whole were no different to the standard cooled group, which is reassuring. However for babies with major intracranial haemorrhage (note n=5), cooling significantly worsened the coagulopathy and the recommendation was to rewarm to 35.5°C if cooling has started whilst aggressively treating the coagulopathy. This particularly applied to the babies with subgaleal haemorrhage (n=4); the one baby with major IVH had a normal outcome. It is not clear on what the recommendation to rewarm to 35.5°C is based.

Therefore a history of difficult/failed ventouse/forceps with clinical evidence of subgaleal haemorrhage (unequal pupils, eye deviation, irritability, tense fontanelle and coma) would indicate that cooling should not be initiated/continued. Clearly the numbers reported are very small and our practice may change as further evidence/experience emerges.
Infants presenting with neonatal stroke

Infants presenting with neonatal stroke should be considered for cooling only if the diagnosis is made within 12 hours of birth as this is currently our “upper limit” for initiating cooling.

Many of the experimental studies used a stroke model to study the efficacy of cooling and there is interest in cooling adult patients following stroke. However the main challenge in the neonate is making an early diagnosis – these infants often present after 24 hours of age with seizures, are not initially encephalopathic and early ultrasound imaging may not detect the stroke. Therefore it is possible that by the time the diagnosis is made the “therapeutic window” has been missed.

However if an infant diagnosed with HIE may have their diagnosis revised to stroke in the first 24-48 hours, and in that case we would continue with a full course of cooling. There is evidence of better outcomes in this group of babies if they are cooled.

Exclusions to initiation of cooling

Cooling is not appropriate if:

- The infant is likely to require surgery during the first 3 days after birth
- There are other abnormalities indicative of poor long term outcome
- There is suspected/confirmed subgaleal or other major intracranial haemorrhage as the cause of NE

Cooling (or continuation of cooling already initiated) may not be appropriate if the infant appears moribund or has persisting extremely severe encephalopathy such that further treatment is likely to be futile.

In general, cooling seems to be safe and well tolerated.

Clinicians must be quick to recognise the “at risk” baby, but not hasty in their evaluation of encephalopathy

Discussion with duty/on call neonatal consultants is always encouraged
Time=Brain is the regional active cooling project which aims:

1. Improve the quality of cooling regionally for all eligible babies
2. Increase the proportion of babies cooled within 3 hours of birth / hypoxic episode
3. Minimise the number of babies not recognised as eligible for cooling
4. Reduce the proportion of babies cooled inappropriately
5. Audit the initial management of babies with neonatal encephalopathy

The project lead is Dr. Peter Reynolds and the sponsor is the SEC Neonatal Operational Delivery Network, hosted at Medway NHS Foundation Trust.

The project has received funding from the SEC Maternity, Children & Young People’s Strategic Clinical Network.

Every baby who meets the initial criteria of being at risk of neonatal encephalopathy should have a clinical pathway completed, and every unit has a folder containing these pathways for completion.
Time = Brain – Decision making process

**Risk of encephalopathy (one of these)**
- Apgar score ≤ 5 or ongoing resuscitation / ventilation ≥ 10 minutes after birth
- Severe acidosis (pH < 7.1 or BE ≥ 12 mmol/l) ≤ 60 min of birth

**Clinical Signs of encephalopathy (either or both of these)**
- Reduced response to stimulation AND
- Reduced or absent reflexes AND
- Abnormal tone
- Seizures / abnormal movements

**Postnatal Collapse**
- Asphyxial ‘event’ with resuscitation and acidosis

**When to cool?**

- **Yes**
  - Is baby less than SIX hours old?
  - Is baby ≥35 weeks gestation?
  - Do clinical HIE Score and start active cooling*
    - *Discuss with local NICU if required

- **No**
  - Speak to regional NICU Neonatal Consultant
  - Discussed with (name)
  - Hospital
  - Time
  - Decision? (circle one)
    - START COOLING
    - DO NOT COOL

**No clinical signs of NE**
- Do not cool
# Time=Brain - Data collection

**Total HIE Scores**

<table>
<thead>
<tr>
<th>Time</th>
<th>Alertness</th>
<th>Tone</th>
<th>Respiratory</th>
<th>Reflexes</th>
<th>Seizures</th>
<th>Feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Alert</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Irritable</td>
<td>Hypertonia</td>
<td>Resp. distress</td>
<td>Hyperreflexia</td>
<td>Suspected</td>
<td>Not fed/tolerating</td>
</tr>
<tr>
<td>2</td>
<td>Poorly responsive</td>
<td>Hypotonia</td>
<td>nCPAP/nHF/Vent*</td>
<td>Hyporeflexia</td>
<td>Confirmed</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Comatose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: nCPAP = nasal CPAP, nHF = nasal High Flow, Vent = ventilated

**First HIE Score**

- Time: [ ]

**Servo cooling started**

- Time: [ ]

**EBS / Transport called**

- Time: [ ]

**Target temp achieved**

- Time: [ ]

**Second HIE Score**

*To be done at handover to transport team or at 6 hours after birth / collapse

- Print Name: [ ]
- Signature: [ ]
- Date: [ ]
Passive Cooling – how to start

In order to be effective, cooling should commence as soon as possible (preferably <1 hour after birth and definitely within 6 hrs). Passive cooling can be achieved by:

- Turning off all external heat sources except for humidification of inhaled gases
- Removing the baby's clothes except the nappy
- Using a closed incubator and keeping all the doors open

Sometimes some more “active” but non-servo cooling is needed
- Using fans (may be needed in hot weather or very warm room)
- If cold gel packs are available from a fridge, the baby’s head can be rested next to one.
- Get bags filled with ice (usually available on labour ward), wrap in thin cotton and place next to baby
- Contacting the KSS transport service ASAP. They will actively cool the baby to improve the consistency of delivery of therapeutic hypothermia across the region.

Full monitoring is required. A surface temperature probe applied to the baby’s back will give a good approximation of core temperature so overcooling can be avoided. The aim is a temperature between 33 and 34 degrees. Be very careful of gel packs and ice, it is easy to overcool.

Once a baby is cooling, there is a risk of undershooting the desired temperature and teams must be vigilant and monitor temperatures frequently (15 minutes) see Appendix 5

Active Cooling – how to start

1. In order to be maximally effective, cooling should commence as soon as possible, normally within 1-2 hours of birth and definitely within 6 hrs. **The Time=Brain pathway aims for all eligible babies to be at target temperature within 3 hours of birth.** The decision to cool a neonate outside of the guideline should be made by the attending or on-call neonatal consultant (see above).
2. Document the discussions and timings of initiation and reaching of target temperature on the Time=Brain documentation
3. Setting up the Tecotherm Neo Unit – see guideline
4. Insert a rectal probe - wear gloves and clean rectal area and buttocks. Lubricate rectal probe and insert 2-3 cms (may need to mark probe prior to insertion) Secure to lower buttock/ upper thigh with steristrips/tape. Replace small nappy and connect probe to monitor lead. Rectal temperature is measured constantly.
5. The aim is to achieve target core body temperature (33.5°C) range within 1 hour of initiation.
6. The total period of cooling and re-warming is for at least 84 hrs consisting of 2 phases:
   - **Active cooling** – for 72 hours from the initiation of cooling.
   - **Rewarming** - 12 hours of gradual re-warming time after completion of 72 hour cooling
7. Sedation is important for ventilated and non-ventilated babies. There is evidence that the benefits of cooling are lost if stress or discomfort are present. Intravenous morphine at 5ug/kg/hr does not usually cause respiratory problems and prevents shivering and discomfort.
8. Changes and potential complications associated with cooling include:
   - Rise in blood pressure and a fall in heart rate (<110 /min). This is normal.
   - If the temperature falls further, several potentially harmful abnormalities may occur: the QT interval increases linearly with the depth of cooling and ventricular tachyarrhythmias may be induced.
   - Neutropenia, thrombocytopenia and hypokalaemia may also occur. These abnormalities are more severe and more common when the core temperature is less than 32°C
   - 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 the infant has been discharged home from hospital. It is recommended that the infant’s skin is closely observed for the development of SCFN. If it develops, weekly calcium levels should be monitored until the clinical resolution of the SCFN occurs and for up to 6 months to prevent the serious complications that can result from hypercalcaemia
What if the baby improves?

**Improvement within 6 hours of birth**
Infants whose clinical condition improves within 6 hours of birth and are no longer encephalopathic would not have been entered into the RCTs on cooling. Careful neurological assessment is essential to demonstrate that the infant does not have any signs of encephalopathy or would not meet any of the non-standard indications. If cooling has been commenced it would be reasonable to slowly rewarm the infant. These infants should be carefully observed over the next 24 hours including CFM recording.

**Improvement after 6 hours of birth**
Infants whose clinical condition improves after 6 hours of birth and are already being cooled should continue cooling for 72 hours. If their clinical condition improves over the subsequent 72 hours then they would be in a good prognostic group, but in the trials these infants remained cooled for 72 hours. CFM recording must continue.

**Rewarming**

Cooling should normally be stopped 72 hours from when a temperature of 33.5°C has been achieved and maintained. Re-warming should be gradual and no faster than 0.5°C /hour until 37°C (normothermia) is attained. (ref TOBY Cooling Register handbook). Rewarming is controlled by the Tecotherm servo unit.

Re-warming may be associated both with peripheral vasodilation resulting in hypotension and also the re-emergence of seizures. If the clinical condition deteriorates during re-warming, stop and discuss further with the consultant. Also see Appendix 1 – Non standard indications for cooling.

The infant’s temperature should be closely monitored for 24 hours after normothermia is achieved to prevent rebound hyperthermia. Rebound is a rare but potentially dangerous condition, and prompt cooling is required to prevent harmful hyperthermia arising.

**The infant who develops ‘rebound’ seizures following re-warming**

Seizures can be regarded as the clinical sign of delayed energy failure. It is prevention of delayed energy failure which is thought to be the reason hypothermia is beneficial. Therefore on going seizures during cooling are an indication of continuing delayed energy failure; similarly the re-emergence of seizures during re-warming is a suggestion that delayed energy failure is “reactivated”. Theoretically maintenance of cooling for a further 24 hours may limit further brain injury, however there is no clinical evidence that routinely prolonging cooling to 96 hours improves neurodevelopmental outcome. CFM recording must continue.

Discussion and documentation about the decision to continue prolonged cooling with the baby’s parents is very important, as they should be aware of the lack of published evidence.
General Intensive Care

Ventilation

Some infants who require cooling will initially require ventilation as a consequence of their encephalopathy or anticonvulsant medication, however many of the moderate HIE cases will not need ventilation support.

Maintain SaO2 >95%
Maintain PaO2 between 6-10KPa and PaCO2 between 5-7KPa.

Overventilation is a common problem. Remember that the lungs are often ‘normal’ – babies are not being ventilated for intrinsic lung disease, and cooled babies produce less CO2 due to the reduced metabolic rate. Low inflation pressures (12-14 cm H2O) and rates (10-20/min) may be quite sufficient to achieve ventilation.

Non-invasive CO2 monitoring should be used.

Watch out for complications such as pneumothorax or meconium.

Do not assume that babies will be able to breathe independently simply because their ventilation requirements are low.

Severe hyperoxaemia with PaO2 greater than 27kPa and hypocarbia with PaCO2 less than 2.6 kPa are associated with poor outcome. Low PaCO2 causes cerebral vasoconstriction

Ventilator gases should be warmed and humidified in the normal way

Cooling does not appear to have any direct effect on central respiratory function. Persistent Pulmonary Hypertension of the Newborn (PPHN) or meconium aspiration may coexist with HIE and should be treated with the necessary ventilatory support including HFOV and nitric oxide if necessary.

Blood gases should ideally be taken from central/peripheral arterial lines. Due to cool peripheries the pH will be low on a capillary sample. Ensure the baby’s core temperature is entered into the blood gas machine when analysing the sample to ensure that correction for temperature is performed by the analyser.

Correction of Acidosis

Correct respiratory acidosis by manipulating ventilatory support. Avoid PaCO2 <5 kPa
Half-correct persisting severe metabolic acidosis with bicarbonate over 30-60 minutes provided ventilation adequate i.e. PaCO2 has been normalised.
Intravenous volume (e.g. 0.9% sodium chloride) should not be given simply to correct metabolic acidosis unless hypovolaemia has been diagnosed.

Cardiovascular

Cardiovascular instability, and hypotension, metabolic acidosis and pulmonary hypertension are commonly seen. Hypotension must not be assumed to be due to blood loss unless this is clinically suspected. In fact, hypovolaemia is not consistently associated with asphyxia and giving volume replacement may worsen cardiac function due to the dysfunctional myocardium.

Blood pressure is a poor predictor of low cardiac output. Assessment of the baby should include assessment of peripheral perfusion (capillary refill time, urine output and lactate). Think about myocardial dysfunction due to asphyxia, hypovolaemia / blood loss, sepsis or mechanical causes such as high mean
airway pressure on mechanical ventilation. Echocardiography is useful to determine filling and contractility and troponin levels are routinely checked on the NE1 blood panel.

As a guide, aim for mean arterial pressure ≥40mmHg

Refer to Guideline on managing hypotension for advice on choosing inotrope and treatment. Do not exceed 20 micrograms/kg/hour of dopamine or dobutamine. Rarely hydrocortisone or epinephrine (adrenaline) infusion may be needed (see formulary for dose).

ECG and biochemical markers, such as troponin levels, may help in the assessment of myocardial dysfunction. Cardiovascular support should be directed at improving cardiac contractility and systemic perfusion.

Bradycardia (<110bpm) is normal during cooling as is a slightly 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 can happen during cooling usually resolve with rewarming.

**Beware a pulse rate >110bpm** – assess for infant distress or pain and consider other causes such as sepsis.

During the rewarming process, a rise in body temperature may cause hypotension by inducing peripheral vasodilatation. However whenever hypotension occurs the cause should be investigated. If hypovolaemia is suspected an initial bolus of 10-20ml/kg of normal saline should be given and repeated if necessary. However fluid boluses should be used with caution in infants with HIE as myocardial function is often compromised and inotropic support should be considered early.

### Fluids and Nutrition

Renal function is likely to be impaired in severe cases of HIE. 40ml/kg/day is usually adequate intake for these infants. Urine output needs to be monitored and a urinary catheter is recommended. Once urine output of 1ml/kg/hr is established after 24 hours, fluids can be cautiously increased.

If they are in renal failure this may be dropped to 30ml/kg/day plus any measured losses. Bolus infusions of saline may be required to treat hypovolaemia if diuresis occurs or vasodilation occurs during rewarming.

Hypoglycaemia can be an issue with infants with HIE. At 40mls/kg/day of 10% dextrose, a total of 2.8mg/kg/min of glucose is administered which would normally be inadequate. However reduced metabolism may mean that BSL are normal and the cooling meta-analysis confirmed that hypoglycaemia is less common in cooled than non-cooled babies. However be vigilant (4 hourly monitoring until stable) and use higher dextrose concentrations if needed. Central access should be obtained early to allow for this (a maximum of 12.5% dextrose can be delivered peripherally). Blood glucose must be regularly monitored and normoglycaemia BSL>2.7 mmol/L (>3 mmol/L preferred) maintained. Care must be taken regarding the potential accumulation of nephrotoxic drugs such as aminoglycosides in the event of renal impairment.

### Feeding

There is now plenty of experience from around the world that babies can be safely fed breast milk and formula during cooling – start at 20ml/kg/day and increase the next day bd-tds as tolerated. In babies with multisystem involvement and severe NE caution is still advised however. Feed intolerance may be seen and there is even a risk of necrotising enterocolitis with concerns about reduced blood flow in tissue microcirculation during cooling. These babies are initially catabolic and parenteral nutrition should be used, especially where feeding is likely to be delayed. Advice and support for mothers regarding expressing and the impact of acute stress on milk production should be provided early. Skin to skin contact should be initiated as soon as possible, even if the baby is nil by mouth or on trophic feeds. If feasible, a SLT assessment should be undertaken in infants where there have been concerns regarding chest status, secretion management, absent or minimal sucking or swallow behaviours noted, although the provision and availability of SLT is sometimes limited.
Electrolytes

Correct electrolyte abnormalities & hypoglycaemia. Check all doses in formulary

Hypoglycaemia: 10% dextrose 2ml/kg bolus, followed by IV maintenance at a higher intake than previous

Hypocalcaemia: Calcium gluconate 10% (0.22 mmol calcium/ml). Give 0.11-0.46 mmol/kg slow iv (0.5-2ml/kg of 10% solution) with ECG monitoring

Hypomagnesaemia: MgSO4 50% solution diluted to 10% (2 mmol Mg2+/ml): Give 0.2 – 0.4 mmol/kg/dose (0.1-0.2ml/kg/dose) every 6-12 hours slow IV

Hypo -hypernatraemia: slow rehydration, dependent on cause

Neurology

The amplitude-integrated EEG (aEEG) is a single or dual channel time-compressed and filtered EEG which is recorded on a cerebral function monitor (CFM) providing a record of global or hemispheric electrical activity.

Continuous aEEG recording during the treatment period is helpful clinically to assess the occurrence of seizures and monitor the severity of encephalopathy. Anticonvulsant therapy and sedative drugs may cause reversible suppression of EEG activity. Ideally the aEEG should be commenced before administering anticonvulsant therapy, although if not available treatment of seizures should not be delayed until an aEEG is performed.

aEEG/CFM monitoring aEEG (Cerebral Function Monitoring) is to be recorded in all infants treated with cooling but cooling should not be delayed until the CFM is started. Please use the dual channel (OBM) monitor if possible. See Appendices 2 and 3 for guidance on placing needle electrodes correctly.

Seizures

There is evidence that seizures can cause additional damage to the brain. Clinical seizures following HIE can be difficult to diagnose and treat. All infants undergoing cooling should have continuous, preferably dual channel, aEEG 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 or prolonged seizures, frequent (3/hr) sub-clinical (aEEG/EEG) seizures should be treated with anticonvulsants. Whilst anticonvulsant treatment is important, it can be useful to document aEEG patterns prior to anticonvulsant administration.

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. It is also important to remember the effect of anticonvulsant therapy on the aEEG/EEG, all of which can suppress the background activity. However we must not add polypharmacy and drug interactions to the problems already faced by these babies.

First Line Therapy: Phenobarbitone

Load with 20 mg/kg IV. Emergency blood levels may be obtained to ensure adequate levels are in place before using second line therapy. Consider a second loading dose to a maximum total loading dose of 30mg/kg of phenobarbitone if ventilated.
Second Line Therapies: Midazolam, Lidocaine, Phenytoin, Clonazepam

Local practices vary and there is no good evidence that any one drug is superior at suppressing seizures in these infants. Discuss escalation of anticonvulsant medication with the Consultant. Phenytoin should not be given any faster than 1mg/minute. Midazolam may accumulate (see formulary)

Do not give phenytoin if there are signs of cardiovascular compromise. Severe bradycardia or ventricular tachycardia may occur after Phenytoin administration. Treatment of this is to discontinue the drug and initiate resuscitation measures.

Other:

If, despite two drug therapies, seizures are still persistent then any further anticonvulsant medication must be discussed with the Consultant. Other causes of intractable seizures in neonates should be considered, e.g. Pyridoxine deficiency and other inborn errors of metabolism. If in doubt discuss with a Paediatric Neurologist.

Only 30-50% of babies will respond to phenobarbitone (control is often defined as a reduction of 80% or more in duration of seizures). In another study >75% babies that failed to respond to phenobarbitone also failed to respond to phenytoin.

Control is more likely in babies with mild-moderate EEG/CFM abnormalities, who are not in status, and this group who are controlled with phenobarbitone alone have a better prognosis.

Phenytoin increases electroclinical dissociation and can therefore be falsely reassuring unless CFM monitoring is used.

The requirement for more than one drug to control seizures is a poor prognostic feature, and the success rates of the second, third line and other drugs is going to be poor regardless.

The decision to use other anticonvulsants (e.g. lorazepam, paraldehyde, thiopentone etc) in acute management, or to vary the order given above, should be decided by a consultant.

Pyridoxine

A trial of Pyridoxine (50-100 mg IV stat) should be performed in conjunction with EEG monitoring if pyridoxine deficiency is suspected in an infant with intractable seizures who does not have an underlying aetiology determined. Documenting cessation of seizures and normalisation of the EEG within minutes of IV pyridoxine often makes diagnosis. However, if there is no initial suppression on the EEG and seizures persist, then a second trial of pyridoxine should be given. Both trials of pyridoxine should be given with EEG monitoring.

Opinions differ about the merits and demerits relating to thiopentone coma in the newborn.

Maintenance / stopping treatment

Ongoing maintenance therapy may be unnecessary, as seizures may “burn out”.

The outcome following neonatal seizures, duration of therapy and decision to stop anticonvulsant medication should be judged on an individual basis taking into account the neurological examination, aetiology of seizures and interictal EEG.

- If seizures have stopped and the neurological examination is normal- stop medication
- Neurological examination is abnormal & EEG normal - taper medication
- Neurological examination & EEG abnormal - continue medication or change medication

Make this evaluation prior to discharge and then review after 6 weeks in clinic
Choices include phenobarbitone, clonazepam, carbamazepine or topiramate, and should preferably be discussed with a neurologist. The general aim of treatment should be monotherapy. Anticonvulsants may be implicated in alteration of brain function and should be prescribed cautiously.

Check all dosages, modes and lengths of administration, side effects and interactions in the current neonatal formulary.

Sedation and Comfort

Experimental evidence suggests that stress may have adverse effects and may influence the therapeutic effect of hypothermia and therefore they may need ventilation for the period of cooling even if they have minimal requirements.

Signs of distress include tachycardia, facial grimacing and irritability. A HR >110bpm consistently in a cooled infant is suggestive of either distress or persistent seizures. It is important to assess 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. We find that an infusion of morphine at 5ug/kg/hr in non-ventilated babies is effective and does not cause respiratory depression.

The PINC scoring charts should be used to document comfort.

Pharmacology in cooling and HIE

In general, moderate hypothermia leads to a reduction in cellular metabolism. This means that the nutritional demands of the infant are reduced, which enables catabolism to be overcome despite fluid restriction.

It also means that cellular waste, such as carbon dioxide, is reduced, reducing ventilatory requirements. Cooling does not reduce the metabolism of gentamicin, however there is often renal impairment in HIE which could lead to excessive levels. A starting dose of 4mg/kg of gentamicin is used with measurement of levels prior to the second dose.

Phenobarbitone levels may also be useful to guide the initiation of maintenance treatment if needed.

Infection

Perinatal infection may co-exist with HIE. All babies should have a septic screen and be commenced on antibiotics (Benzyl Penicillin 25 mg/kg and Gentamicin 4mg/kg) as soon as possible after birth. It is important to consider viral infections such as herpes simplex. A clear history should be taken and the use of aciclovir considered. Whilst cooling is associated with increased risks of pneumonia in adults, no association has yet been described for neonates being cooled. Beware the cooled infant with tachycardia, they may be septic.

Impaired synthetic liver function/consumptive coagulopathy

Disseminated intravascular coagulopathy (DIC) is a significant risk after hypoxic injury to the liver. Liver function tests, clotting and platelets should be monitored regularly. Standard treatments (e.g. FFP, cryoprecipitate, platelets, vitamin K) should be given to treat disturbances in clotting or low platelets.

If the infant already has DIC, cooling may aggravate it. In the event of clinically significant bleeding despite active management, aggressive correction of coagulopathy should ensue. If active bleeding is present it is important to exclude intracranial haemorrhage as this may necessitate neurosurgical management.
INVESTIGATION OF NEONATAL ENCEPHALOPATHY

Laboratory Investigations

NE1 blood profile should be requested each day during the period of cooling.

Further investigation of encephalopathy consider

- FBC
- Blood film
- U&E including calcium and magnesium
- Clotting screen including fibrinogen
- Cord and Blood gases including lactate and glucose
- Liver function including gammaGT
- CRP
- Blood culture
- CSF culture (consider bacterial, viral, metabolic investigations)
- Urine culture
- Congenital infection screen
- Maternal Kleihauer (if anaemia in baby or APH)
- Creatine kinase
- Metabolic screen including ammonia, amino acids, uric acid
- Urine for amino and organic acids, ketones, reducing substances
- Genetic investigations if dysmorphic features

Other

- ECG if cardiac involvement suspected
- Thrombophilia screening can be carried on parents. Speak to haematologist beforehand.

In the presence of

- parental consanguinity
- abnormal intracranial anatomy
- severe IUGR
- unusual pattern of injury on ultrasound and/or abnormal MRI scan
- normal ultrasound / MRI scan in face of ongoing neurological problems

think about rarer diseases and consider getting expert help.

Use the investigation flow chart (Appendix 5) and keep it in the baby’s notes

Placental assessment – important and often not done. Go and look at it yourself. Ask the obstetric registrar for help if you are uncertain. Do not allow it to be discarded!

Appearance, pale/gritty/complete, weight, cord insertion

Ask for placenta to be sent for histology with full description of events leading to birth of baby.
Imaging

X-ray
Chest / abdominal films should be performed in babies who are ventilated / have umbilical or other central lines / if concerns about respiratory distress / meconium or any other clinical concerns. If images have been performed in local hospitals, ensure that urgent image linking is done and request disc copies if this is not possible.

Cranial ultrasound
Scans should be performed on admission (<4 hrs if possible) and then daily for the first three days of life, then again at 1 and 2 weeks. Remember to use the term baby setting on the US machine. Some changes only appear at 72-96 hours after delivery. Estimation of resistance index may be useful. Reduced resistance index (<0.55) in anterior cerebral artery after 24 hours of life is associated with cerebrovascular vasodilatation and is linked with an increased risk of adverse outcome.

Look for:
- Evidence of normal anatomical development
- Abnormal echogenicity from the parenchyma present on first scan (suggesting recent insult pre-dating labour and delivery or e.g. evidence of calcification suggesting longer standing problem)
- Haemorrhage – existing at birth and developing haemorrhage
- Loss of normal tissue differentiation
- Narrow ventricles may be normal and “cerebral oedema” is probably overdiagnosed
- Early cerebral oedema – generalised increase in echogenicity, indistinct sulci and narrow ventricles with a hazy appearance
- Cortical highlighting with enhanced contrast between the cortex and the subcortical white matter
- After 2-7 days of age, increased echogenicity of thalami and parenchymal echodensities
- After 7 days more significant changes including ventricular enlargement, parenchymal cysts/lucency and evidence of cortical atrophy may be seen
- Relative increase of end-diastolic blood flow velocity compared to peak systolic blood flow velocity
- Beware haemorrhage in the posterior fossa which can be difficult to define
- Extracerebral haemorrhage is often of intermediate or low echogenicity

All cranial ultrasound scans will be reviewed in a weekly meeting. Junior staff are not expected to give or explain ultrasound findings to parents unless they feel confident and experienced in doing so. Results do not normally need to be discussed out of hours.

Magnetic Resonance Imaging (MRI)
MRI is the imaging modality of choice for assessing the distribution of injury and likely prognosis and to support a diagnosis of hypoxic ischaemic encephalopathy.

Getting a good image is important, and the use of chloral hydrate 100mg/kg about 45 minutes prior to the scan is often useful. Babies must be accompanied by neonatal staff and monitored throughout their scan. Babies and staff must have metal checks done (MR staff will perform) before the scan starts.

Early conventional imaging (within the first 5 days of life) may not reflect the true extent of the injury, although abnormalities may be seen on diffusion weighted imaging. Early imaging may be considered in very sick infants where discontinuation of intensive support may be being considered or where the clinical assessment is suggestive of other causes of encephalopathy (e.g. subdural haemorrhage).

The most accurate prognostic information can be obtained at 7-10 days of age. Infants who develop signs of HIE following an acute sentinel event (e.g. placental abruption) often sustain bilateral and usually symmetrical lesions within the basal ganglia and thalami, and exhibit an abnormal appearance in the posterior limb of the internal capsule (PLIC). Abnormality seen in the PLIC is an excellent predictor of abnormal neuromotor outcome. More chronic hypoxia-ischaemia is associated with cortical and subcortical abnormalities.

Parents should be advised that formal scan reports may take 2 or more weeks to be available as they are reported by a paediatric neuroradiologist. It is important that we do not give preliminary results which may be inaccurate.
Neurophysiology

Cerebral Function Monitoring (CFM) of the aEEG

The amplitude-integrated EEG (aEEG) is a single or dual channel time-compressed and filtered EEG which is recorded on a cerebral function monitor (CFM). The aEEG provides useful information on overall global or hemispheric electrical activity. Continuous aEEG recording during the treatment period is helpful clinically to assess the occurrence of seizures and monitor the severity of encephalopathy. Anticonvulsant therapy and sedative drugs may cause reversible suppression of EEG activity.

Ideally the aEEG should be commenced before administering anticonvulsant therapy, which should be discussed with the network NICU consultant on duty for babies in other hospitals without access to CFM monitoring.

Abnormal aEEG may be a reason to initiate cooling even if a baby is outside standard TOBY criteria. A normal aEEG record in the first 6 hours of postnatal life indicates a high probability of normal outcome if clinical signs of encephalopathy are absent AND the baby is not cooled. However cooling appears to reduce the predictive value of the aEEG, so caution is needed stopping cooling early is being considered. Apparent improvement of the aEEG after 6 hours of age, however, is not an indication for discontinuing cooling.

Full EEG

A formal EEG provides information on regional background cerebral activity and can detect some seizures and other abnormalities not seen using aEEG. The most useful prognostic information can be obtained once the infant has been rewarmed and is off anticonvulsant medication.

Discuss with the attending consultant the requirement for formal EEG. It is preferable for the baby to attend the neurophysiology department for this test.

Further investigations

Sometimes specialist advice may be sought from paediatric neurology / paediatric musculo-skeletal specialists. Specialist investigations may be requested which cannot be performed at St. Peter’s (e.g. nerve conduction studies) and may require transfer of the baby.
PROGNOSIS

The prognosis for infants with HIE depends on the evolution of encephalopathy over the first 72 hours and it can be difficult to assign prognosis until this time. Careful neurological scoring, examination and documentation are important and together with information from neurophysiology and imaging investigations can provide valuable early prognostic information.

When counselling parents it is important to emphasize that it is never possible to be entirely confident regarding long term neurodevelopmental outcome based on early findings and to this end long term follow up is important to ensure that problems, if apparent, are identified early and appropriate referral to specialist services are made in an expedient manner.

The British Association of Perinatal Medicine (BAPM) currently recommends that a formal neurological examination and a psychomotor assessment should be carried out at approximately 2 years of age. Other problems may emerge later in childhood.

The 2012 NICHD study of 6-7 year olds treated with cooling showed that cooling decreased the rate of death or IQ <70 (combined outcome) from 62% (no cooling) to 47% (cooled). The rate of death was significantly reduced in the children who had the cooling treatment to 28 percent, versus 44 percent for the standard treatment.

The prognostic values of early clinical assessment, electrophysiological tests and imaging is below.

<table>
<thead>
<tr>
<th>Test</th>
<th>Timing</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apgar Score</td>
<td>10 minutes</td>
<td>Score of 5 (range 4-7) predicts survival to discharge, score of 3 (range 0-5) predicts death before discharge (p&lt;0.001)</td>
</tr>
<tr>
<td>Sarnat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early onset neonatal encephalopathy is the best single predictor of long-term outcome</td>
<td>ensitivity of the acute encephalopathy predicts the overall risk of death and severe handicap</td>
<td></td>
</tr>
<tr>
<td>Quick recovery is associated with a better outcome</td>
<td><strong>Stage 1 HIE</strong> – normal neurologic outcome in greater than 90% of cases</td>
<td></td>
</tr>
<tr>
<td>Persistence of Stage 2 &gt; 7 days</td>
<td><strong>Stage 2 HIE</strong> – incidence of poor outcomes ranges from 30- 60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Stage 3 HIE</strong> – poor neurologic outcome (death or severe disability in almost all cases)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>However babies difficult to classify and often cross between stages, making prognostication impossible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurological impairment or death</td>
</tr>
<tr>
<td>Thompson (full)</td>
<td>Horn et al</td>
<td>Can predict encephalopathy. However no data yet for the modified score collected on Badgernet</td>
</tr>
<tr>
<td>Seizures</td>
<td>Early onset of seizures</td>
<td>May predict a poorer neurodevelopmental outcome, independent of the severity of hypoxic-ischaemic brain injury</td>
</tr>
<tr>
<td>Time to spontaneous respiration</td>
<td>Greater than 30 minutes</td>
<td>Overall risk of death or severe handicap 72%</td>
</tr>
<tr>
<td>Time to feed, fix and follow</td>
<td>By 7 days</td>
<td>Generally a good prognosis</td>
</tr>
<tr>
<td></td>
<td>By 10-14 days</td>
<td>May still have significant basal ganglia injury with choreo-athetoid CP development but preservation of intellect and head growth</td>
</tr>
<tr>
<td></td>
<td>2-3 weeks adequate feeding</td>
<td>Often have slightly slow visual attention. May look well but have significant white matter injury that will lead to relative microcephaly and some slowness in learning, sometimes without a major motor problem</td>
</tr>
</tbody>
</table>
### Electrophysiology

<table>
<thead>
<tr>
<th>Test</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>aEEG / CFM</strong></td>
<td>aEEG at an early age (within several hours after birth) can differentiate between babies with later severe neurologic deficits and babies with mild deficits or normal outcomes</td>
</tr>
<tr>
<td></td>
<td>Severe abnormal aEEG 28% survive to discharge, 81% die</td>
</tr>
<tr>
<td></td>
<td>The course of aEEG background activity adds to the prognostic value of aEEG monitoring in asphyxiated babies</td>
</tr>
<tr>
<td></td>
<td>Normalisation of initially abnormal background patterns (burst suppression, continuous low voltage, flat trace) by:</td>
</tr>
<tr>
<td></td>
<td>▪ 6 hours of age is predictive of good outcomes – positive predictive value (PPV) 91%</td>
</tr>
<tr>
<td></td>
<td>▪ 24 hours of age is less predictive of good outcome – PPV 61%</td>
</tr>
<tr>
<td></td>
<td>▪ Normalisation after 24 hours in infants cooled may be associated with a good outcome</td>
</tr>
<tr>
<td></td>
<td>▪ Severe abnormal patterns persisting beyond 24 hours are predictive of adverse neurodevelopmental outcomes</td>
</tr>
<tr>
<td></td>
<td>▪ Adverse outcome is x 19 more likely when abnormal background pattern (burst suppression or worse) occurs between 24 –36 hours</td>
</tr>
<tr>
<td></td>
<td>▪ Onset of sleep wake cycling within 36 hours of birth, is predictive of good neurodevelopmental outcome – PPV 92.1%</td>
</tr>
<tr>
<td></td>
<td>Background is affected by several medications and must be considered when interpreting the aEEG trace</td>
</tr>
<tr>
<td></td>
<td>The predictive value of aEEG is reduced by cooling (Thorenson)</td>
</tr>
</tbody>
</table>

#### EEG

<table>
<thead>
<tr>
<th>Test</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>First few days of life after HIE</td>
<td>Background EEG abnormalities, detected in the first few days of life after HIE can provide prognostic information even in babies treated with hypothermia</td>
</tr>
<tr>
<td></td>
<td>Grade of abnormality predicts the rate of death or severe handicap</td>
</tr>
</tbody>
</table>

#### Imaging

<table>
<thead>
<tr>
<th>Test</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial Doppler</td>
<td>Resistive index measurement 24 hours after insult</td>
</tr>
<tr>
<td></td>
<td>Resistance index (RI) &lt;0.55 predicts adverse outcome with a sensitivity of 100% and specificity of 81%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI 1 – 30 days of age</td>
<td>Meta-analysis for predicting outcome: thirty-two studies (860 infants with NE). Conventional MRI during the neonatal period (days 1-30) had a pooled sensitivity of 91% (95% confidence interval [CI]: 87%-94%) and specificity of 51% (95% CI: 45%-58%). Late MRI (days 8-30) had higher sensitivity but lower specificity than early MRI (days 1-7).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRS 1 – 30 days of age</td>
<td>Proton MR spectroscopy deep gray matter lactate/N-acetyl aspartate (Lac/NAA) peak-area ratio (days 1-30) had 82% overall pooled sensitivity (95% CI:74%-89%) and 95% specificity (95% CI: 88%-99%)</td>
</tr>
</tbody>
</table>
Parents and “Scripts”

Talking to parents in clear and non-technical language is essential. All discussions should be documented in the notes (on the yellow communication sheets) with details of what was discussed and who was present. It is not acceptable to merely write “parents updated” or similar.

The first time parents are spoken with, go over the history and document their version of events. It may be useful for a midwife or obstetrician to speak to them early as many parents will be concerned that something could or should have been done to prevent the situation.

- Tell them the current problems
- Explain that investigations will be done and when we might expect some results
- Explain the degree of certainty or uncertainty about current problems and present situation
- When they will get some more information,
- When they can talk to the Consultant

When a baby with HIE is admitted to the Neonatal Unit the parents must be fully updated by the most senior clinician available. The decision to treat with cooling should be explained to the parents and the Parent Information Leaflet should be provided.

All discussions with the parents about their infants treatment should be documented clearly in the infant’s notes. Parents should be updated regularly and signposted to available information and support networks (Appendix 1).

Whilst slightly artificial, the table of “scripts” below aims to help less experienced neonatal staff give clear and consistent information to parents. These are not designed to be regurgitated exactly as written, but to give an idea of the clarity and information that is expected.

The Time=Brain project has developed a parent leaflet in use across the South East Coast which can be downloaded for use.
<table>
<thead>
<tr>
<th>Area</th>
<th>Script</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction and clarification of who is who</strong></td>
<td>Hello. My name is XXX. I am a XXX working on the neonatal unit. May I ask who you are? I have come to tell you about what is happening with your baby</td>
</tr>
<tr>
<td><strong>Resuscitation</strong></td>
<td>Your baby needed significant medical help after he/she was born to help him/her breathe. His/her heart was not beating / he/she was not breathing when he/she was born, and this only started XX minutes later. He/she appears to have suffered from the effects of lack of oxygen and blood supply to the brain</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>About 1-2 in 1000 newborn babies suffer from the effects of reduced blood flow or oxygen supply to their brain around the time of birth</td>
</tr>
<tr>
<td><strong>Consequences</strong></td>
<td>This can result in brain damage from direct injury and also from ongoing changes that begin around six hours after the injury.</td>
</tr>
<tr>
<td><strong>Could this have been prevented?</strong></td>
<td>That is a difficult question, and I will arrange for your midwife / an obstetrician to meet with you to discuss the delivery of your baby. It is not something that I can answer now as I don’t have the expertise to be able to tell you.</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>We don’t have any one test that gives you all the information you want. We will be doing quite a lot of tests which will help us work out how severe the problem is, and we will be able to tell you how severe the brain injury is likely to be. About 30 to 60% of babies may develop long-term problems. However some also have the ability to partially repair brain damage, which makes accurate predictions more difficult.</td>
</tr>
<tr>
<td><strong>Openness and transparency</strong></td>
<td>I can reassure you that we won’t hide any information from you. We always tell parents what is going on, and some days that will be good news and some days it will be bad news. But I can promise that we will be open and honest with you, and that we will try to answer all the questions that you have.</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>We want to give your baby cooling treatment as well as standard intensive care support. We will slowly lower his/her temperature to between 33 to 34°C and keep him/her cool for up to 72 hours. We use using specialist cooling equipment which automatically keeps the temperature stable. We need to put a temperature monitor in his/her bottom to do this. We will aim to keep your baby comfortable during cooling and we may use morphine or other sedation. After 72 hours of cooling, he/she will be slowly rewarmed to a temperature of 37°C. Cooling cannot completely prevent brain damage, but for many babies it reduces it.</td>
</tr>
<tr>
<td><strong>Transfer</strong></td>
<td>We want to transfer your baby to an intensive care unit. They will continue the cooling treatment and give any other treatments needed as well. A specialist team will come to collect and move your baby. They will explain to you what the process is.</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Cooling seems to be safe, but it should always be done in an intensive care unit. Your baby may be unwell and need intensive care, and there are some rare complications of cooling which we will monitor him/her carefully for.</td>
</tr>
<tr>
<td><strong>Feeding</strong></td>
<td>We would be happy to give your baby small amounts of breast milk. We can help you with how to express and store your milk.</td>
</tr>
<tr>
<td><strong>MRI Scan</strong></td>
<td>The MRI brain scan will be done on XXX, but it might take up to a month to get the formal report. It is reported by an expert from Great Ormond Street which is why there is a delay. If there was anything needing urgent treatment on the scan then of course we would tell you, but otherwise we plan to (a) have the result for you when you come back to the outpatient clinic or (b) send the result over to your baby’s paediatrician at XXX hospital who will discuss it with you in the outpatient clinic.</td>
</tr>
</tbody>
</table>
Withdrawal of intensive support

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

The bereavement services on NICU at St. Peter’s are excellent, but parents have other choices as to where their baby may be allowed to be extubated. For example the transport team could transfer an infant planned for palliative care to a hospice. Alternatively babies can be moved to a baby unit closer to home. There are also increasing situations where parents have extubated babies at home, with support from the transport team and other clinicians. Such transfers need careful planning, including notifying the coroner and the police, as these can be highly unusual events and vigilant members of the public may misinterpret the situation otherwise. The EMBRACE team have advice and checklists which may be useful (www.sheffieldchildrens.nhs.uk/embrace).

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 regional NICU. These cases should be discussed with the transport team and the NICU Consultant.

Staff and Communication

These cases are often difficult for everyone involved. In addition to the upset for families, staff in both the maternity and neonatal service may feel very sad and anxious about the delivery of a baby with NE. In addition, staff may have to deal with intense anger, hostility, sadness and other emotions from parents and families. This can be emotionally draining, especially as you need to carry on for your other patients.

Talk to the midwives and obstetricians involved and keep them abreast of the baby’s progress. Keep the midwives on the post-natal ward informed, as they will have close interactions with the parents. Let the GP and Health Visitor know early as they will be able to offer the family support.

All cases should be discussed openly in the morbidity and mortality meetings so that all staff have the opportunity to speak freely and have any thoughts, ideas or concerns documented. If you, or one of your colleagues, are feeling the emotional effects of any difficult case, then please ensure that you/they get the necessary support needed. It is normal to feel sad or upset for parents who have found themselves in a dreadful situation, but parents do not expect us to be as sad or upset as they are.

Risk Management

These cases are usually considered to be serious events. As well as the detailed notes, staff will often be expected to prepare a statement of their involvement in the case. If you are not experienced (yet) in writing such reports, please ask for advice from a senior colleague. Doctors may also get advice from their medical protection organisation. Remember that the purpose of these reviews is to establish if there were preventable factors from which we can all learn.

In addition, it may be appropriate to complete a risk-management form online, especially if you have any specific concerns. Online form here http://vesuvius/datix/live/index.php

For babies who have been transferred in from other hospitals, the consultant will inform the referring hospital about the case especially if there are risk management concerns.

Follow up

Babies who die see Bereavement Guidelines. Post-mortem examination should be strongly encouraged, as it may help to explain why a baby did not tolerate labour/delivery unexpectedly. There may be an additional unexpected diagnosis found in up to 30% of post mortems which may also have implications for future pregnancies.
Babies who are transferred back to their local hospital. All neurodevelopmental and medical follow up will be carried out by the local hospital. However we should try to encourage parents to come and visit us if they are passing nearby. In addition, we will ask them to return for a detailed neurodevelopmental assessment when they are 2 years old (corrected).

Babies who are being followed up at ASPH. The neonatal community nursing team should be involved early to plan the discharge of the baby. Babies may need to be discharged e.g. on nasogastric feeding and suction and high levels of parental training are needed. Resuscitation training will be required and an apnoea monitor may be offered.

An appointment should be arranged to see the named neonatal consultant about 6 weeks after discharge. If there are any special medical needs, then please discuss with the attending or named consultant. The community neonatal nursing team may also have input, and there may be involvement of physiotherapy or SALT for example. Some babies may need surgical referral for e.g. severe gastro-oesophageal reflux disease, insertion of gastrostomy, insertion of central lines etc

In addition, these babies will be seen at 6 months of age in the Neuro-developmental clinic which aims to detect emerging signs of cerebral palsy at an early stage to ensure that the community services, where available, can be mobilised. Early involvement of specialist services through White Lodge is recommended and the Health Visitor should be asked to undertake a referral with the parents’ consent.

If babies have particular medical dependencies (e.g. nasogastric tube feeding, home oxygen, congenital anomalies, severe brain injury etc) then an open access letter for A+E attendance should be provided to ensure that they will be reviewed by a paediatric doctor if they present to A+E for any reason

All babies will be offered a 2-year Bayley developmental assessment regardless of where their local follow up is.

Detailed documentation is essential, and a registrar should sign off the Badgernet summary for these complex cases. Parents should be given a copy of the summary at the time of discharge.

Research

Research is the only way that we can make progress, and the laboratory, animal and human research that led to the development of cooling is now saving the lives and brains of babies every day. More research is underway to consider different temperatures and durations of cooling, and the addition of other neuroprotective strategies such as the use of inhaled xenon, as well as looking at neuronal markers for prognosis. It is likely that “combination” neuroprotection will be more effective than single “magic bullets”, and future research will inevitably focus on targeting different types of neuroprotection depending on the underlying cause as well as predicting optimal responses to neuroprotective interventions. We participate in clinical research studies on NICU at St. Peter’s Hospital and we may approach families to offer them the chance to enrol their babies in studies.

Network and commissioning

Across our network, neuroprotection should aim to be consistent and to give parents and families consistent information, which is one of the aims of the Time=Brain project. Cooling is a standard of care. It does not “prevent brain damage” and families should never be told that their baby is being transferred so that everything can be “fixed”, which is a message that they sometimes seem to carry. Managing expectations is essential.

It is hoped that these cases would result in a consultant to consultant discussion. We should continue to encourage consultants to discuss babies who may benefit from cooling and general intensive care, so that they can be moved quickly from Special Care and Local Neonatal Units to the Neonatal Intensive Care Units. It is an accepted standard that all babies undergoing cooling should be in a NICU as part of intensive care and neuroprotection strategy.
Appendix 1

Useful Charities and Organisations

This is a non-exhaustive list of charities and contacts that may be useful to pass on to parents and families

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Description and Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bliss</td>
<td>For baby born too soon, too small, too sick – the special care baby charity, provides vital support and care to premature and sick babies across the UK. 0500 618 140 <a href="http://www.bliss.org.uk">www.bliss.org.uk</a></td>
</tr>
<tr>
<td>Child Bereavement Trust</td>
<td>Provide specialised support, information and training to all those affected when a baby or child dies, or when a child is bereaved. 01494 568 900 <a href="http://www.childbereavement.org.uk">www.childbereavement.org.uk</a></td>
</tr>
<tr>
<td>Child Death Helpline</td>
<td>The Child Death Helpline is a helpline for anyone affected by the death of a child of any age, from prebirth to adult, under any circumstances, however recently or long ago. Freephone 0800 282 986 Freephone for mobiles 0808 800 6019 <a href="http://www.childdeathhelpline.org.uk">www.childdeathhelpline.org.uk</a></td>
</tr>
<tr>
<td>Compassionate Friends</td>
<td>A charitable organisation of bereaved parents, siblings and grandparents dedicated to the support and care of other bereaved parents, siblings, and grandparents who have suffered the death of a child/children 0845 123 2304 <a href="http://www.tcf.org.uk">www.tcf.org.uk</a></td>
</tr>
<tr>
<td>Newlife</td>
<td>Provides practical support for disabled children throughout the UK, cares for the carers, funds medical research, creates awareness and campaigns for change. 01543 462 777 <a href="http://www.newlifecharity.co.uk">www.newlifecharity.co.uk</a></td>
</tr>
<tr>
<td>SANDS</td>
<td>Stillbirth and neonatal death charity – supporting anyone affected by the death of a baby and promoting research to reduce the loss of babies’ lives 020 7436 5881 <a href="http://www.uk-sands.org">www.uk-sands.org</a></td>
</tr>
<tr>
<td>Scope</td>
<td>Support disabled people and their families through practical information and support, particularly at the time of diagnosis. 0808 800 3333 <a href="http://www.scope.org.uk">www.scope.org.uk</a></td>
</tr>
<tr>
<td>Together for Short Lives</td>
<td>For all children with life-threatening and life-limiting conditions, supporting families, professionals and childrens hospices 0845 108 2201 <a href="http://www.togetherforshortlives.org.uk">www.togetherforshortlives.org.uk</a></td>
</tr>
</tbody>
</table>
Appendix 2

Sub-dermal Needle Electrode Placement for Natus OBM4 Dual Channel monitor

Use the positioning strips to ensure that the needles are correctly sited, or else the tracing is very hard to interpret.

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Position infant supine</td>
</tr>
<tr>
<td>2</td>
<td>Place the sensor positioning strip vertical and parallel to the face, and align it so that the letter (A, B etc) is the same at both the ear tragus and on the sagittal suture. The forward edge of the strip should touch the ear tragus. A close up view of the strip is presented in Appendix 3</td>
</tr>
<tr>
<td>3</td>
<td>Mark the sites for electrode insertion on either side of the two-headed arrow on the positioning strip. Note: DO NOT shave these insertion marks.</td>
</tr>
<tr>
<td>4</td>
<td>Clean the scalp around the insertion sites with cleaning solution appropriate for gestation age. It may help to create a vertical part in the hair.</td>
</tr>
<tr>
<td>5</td>
<td>Site electrodes in the following manner. Insert a needle electrode subdermally at insertion sites. Ensure all leads are directed to the top of the head (so needles angle downwards) Secure electrode with a small amount of tape using a cross over method Connect electrodes to the sensor adaptor set</td>
</tr>
<tr>
<td>6</td>
<td>Gently turn infants head over and repeat process.</td>
</tr>
<tr>
<td>7</td>
<td>Discard the paper sensor positioning strip – it is a single patient use item</td>
</tr>
<tr>
<td>8</td>
<td>The reference electrode can be sited subdermally in the midline, adjacent to the anterior fontanelle, or a hydrogel (stick-on) can be placed on a site with no hair, or near the shoulder Clean the area with water and gauze Site electrode with lead directing towards the top of the head</td>
</tr>
<tr>
<td>9</td>
<td>Plug into the data acquisition unit (DAU)</td>
</tr>
</tbody>
</table>
Appendix 3

Close up view of Natus positioning strips
Appendix 4

Sub-dermal Needle Electrode Placement for Olympic 6000 single channel CFM

Biparietal placement

If using the single channel monitor (because the dual channel monitor(s) is/are unavailable, then the positioning of the 3 electrodes is different.

They should be placed as below. Please use a tape measure to ensure correct placement.

![Diagram showing electrode placement](image)
Appendix 5

PASSIVE COOLING PROTOCOL

BABY FITS COOLING CRITERIA

Nurse baby naked in open incubator with heat switched off
Start continuous rectal temperature monitoring
Record rectal temperature every 15 minutes

ASSESS BABY’S TEMPERATURE & TAKE ACTION
Aim to achieve therapeutic range within 2 hours of commencing cooling

TARGET TEMPERATURE 33 - 34°C

Temp >34°C
Consider use of fan
See guidelines for other cooling options
CARE as temp approaches 34°C not to OVER COOL

Temp <33°C
Put hat on baby
Turn on incubator to lowest setting and adjust accordingly
REWARM at 0.5°C/hr until at TARGET TEMPERATURE

Maintain temperature within this range
May need to add hat/turn on incubator to lowest setting or use fan as appropriate

RECORD TEMPERATURE EVERY 15 MINUTES
## Appendix 6
### Investigations Flow Chart for Notes

Name:  
DOB:  
Hospital number:  

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Sample</th>
<th>1st - 4th line?</th>
<th>Date sent</th>
<th>Date chased</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imaging/traces etc.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrUS</td>
<td>N/A</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFM</td>
<td>N/A</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEG</td>
<td>N/A</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>N/A</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>N/A</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord gases</td>
<td>Cord blood gas</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placental histology</td>
<td>Placenta</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal kleihauer</td>
<td>Maternal blood</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood gas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABG</td>
<td>Blood gas</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood - 10ml should be sufficient except thrombophilia screen (d/w haematologist)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U&amp;E’s</td>
<td>1 yellow for all these tests…</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFT’s</td>
<td></td>
<td>2</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ca++</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg++</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td>2</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cardiac enz</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CK</td>
<td></td>
<td>4</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TORCH scr</td>
<td>1 full yellow</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amino acids</td>
<td>1 full yellow</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum save</td>
<td>1 full yellow</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBC</td>
<td>1 purple</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood film</td>
<td>1 purple</td>
<td>2</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Clotting</td>
<td>1 full blue</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spun PCV</td>
<td>1 cap. tube</td>
<td>1</td>
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<td></td>
<td></td>
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<tr>
<td>BC’s</td>
<td>1 BC bottle</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ammonia</td>
<td>1 full green (inform lab)</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosomes</td>
<td>1 full green</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>See above</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CSF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF M,C&amp;S</td>
<td>CSF</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>CSF</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>CSF</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyruvate: lactate ratio</td>
<td>CSF</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td>CSF</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frozen CSF</td>
<td>CSF</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV DEAFF</td>
<td>Urine</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amino acids</td>
<td>Urine</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic acids</td>
<td>Urine</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red. subs.</td>
<td>Urine</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketones</td>
<td>Urine</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicology</td>
<td>Urine</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frozen urine</td>
<td>Urine</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 7

Hammersmith Neurological Examination

The Hammersmith Short Neonatal Neurological Examination is reproduced below. It assesses the following areas:

1. Posture / tone
2. Movements
3. Reflexes
4. Orientation and behaviour

This can be printed out and then simply ticked/circled as indicated to generate a structured neurological examination. File the paper copy in the notes for the correct day.

It is most useful to fill this in regularly for babies with ongoing neurological concerns.

The targets in Appendix 7 can be printed off to assess visual attention.

Also note whether:
- secretions are copious
- suction is needed
- gag reflex present
- pupils are reactive/small/large
- spontaneous eye opening/movements
- tongue fasciculation is present
- there is excessive jitteriness or myoclonic type jerking
- when sucking movements start
- when feeding is established
<table>
<thead>
<tr>
<th>Posture</th>
<th>Legs</th>
<th>Posture</th>
<th>Legs</th>
<th>Posture</th>
<th>Legs</th>
<th>Posture</th>
<th>Legs</th>
<th>Posture</th>
<th>Legs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baby lying on back. Look mainly at position of the legs, but also note arms. You may change drawing.</td>
<td>arms &amp; legs extended</td>
<td>legs slightly flexed</td>
<td>legs well flexed but not adducted</td>
<td>legs well flexed &amp; adducted near belly</td>
<td>arms very flexed, legs very extended</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ARM RECOIL</strong> Quickly extend (straighten) both arms; put next to body. Count to two. Let go. Repeat 3 times.</td>
<td>arm does not flex</td>
<td>arm flexes slowly, not always, not completely</td>
<td>arm flexes slowly, more completely</td>
<td>arm flexes and remains flexed</td>
<td>arm difficult to extend; snap back forcefully</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ARM TRACTION</strong> Hold wrist and pull upward. Note flexion at arm, and resistance while shoulder lifts off table.</td>
<td>arm remains straight - no resistance</td>
<td>arm flexes slightly or some resistance fell</td>
<td>arm flexes well till shoulder lifts, then straightens</td>
<td>arm flexes and remains flexed as shoulder lifts up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LEG RECOIL</strong> Take both ankles, bend hips+knee. Quickly extend when infant not pushing. Let go. Repeat X 3</td>
<td>no flexion</td>
<td>incomplete flexion, not every time</td>
<td>complete slow flexion</td>
<td>complete fast flexion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LEG TRACTION</strong> Hold ankle, pull leg upwards. Look at flexion &amp; resistance as bottom pulled up.</td>
<td>leg straight - no resistance</td>
<td>leg flexes slightly or some resistance felt</td>
<td>leg flexes well till bottom lifts up</td>
<td>knee flexes - remains flexed when bottom up</td>
<td>flexion stays when back-bottom up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>POPLITEAL ANGLE</strong> Fix knee on abdomen (belly), try to extend knee with first finger. Note distance (angle) between upper and lower limb.</td>
<td>infant tries: effort better felt than seen</td>
<td>infant tries: effort better felt than seen</td>
<td>raises head but drops forward or back</td>
<td>raises head: remains vertical, wobbles</td>
<td>head upright or extended; cannot be passively flexed (pushed forward)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HEAD CONTROL (1)</strong> Baby sitting upright. Encircle chest with both hands holding shoulders. Let head drop forward.</td>
<td>no attempt to raise head</td>
<td>raises head but drops forward or back</td>
<td>raises head: remains vertical, wobbles</td>
<td>head in front of body</td>
<td>head up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HEAD CONTROL (2)</strong> Baby sitting upright. Encircle chest with both hands holding shoulders. Let head drop backward.</td>
<td>no attempt to raise head</td>
<td>infant tries: effort better felt than seen</td>
<td>raises head but drops forward or back</td>
<td>raises head: remains vertical, wobbles</td>
<td>head upright</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HEAD LAG</strong> Pull baby to sit by the wrists &amp; support head slightly.</td>
<td>head drops &amp; stays back</td>
<td>able to lift head slightly</td>
<td>lifts head in line</td>
<td>head in front of body</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VENTRAL SUSPENSION</strong> Hold baby horizontal under the belly. Look at posture of back, arms, legs, and head. If it looks different, DRAW!</td>
<td>back curved, head &amp; limbs hang straight</td>
<td>back curved, head &amp; limbs slightly flexed</td>
<td>back slightly curved, limbs flexed</td>
<td>back straight, head in line with body, limbs flexed</td>
<td>back straight, head above body</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Movements

<table>
<thead>
<tr>
<th>State</th>
<th>Asymmetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPONTANEOUS MOVEMENT</td>
<td>Watch baby while (s)he is lying on back.</td>
</tr>
<tr>
<td>no movement</td>
<td>few stretches, no other movement</td>
</tr>
<tr>
<td>jerky movement, stretches, but also some smooth movement</td>
<td>smooth movements of arms + legs</td>
</tr>
<tr>
<td>fits, cramped or other abnormal movements: DESCRIBE!!</td>
<td></td>
</tr>
</tbody>
</table>

| ABNORMAL HAND OR TOE POSTURES | Hands open |
| hands listed or thumbs adduct intermittently but open | hands fist or thumb adducts, or finger & thumb oppose |
| tremor only when crying or after Moro reflex | some tremor when awake |
| 2 or 3 spontaneous startles | big toe up (extended) or all toes flex |
| continuous tremors | |

| TREMOR | STARTLE |
| no tremor | no startle |
| tremor only when crying or after Moro reflex | startle to sudden noise or bang on table |
| some tremor when awake | 2 or 3 spontaneous startles |
| frequent tremors | 3 - 5 spontaneous startles |
| continuous tremors | more than 6 spontaneous startles |

## Reflexes = test both sides

| Suck & Gag | no gag / no suck |
| short, weak flexion of fingers | Infant suck well on the breast |
| strong flexion of fingers | strong suck: (a) irregular (b) regular |
| strong finger flexion, shoulder ↑ | Good stripping |
| strong finger flexion, whole body ↑ | |

| Palmar Grasp | no reaction |
| short, weak flexion of fingers | |
| toes flex (bend) slightly | toes curve around finger |

| Plantar Grasp | no response |
| full abduction of the arms, extension at the elbow, no adduction | full abduction, little or delayed adduction |
| arms do not fully abduct but good adduction | |
| • adduction only | • extension at the elbow only |

| Moro Reflex | Put baby in position shown in drawing 1 below. Bring head forward and suddenly let it fall back slightly. |
| nothing happens | baby flexes ankle |
| baby flexes hip, knee, and ankle & steps on table |

## Orientation and Behaviour

| EYES | does not open eyes |
| normal eye movement, eyes move together | abnormal eye movements: DESCRIBE!! |

| Auditory Orientation | Must not be asleep. Wrap infant. Hold rattle 10-15 cm (4-6 inches) from ear. |
| no reaction | brightens (wakes up) |
| turns eyes and sometimes turns head a bit also |
| turns eyes and head fully to side of noise |
| turns head and eyes strongly to noise; does not tire |

| Visual Alertness | Wrap infant, wake up with rattle if needed or rock baby a bit. Look if baby can see and follow red ball (R) or target (T). |
| does not follow or focus on red ball or target | stills, focuses, follows very briefly to side and up but loses it quickly |
| follows with eyes to the side and up, may turn head |
| follows with eyes to the side and up; turns head always |
| follows in a circle |

| ALERTNESS | Tested as response to red ball (R) or target (T). How long infant interested. |
| will not respond to red ball | when awake, looks only briefly |
| when awake, looks at red ball but loses it |
| keeps interest in red ball |
| does not tire |

| PEAK OF EXCITEMENT | Circle “H” if high-pitch cry |
| quiet all the time | awakes briefly, does not cry |
| awakes briefly, cries sometimes |
| cries always when handled |

| CONSOLABILITY | How easy is it to make baby quiet? |
| never awake or crying | wakes up or crying, consoling not needed |
| becomes quiet when talked to | needs picking up to console |
| cannot be consoled |

## Comment

| EXAMINER: | |

Appendix 7

Targets for assessing visual attention in the newborn (can be printed and cut out)
Appendix 8

References and useful reading (some references show key points from study)


www.BeBoP.nhs.uk  NHS Midlands and East Baby Brain Protection Website


East of England Perinatal Network Guideline for HIE


Harbert MJ et al. J Child Neurol 2011;26:1126 (better outcome in babies cooled with stroke)


Horn et al BMC Pediatrics 2013 April;13:52 (Thompson score predicts encephalopathy at 6 hours)


Lemmers PM et al Pediatr Res. 2013 May (Near infrared spectroscopy-monitored cerebral oxygen saturation in HIE)


Li T et al Hosp Pract (Minneap) 2009;37:147 (cooling up to 10 hours after birth)


Massaro AN et al Pediatr Crit Care Med. 2013 Mar;14:310 (glial fibrillary acidic protein)


Oza V; Treat J; Noah Cook; Michael T. Tetzlaff; Albert Yan. Subcutaneous Fat Necrosis as a complication of Whole-Body Cooling for Birth Asphyxia, Arch Dermatol. 2010;146(8):882-885.


Shankaran S et al Pediatrics 2011 Jul;128(1):e112 (Early aEEG does not change prognosis in moderate / severe HIE)


Statewide Maternity and Neonatal Clinical Guideline: Hypoxic-ischaemic encephalopathy (SMNCG: HIE), Queensland, Australia. May 2010


Thoresen M et al. Pediatrics. 2010 Jul;126(1):e131 (Hypothermia reduces the predictive value of the aEEG)

