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Fifteen Minute Consultation: Therapeutic Hypothermia for infants with hypoxic ischaemic encephalopathy: Translating jargon, prognosis and uncertainty for parents

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TITLE:
Fifteen Minute Consultation – Therapeutic hypothermia for infants with hypoxic ischaemic encephalopathy: Translating jargon, prognosis and uncertainty for parents

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Abstract:

Hypoxic Ischaemic Encephalopathy (HIE) may lead to death or severe long-term morbidity. Therapeutic Hypothermia (TH) increases survival without impairments in childhood, but prognostic uncertainty may remain for years after birth. Clear and accurate communication is imperative but challenging. This article explores the predictive value of routinely performed assessments during TH, as well as the qualitative research relating to parental experience. This article will benefit the paediatric trainees, consultants and nurse practitioners, in providing 1) the background information needed for initiating a conversation with parents regarding outcome and 2) optimising their communication with parents in translating jargon, prognosis and uncertainty.
Main text:

Neonatal Hypoxic Ischaemic Encephalopathy (HIE) is a potentially devastating condition, which may progress to moderate to severe short-term morbidity, long-term disabilities or death.[1-5] Controlled reduction of an encephalopathic infant’s core temperature, known as Therapeutic hypothermia (TH), increases survival without impairment in childhood. TH is the standard care in developed countries.[1-2]

TH is indicated in newborn infants with evidence of perinatal asphyxia resulting in moderate to severe encephalopathy. Grade of encephalopathy is determined clinically (based on Sarnat score) and/or with amplitude-integrated electroencephalography (aEEG; moderate or severely abnormal pattern). Criterion for perinatal asphyxia typically includes meeting any one of: [1, 4-5]

- Acidosis on blood sample from cord or within 1 hour of age: pH<7.0 or base excess ≤-16mmol/L
- Apgar score ≤ 5 at 10 minutes
- Need for resuscitation at 10 minutes after birth (Such as endotracheal or mask ventilation )

During TH, core temperature is reduced to 33-34°C for 72 hours, using a servo-controlled (automatic feedback) cooling wrap, mattress or cap. Infants require intensive care support and monitoring and are therefore frequently transferred to a tertiary neonatal intensive care unit, away from their parents.

Clear and accurate communication is imperative in order to minimise parental distress, but this can be difficult. Clear and effective communication can be achieved if:

1) Clinicians are aware of the accuracy of the prognostic tests they have performed, together with the level of uncertainty that exists
2) Clinicians have an appreciation of the turbulent parental experience and are able to filter the frequency, volume and detail of their communications to meet the needs of the parents in a step-wise fashion.
3) Clinicians are able to translate medical terms relating to the current condition of the baby, and the future implications of this, into plain/simple language.

This paper will explore each of these three points in turn. Firstly, by considering what prognostic information is available, and what weighting a clinician should place on this when considering certainty of outcome.

1) DETERMINING PROGNOSIS & UNCERTAINTY

Determining prognosis for an infant undergoing TH is a challenge for the attending clinician for many reasons:

- The initial working diagnosis of HIE may be incorrect (eg; encephalopathy due to sepsis, or metabolic conditions) and could be associated with other comorbidities (eg: cardiac or surgical problems)
- Pharmacological sedation may limit assessment
- No test is 100% predictive of infant outcome
- TH modifies the prognostic value of clinical and aEEG assessment[6]
- The prognostic value of many predictive markers may not be apparent until several days into the evolution of the infant’s abnormal neurological state
• Clinical trials report the composite outcome of ‘death and major neurodisability’, whereas clinicians must pragmatically try to separate these two entities[1, 4-5]

• Clinical trials and observational studies of cooled infants divide outcome into severe (death or disability) versus non-severe (survival without disability). Disability is often defined as the developmental scores being 1-2 standard deviations below the population mean, whereas a spectrum of neuromotor, cognitive and behavioural impairment may present through childhood[2-3, 7]

Death

Death following HIE is the most imminent outcome to prognosticate as this has immediate ramifications for both clinicians and parents. Accurate prognostication of death helps to 1) avoid futile but potentially distressing medical interventions, 2) offer appropriate palliative care with amelioration of pain and distress in the infant and 3) prepare parents for palliative care and/or death as much as possible (including attention to wider family, social support and cultural or religious requirements).

Death may occur due to global multi-organ injury, or following re-orientation of care due to severe brain injury. The ability to determine which infants are at highest risk of severe brain injury, in order to consider re-orientation of care, is, however, limited. Likewise, clinical trials are limited in their ability to provide prognostic markers of death of any cause. Nearly 75% of deaths reported in the TH clinical trials are following withdrawal or withholding of life-sustaining treatment, and are thus subject to bias.[1] This is reflected by the variable death rates in the contemporary cohorts of TH (6% - 23%). [8-11]

Clinicians should be alert to:

- **Imminent or inevitable death** in infants with severe encephalopathy and multi-organ failure who are deteriorating despite maximal intensive care support.

- **Infants in whom TH is futile and death highly likely.** These infants may only be identified with time, as sequential evidence of a severe hypoxic-ischaemic insult and absence of neurological recovery is required: [12]
  - Severe asphyxia: Apgar score < 3 at 10 min, and/or need for adrenaline during resuscitation, and/or an umbilical cord or first newborn blood gas pH<6.8 [12]
  - Initial severe encephalopathy: Abnormal aEEG background (continuous low voltage or flat trace) at 6-12 hours after birth [12]
  - Persistent abnormal aEEG background pattern at 24 hours of TH without improvement [12]

In all decisions relating to end-of-life care, the burden of treatment must be considered (e.g. are medical interventions causing non-ameliorable harm or discomfort without reciprocate benefit). In addition, clinicians must carefully examine their primary diagnosis of HIE to ensure potential reversible causes are not missed.

Disability
Neurodevelopmental disabilities in survivors include cerebral palsy, developmental delay or intellectual impairment, blindness, and deafness (definitions and incidences of neurodisability are provided in Table 1).[1, 14]

Table 1

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Percentage of Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Neurodisability at 18 to 24 months in survivors</td>
<td></td>
</tr>
<tr>
<td>Infants with moderate encephalopathy at baseline</td>
<td>29-32%</td>
</tr>
<tr>
<td>Infants with severe encephalopathy at baseline</td>
<td>20-27%</td>
</tr>
<tr>
<td>Infants with moderately abnormal aEEG at baseline</td>
<td>37-71%</td>
</tr>
<tr>
<td>Infants with severely abnormal aEEG at baseline</td>
<td>12%</td>
</tr>
</tbody>
</table>

Component outcomes within ‘Major Neurodisability’ (Definitions are provided in brackets)

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Percentage of Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromotor delay in survivors (Bayley Scales of Infant Development – PDI &gt;2 SD below mean)</td>
<td>26%</td>
</tr>
<tr>
<td>Developmental delay in survivors (Bayley Scales of Infant Development – MDI &gt;2 SD below mean)</td>
<td>25%</td>
</tr>
<tr>
<td>Cerebral palsy in survivors (Range of movement difficulties affecting posture and motor function and often associated with difficulties of vision, hearing, intellect, communication and feeding)</td>
<td>11-23%</td>
</tr>
<tr>
<td>Blindness in survivors (Vision &lt; 6/60 in both eyes)</td>
<td>6%</td>
</tr>
<tr>
<td>Deafness in survivors (Sensorineural deafness requiring amplification)</td>
<td>4%</td>
</tr>
</tbody>
</table>

Other outcomes not included in ‘Major Neurodisability’

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Percentage of Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>NG Feeds at Discharge</td>
<td>11%</td>
</tr>
<tr>
<td>Seizures/anticonvulsant treatment at follow-up</td>
<td>9-12%</td>
</tr>
</tbody>
</table>

Table 1: 18 to 24 month neurodevelopmental outcomes for infants treated with therapeutic hypothermia for Hypoxic Ischaemic Encephalopathy: Data extracted from [1, 10, 11, 14]. aEEG: Amplitude Integrated Electroencephalography, PDI: Psychomotor Development Index, SD: Standard Deviation, MDI: Mental Development Index.

Prognostic markers

Published studies typically reference the predictive value of prognostic markers relative to the composite outcome of death and major neurodisability. Based on data from these studies, many routinely performed assessments may be used to help further stratify ongoing risk of mortality and long-term disability. TH reduces the positive predictive value of many of these assessments:

A) Early markers of newborn condition: 
TH decreases ongoing brain injury following HIE. The predictive values of early markers of infant condition, such as the Apgar score, early blood pH and base excess, and admission Sarnat stage, are therefore reduced, with the exception of infants at the very extremes of poor condition.[6, 15-19]

B) Serial clinical neurological assessment using modified Sarnat staging: 
Impairment of renal and liver function, and reduced core temperature during TH, prolong the effect of sedatives. The evolution of an infant’s encephalopathic state, reflected by their Sarnat stage, is therefore modified. In addition, intensive care procedures, such as tracheal intubation, present barriers to clinical neurological examination. Neurological examinations performed after rewarming, and at discharge, have a lower false positive rate for death and disability, when compared with examination prior to commencing, or during, TH.[4, 18-19]
C) **Amplitude Integrated Electroencephalography (aEEG):**
aEEG provides clinicians with a continuous, objective measure of brain function. Time to normalisation of the background voltage pattern, as well as time to develop sleep-wake cycling, are currently the best predictors of survival without major neurodisability, during TH. Persistence of an abnormal aEEG background beyond 48 - 72 hours of age is highly predictive of later disability.[11, 20-21]

D) **Pattern of brain injury on Magnetic Resonance (MR)Imaging:**
Identification of moderate to severe abnormalities of the basal ganglia, thalami, internal capsule or white matter, following expert interpretation of MR brain scans, holds a high predictive value of death or major disability.[13, 22-23]

E) **Metabolite ratio and quantification on brain magnetic resonance spectroscopy:**
Thalamic Lactate-N acetyl aspartate (NAA) ratio > 0.22 predicted death or disability with an accuracy of 90%. Although spectroscopy offers an objective measure of brain injury, it requires post processing and is currently not in routine clinical use. Neurodevelopmental abnormalities may still occur, however, in infants with no obvious, or only minor brain tissue, diffusion-weighted or spectroscopy MR abnormalities.[13, 22-24]

**Figure 1** provides a chronological reference of predictive values of death and major disability, before, during and after TH. Accurate neurological examination and aEEG pattern interpretation are essential for achieving the stated prognostic values. Adequate training is essential for trainees to achieve competence in these skills. Normalisation of aEEG within 48hours of cooling, mild or no encephalopathy after rewarming or at discharge and a normal brain MR imaging increase the chances of a good prognosis.

**[Figure 1.]**

Prognostic certainty therefore increases with time, as more clinical, neurophysiological (aEEG), and neuroimaging information becomes available. Nevertheless, a degree of uncertainty will persist; clinicians should be open with parents regarding uncertainty. The degree of uncertainty portrayed is a fine balance; over- or understating uncertainty may unfairly give parents an unrealistic perception of their child’s risk of long-term impairment (see figure 2). Parents should be aware that no test or assessment is 100% predictive for death or severe disability.

**[Figure 2.]**

**Later Childhood Outcomes**

Follow-up data from TH trials, in children aged 6 to 7 years, are supportive that the neuroprotective benefits of TH continue into school-age. Benefits extend to both motor and cognitive domains, with increased survival with intelligence quotient ≥85, reduced rates of cerebral palsy and better gross motor function and manual ability scores.[2-3, 7] School-age outcomes for infants who received TH are shown in **table 2**.

**Table 2**

<table>
<thead>
<tr>
<th>Outcomes at 6 to 7 years following TH</th>
<th>Percentage of Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival[2, 3]</td>
<td>71-72%</td>
</tr>
<tr>
<td>Neurodisability in survivors[2, 3]; (Definitions are provided in brackets)*</td>
<td>14-16%</td>
</tr>
</tbody>
</table>

*Neurodisability in survivors includes a range of disabilities such as cerebral palsy, developmental delays, and cognitive impairments.*
(IQ <55 (<3 SD), GMFCS 4 or 5 (needs adaptive seating or has severely limited mobility), or no useful vision)

Moderate disability
(IQ 55-69 (2-3 SD), GMFCS 2[2] or 3[2, 3] (minimal ability to perform gross motor skills or requires assistance with walking), moderately reduced vision[2], bilateral deafness[3], or epilepsy requiring anticonvulsant therapy[3])

Mild disability
(IQ70-84 (1-2 SD), GMFCS 1[2, 3] or 2[3] (able to walk independently but may have some gait abnormalities), or abnormality in one or both eyes with normal or nearly normal vision[2])

No disability
(IQ ≥85 (≥1 SD), with no cerebral palsy, hearing or visual deficits, or epilepsy)

Specific neurological impairments in survivors[2, 3, 11]:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Palsy</td>
<td>11-21%</td>
</tr>
<tr>
<td>Bilateral blindness</td>
<td>1-1.5%</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>4-5%</td>
</tr>
<tr>
<td>Seizures or confirmed epilepsy</td>
<td>10-13%</td>
</tr>
</tbody>
</table>

Cognitive Function in survivors[7]:

<table>
<thead>
<tr>
<th>IQ Measure</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IQ: 80.9 (Range: 39 to 121)</td>
<td>---</td>
</tr>
<tr>
<td>IQ ≥85 (&gt;1 SD below the mean IQ)</td>
<td>48%</td>
</tr>
<tr>
<td>IQ ≥70 (&gt;2 SD below the mean IQ)</td>
<td>75%</td>
</tr>
</tbody>
</table>

Special Educational Needs in survivors[2, 7]:

<table>
<thead>
<tr>
<th>Need</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental reported behavioural problems</td>
<td>7%</td>
</tr>
<tr>
<td>Mainstream school with academic or behavioural educational support</td>
<td>31%</td>
</tr>
<tr>
<td>Special educational needs school</td>
<td>14%</td>
</tr>
</tbody>
</table>

Table 2: Outcomes at 6 to 7 years in children who received therapeutic hypothermia. *Differences in trial definitions are individually referenced. IQ: Intelligence Quotient, GMFCS: Gross Motor Function Classification System, SD: Standard Deviation.

A spectrum of neuromotor and cognitive impairment may thus occur. Cognitive impairment may occur even in the absence of cerebral palsy. Predicting isolated cognitive impairment at birth is not possible, but infants with cognitive or language difficulties at 18-24 months are at highest risk and are a group likely to benefit from preschool identification and early, pro-active, educational intervention.[25]

2) PARENTAL COMMUNICATION CHALLENGES

Parents experience uncertainty that may persist years into their child’s development.[26-27] The combined use of unexplained jargon and medical acronyms, as well as potentially contradictory statements by medical personnel risks augmenting parental confusion and their distress.[26]

Understanding Parental Experience and Expectations

Clinicians must be sensitive to the extreme stress parents are placed under, following the delivery and neonatal admission of an infant with suspected HIE. Parents are presented with an unexpected, rapidly emergent, adverse event that may threaten the life of their newborn child. Parents will have little control and little understanding, whilst the actions of the perinatal teams may appear chaotic.[26-27]

Information given in the early stages of an infant’s admission may be forgotten or misconstrued. Qualitative research identifies that parents often feel they are provided with infrequent and fragmented updates. Parents struggle to retain and organise information into logical thought.
processes.[26] Conceptualising ongoing uncertainty is then very difficult to achieve and, critically, involvement in complex decision-making is compromised.[26-27]

Optimal communication with parents

Clinicians may lessen the burden of communication in several ways. Parents benefit from frequent updates, use of plain English, and regular sign-posting to the next-step in their infant’s assessment and treatment. Summary discussions that review the infant’s progress from admission provide a vital opportunity to correct misunderstandings.[26-28] Communication to parents who cannot understand or speak the English language must include use of a qualified medical translator.

Parental-infant attachment is challenged due to early and prolonged separation. TH apparatus, ventilator tubing and monitoring present both physical and psychological barriers.[27-28] Opportunity to be involved in infant cares from an early stage, milk expression and normalisation of infant handling following rewarming may help.[27]

Parents face ongoing uncertainty about their child’s future following neonatal discharge. This is a significant source of distress. A clear post-discharge follow-up plan should be offered.[27]

Table 3 lists some of the key learning points that have been identified by qualitative research studies into parental experiences.

### Table 3

<table>
<thead>
<tr>
<th>§ 1) Consistent &amp; Frequent Communication:</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Brief update by the neonatal team prior to transfer to the Neonatal Unit</td>
</tr>
<tr>
<td>➢ Senior member of the neonatal team should update parents as soon as possible after admission</td>
</tr>
<tr>
<td>➢ If the mother is unable to come to the neonatal unit, the neonatal team should go to the mother (or direct telephone call where in a different hospital)</td>
</tr>
<tr>
<td>➢ Medical updates should be provided at least daily or after any significant event</td>
</tr>
<tr>
<td>➢ Ideally both parents, or alternatively an additional supporting family member, should be present for significant updates</td>
</tr>
<tr>
<td>➢ Summary discussions should be provided to clarify parents’ total understanding of events</td>
</tr>
<tr>
<td>➢ Obstetric debrief, before the mother’s discharge, will be beneficial for parental understanding of delivery events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>§ 2) Avoid Jargon &amp; Acknowledge Prognostic Uncertainty:</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Use simple lay language: explain jargon if used</td>
</tr>
<tr>
<td>➢ TH within guideline criteria is not experimental; parents should be reassured it is well-researched and ‘proven’</td>
</tr>
<tr>
<td>➢ Be honest regarding uncertainty; this is inevitable</td>
</tr>
<tr>
<td>➢ Share what prognostic information is known openly and honestly</td>
</tr>
<tr>
<td>➢ Ensure post-discharge follow-up is offered with sufficient time to address parental anxiety and questions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>§ 3) Address Barriers to Attachment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Parents should see, and by preference have physical contact with, baby prior to transport from delivery room</td>
</tr>
<tr>
<td>➢ Maximise opportunities for parental physical contact and involvement (e.g. stationary holding of infant’s hand, scheduled cares/nappy changes, and feeding if started)</td>
</tr>
<tr>
<td>➢ Ensure pain is monitored and attended to; reassure parents of this</td>
</tr>
<tr>
<td>➢ Provision of parent room on unit or patient hotel, if distance from home is barrier to parental visiting</td>
</tr>
<tr>
<td>➢ Explain the function of monitoring equipment used in basic terms</td>
</tr>
<tr>
<td>➢ Ensure early parental orientation to hospital facilities and unit routines (including coffee room / vending machines / restaurant, ward round / hand-over times, visiting hours for extended family &amp; parking)</td>
</tr>
</tbody>
</table>

**Table 3:** Key learning from qualitative studies investigating parental experiences following admission of an infant with Hypoxic Ischaemic Encephalopathy for Therapeutic Hypothermia (TH)[26-28]

### 3) TRANSLATING JARGON AND PUTTING IT ALL TOGETHER
Medical jargon related to TH and HIE will be novel, daunting and difficult for parents to recall. Use of clear language is important for parental understanding, and this is the immediate priority. It is, however, inevitable that parents will read or overhear medical terms during the course of their infant’s neonatal admission. For this reason, key medical terminologies should be explained to parents once their baseline understanding has been established. Common medical terms relating to HIE, with examples of lay explanations that parents may find helpful, are provided in the online supplementary figure 1.

Vague/ambiguous terms should be avoided, even in the presence of uncertainty. For example, ‘Developmental Delay’ is commonly used, but can be interpreted in many ways and should be avoided unless further clarification is provided. Parents may infer that their child will eventually attain all their milestones whereas there may be significant risk that the infant’s ability to walk, see, hear, communicate and learn will be permanently impaired.

Communication with parents should progress through several stages (Table 4). Each stage may need to be adapted if infant condition is critical, worsening, and ongoing treatment considered futile. Communication should be delivered in conjunction with multidisciplinary support, including the nursing team, family worker or perinatal psychologist.

### Table 4

<table>
<thead>
<tr>
<th>1. Immediate parental update (ideally in delivery room)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address the infant by name if parents have chosen one for their baby. Explain that:</td>
</tr>
<tr>
<td>a. Infant has been unwell and has required help/resuscitation at birth</td>
</tr>
<tr>
<td>b. Ongoing support if required (e.g. ventilation)</td>
</tr>
<tr>
<td>c. It is possible that the baby has had a period of reduced blood flow and oxygen to the whole body. This may lead to injury to the baby’s brain and other vital organs including the kidney, liver and heart.</td>
</tr>
<tr>
<td>d. It is too early to know how severely the baby has been affected</td>
</tr>
<tr>
<td>e. The infant will be admitted to the neonatal unit for further assessment and may need a treatment called ‘Cooling’ to protect the brain from ongoing injury</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Parental update following admission and TH commenced (undertaken by both medical and nursing team member looking after the infant):</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Ascertain parental understanding</td>
</tr>
<tr>
<td>b. Provide explanation of general condition of baby (including multi-organ support if relevant) and reiterate support they needed after birth (explain ventilation, chest compressions, medications)</td>
</tr>
<tr>
<td>c. Explain what HIE is (including risk of death or major disability)</td>
</tr>
<tr>
<td>d. Explain role and duration of TH &amp; need for transfer to ‘cooling centre’ (if relevant)</td>
</tr>
<tr>
<td>e. Explain TH improves survival and reduces the number of babies with severe long-term disability</td>
</tr>
<tr>
<td>f. Explain prognosis is uncertain but that over the next week it will become clearer how severely the baby has been affected; as response to TH is observed and results of investigations are available</td>
</tr>
<tr>
<td>g. Reassure infant will be kept comfortable and monitored by experienced staff</td>
</tr>
<tr>
<td>h. When at cotside: briefly explain the role of monitoring leads connected to baby (Pulse-oximeter, ECG, aEEG)</td>
</tr>
<tr>
<td>i. Summarise discussion at end, clarify parental understanding, offer time for questions and sign-post when next update is expected and what further information may be known at that time</td>
</tr>
<tr>
<td>j. Ensure parents will be given tour of neonatal unit, and that visiting rules, parking and hospital facilities will be explained</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Updates day 1 – 3 (in TH centre, preferably as a multidisciplinary team with nurses, family worker or psychologist):</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Update at least daily:</td>
</tr>
<tr>
<td>i. Overall clinical condition (e.g. Lung/Heart/Kidney function)</td>
</tr>
<tr>
<td>ii. Level of encephalopathy &amp; interpretation of aEEG if this aids with assessment of prognosis</td>
</tr>
<tr>
<td>iii. Seizure management, if required</td>
</tr>
<tr>
<td>iv. Explain timeline for rewarming and pre-warn of potential risk of further seizures and risk of extension of duration of TH</td>
</tr>
</tbody>
</table>
v. Consider early discussion relating to limit of escalation of therapy if infant critically unwell, high risk of death or treatment considered futile
b. Ensure the junior medical team and nursing team caring for the family are in agreement with the information given to the family. Clear any misunderstandings within the team about prognosis to avoid parents being told confusing and variable information

4. Update day 4: rewarming (in TH centre):
   a. Explain how baby has coped with re-warming and, following clinical assessment of the baby’s encephalopathy and aEEG, discuss what this may indicate for their prognosis

5. Subsequent updates: (May take place in TH centre or at local hospital)
   a. When MRI brain scan is anticipated and when the result of this will be known
   b. Pre-Discharge:
      i. Summarise neonatal admission including treatment that baby has received and results of investigations
      ii. Update parents on what the results of the investigations may mean for the baby’s future development and needs
      iii. Clarify the level of uncertainty that remains, sign-post follow-up plan and explain what support will be made available if the baby needs

Table 4: Stages of parental communication. TH: Therapeutic Hypothermia, HIE: Hypoxic Ischaemic Encephalopathy, ECG: Electrocardiogram, aEEG: amplitude-integrated electroencephalography.

See also parental communication flow chart: figure 3.

Further written parental guidance may be sought from the Bliss Patient Information Leaflet: “HIE (Hypoxic-ischaemic encephalopathy) information for parents”[29]

Worked examples of using this paper to construct parental communication are provided in the online supplement 2. This may be used for personal reflection or for supervised group education.

[Figure 3.]
Acknowledgments
The authors would like to thank Satomi Okano for collecting local parental perceptions which helped inform this article, as well as the parents for providing these insights.

Contributors
PC wrote first draft. EC is senior author and revised manuscript. All authors contributed to article planning and concept, and approved the final version.

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References:


Figure Legends:

**Figure 1:** Risk of Death or Major Disability (moderate to severe disability as defined in tables 1 & 2): Routinely available prognostic markers from birth to discharge in infants treated with Therapeutic Hypothermia for Hypoxic Ischaemic Encephalopathy. Only markers with outcome data at >12-24 months included. *Caution: small number of participants, †Combined hypo/normo-thermia group data, ‡Major MRI abnormality = Moderate/severe basal ganglia or thalamic lesions, severe white matter lesions, or an abnormal posterior limb of the internal capsule. PPV: Positive Predictive Value, NPV: Negative Predictive Value, aEEG: amplitude integrated Electroencephalogram, NG: Nasogastric, MRI: Magnetic Resonance Imaging.

**Figure 2:** Schematic demonstrating the spectrum of prognostic uncertainty in Hypoxic Ischaemic Encephalopathy. Clinicians must balance the predictive value of prognostic markers with the level of reassurance/uncertainty reported to parents.

**Figure 3:** Parental communication flow-chart. HIE: Hypoxic Ischaemic Encephalopathy, USS: Ultrasound Scan, aEEG: Amplitude Integrated Electroencephalogram, MR: Magnetic Resonance, EEG: Electroencephalogram.
Risk of Death or Major Disability: *Infants Treated with Therapeutic Hypothermia*

### Clinical:
- **10 minute Apgar score 0**: PPV 73%
- **Meets trial criteria for cooling**: PPV 46%

Grade of clinical encephalopathy by modified Sarnat staging - first 6 hours:
- **Moderate encephalopathy**: PPV 32%
- **Severe encephalopathy**: PPV 72%

#### aEEG classification prior to active cooling:
*(Most severe trace sustained for 30 minutes in 1st 6 hours)*
- **Moderately abnormal voltage**: PPV 26%
- **Severely abnormal voltage**: PPV 77%

**: NPV 100%* *(i.e Normal voltage, no electrical seizures)*

### Cooling Phase

#### aEEG:
<table>
<thead>
<tr>
<th>Age at assessment</th>
<th>Moderately or severely abnormal aEEG trace by voltage criteria</th>
<th>Sleep-Wake Cycling not achieved**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPV</td>
<td>NPV</td>
</tr>
<tr>
<td>24 hours</td>
<td>62%</td>
<td>96%</td>
</tr>
<tr>
<td>36 hours</td>
<td>78%</td>
<td>96%</td>
</tr>
<tr>
<td>48 hours</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>72 hours</td>
<td>96%</td>
<td>87%</td>
</tr>
</tbody>
</table>

**Cranial Ultrasound at 24 – 72 hours:** **Resistance Index ≤0.55**: PPV 60% | NPV 78%

#### Craniocerebral Ultrasound at 24 – 72 hours:
- **Resistance Index ≤0.55**: PPV 60% | NPV 78%

### Clinical:
- **Sarnat & Sarnat Staging on Day 4 (Post-Warming)**:
  - **Severe (Grade 3) Encephalopathy**: PPV 89%
  - **Moderate (Grade 2) Encephalopathy**: PPV 31%
  - **Mild (Grade 1) Encephalopathy**: PPV 29%

**NICHD Clinical Encephalopathy Stage at Discharge**:
- **Moderate/Severe Stage at Discharge**: PPV 84%
- **Mild/No Encephalopathy at Discharge**: PPV 31%
- **NG/Gastrostomy Fed at Discharge**: PPV 84% | NPV 76%
- **Hypertonia at Discharge**: PPV 69% | NPV 73%
- **Fisted hand at Discharge**: PPV 72% | NPV 68%
- **Gag reflex absent at Discharge**: PPV 76% | NPV 75%

### MRI (at 1 to 4 weeks of age):
- **Major MRI abnormality**: PPV 76% | NPV 91%
  - **Normal MRI**: PPV 91% | NPV 56% *for Survival/IQ>70 by 6-7 years*
  - **Survivors with normal MRI**: PPV 91% | NPV 56% *for Survival/IQ>70 by 6-7 years*
  - **50% No Disability or IQ≥85**
  - **34% Mild Disability or IQ70-84**
  - **16% Moderate Disability or IQ55-69**
  - **0%* Severe Disability or IQ<55**
Spectrum of prognostic uncertainty in Hypoxic Ischaemic Encephalopathy

Clinical Example:
Infant A, B & C all met identical entry criteria for cooling, their subsequent risk of severe disability may be estimated by the evolution of their encephalopathy, as assessed clinically and using aEEG:

**Infant A**
- Normalisation of aEEG voltage by 6 hours
- Sleep-Wake Cycling at 24 hours
- Grade 0 encephalopathy on day 4

**Infant B**
- Normalisation of aEEG voltage by 48 hours
- Sleep-Wake Cycling by 60 hours
- Grade 2 encephalopathy on day 4

**Infant C**
- Severely abnormal aEEG at 72 hours
- Did not demonstrate sleep-wake cycling
- Grade 3 encephalopathy and seizures on day 4

Outcome:

**Severe disability highly unlikely**
- Whilst outcome is not certain, severe disability would be highly unlikely. Overstating ‘uncertainty’ to parents would be unnecessarily non-reassuring for parents

**Moderate likelihood of severe disability**

**Severe disability highly likely**
- Whilst outcome is not certain, disabilities are expected: Purely reporting ‘Uncertainty’ would be falsely reassuring for parents
Parental Communication in Hypoxic Ischaemic Encephalopathy

Suspected Hypoxic Ischaemic Encephalopathy

Immediate Parental Update – Delivery Suite

Current condition of infant
Concerns relating to HIE & plans regarding cooling
Be open regarding prognostic uncertainty early on

Show infant to parents
Encourage skin contact where possible
- However brief -

Admit, Clarify Diagnosis & Decision to Cool

Frequent Further Updates
- Brief: At Baby’s Cotside
- If significant bad news: Quiet Room
- Both parents present where possible
- What is known / What is still uncertain
- When more information is expected
- If cooling outside criteria – make this clear

Stratify Prognosis - (See FIGURE 1)
- Grade & Evolution of Encephalopathy
- Multi-Organ Involvement/ Intensive Support
- Cranial USS
- aEEG Interpretation: Background / Sleep-Wake Cycling
- MR Brain Scan

Discharge
- Ensure parents have clear understanding of events since birth, treatment given & results of relevant investigations
- If reports are awaited (e.g. EEG / MR) ensure parents are told when they can expect to know the results and when the infant will next be seen in outpatients
Medical jargon with suggested lay explanations

Initial Consultation [Delete as appropriate]
Your baby needed resuscitation at birth, this included: help with the breathing | chest compressions due to a slow/absent heart beat | resuscitation medications.

He/she continues to need help including; use of a breathing machine | drip fluids | Sedation/ Pain relief | Medications to support the heart.

We are concerned that he/she is showing signs of having suffered lack of blood supply and oxygen around the time of birth. This can damage his/her vital organs, including the brain. It is too early to know if the baby has been severely affected and we are monitoring them closely. Although other organs including heart, liver, lungs and kidneys could be affected, they are very likely to fully recover. However, the brain may not fully recover. There is a risk of death or long-term disability. Therefore, we will be starting a special standard treatment called cooling therapy, where we carefully cool the baby, reducing his/her body temperature for 3 days. Cooling therapy has been shown to reduce brain injury and improve survival without disabilities.

We will monitor baby closely, ensuring they have appropriate medication for any discomfort. We will know more about the risk of long-term effects as we see how baby progresses over the next 4 days, and after a brain scan in approximately 1 week. Baby is at risk of seizures in the next 3 to 4 days which we may pick up on our monitoring equipment. If we are concerned that baby is becoming more unwell we will inform you.

“HIE” - Hypoxic-Ischaemic Encephalopathy
Hypoxic-Ischaemic: a state of reduced oxygen and reduced blood supply to vital organs. This may also be termed “perinatal asphyxia” when relating to an episode of reduced oxygen delivery to the baby, from the placenta, around the time of birth.
Encephalopathy: abnormal brain function. In a baby this may present as abnormal posture, abnormally stiff or floppy muscle tone, altered consciousness or seizures.
Hypoxic-Ischaemic Encephalopathy: a baby with abnormal brain function following an episode of reduced oxygen and blood supply to the brain.

Cooling (Therapeutic Hypothermia)
A treatment where a newborn baby is cooled a few degrees below their normal body temperature. This is achieved using a special cooling hat or mattress, which keeps the baby’s temperature within a strict temperature range. Cooling is usually undertaken for 72 hours, before gentle rewarming.

Cooling may reduce the amount of damage to brain cells following a reduction of blood and oxygen supply to the brain around the time of birth. Cooling reduces risk of death, and reduces risk of severe disability in survivors.

“CFM” - Cerebral Function Monitor
Continuously monitors your baby’s electrical brain activity using monitoring leads which may be placed on or just under the skin of the head. Usually attached for the majority of a baby’s cooling, & rewarming period.

“EEG” - Electroencephalogram
A detailed study of the electrical activity of your baby’s brain using many monitoring leads which may be placed on or just under the skin of the head. EEG provides more detailed information than a CFM but is usually performed for 30 to 90 minutes.

Cranial Ultrasound
An ultrasound scan performed over your baby’s ‘soft-spot’ on their head. Produces images of the brain, and blood flow through the major blood vessels can be measured. A ‘normal’ Cranial Ultrasound is not detailed enough to rule out risk of future disability.

“MRI” - Magnetic Resonance Imaging
A detailed brain scan using a strong magnetic field and radiowaves. An MRI may be used to assess for injury in specific areas of the brain and can be used to help predict if future major disability is likely.

Neurodevelopmental Delay
A delay in meeting milestones through childhood which may relate to difficulties in movement, including balance and co-ordination, difficulties in learning and communication, as well as difficulties in behaviour. As well as causing delay, brain injury may lead to permanent disabilities which may include both physical and learning disabilities. For this reason, all babies who have been affected by HIE will be followed-up after discharge from hospital, in order to diagnose difficulties and provide appropriate support from an early stage.

Soon after birth it is usually too early to predict risk of severe disability. However, using results from your baby’s brain scans, electrical brain activity and through examination, it may be possible to give a clearer indication of the risk that your baby may experience disabilities in the future, over the first week of age. No test will give a result with 100% confidence.

Cerebral Palsy
A group of conditions which result in physical disability from difficulties in movement and/or co-ordination. This is an umbrella term for which the type and severity of difficulties experienced varies widely.

Online Supplementary figure 1: Medical jargon with example lay explanations.
Online Supplement 2

Spectrum of prognostic uncertainty in Hypoxic Ischaemic Encephalopathy

**Worksheets: Infants A, B & C**

These worksheets may be used for personal reflection, or as part of a supervised group education session.

Figure 2 presents 3 brief clinical scenarios of infants A, B & C. Readers may use tables 1-2 and figure 1 to assess each of Infant A, B & C’s prognoses. Subsequently, they can use the information provided in tables 3 & 4, figure 3, and the online supplementary figure 1, to structure how they may communicate this with the infants’ parents at 4 different time points:

1) Immediate update in delivery room, 2) parental update following admission and initiation of TH, 3) at days 1 – 3, and 4) at day 4, after rewarming has completed (or prior to this if re-orientation of care is under consideration).

A blank template is provided for each infant, followed by a completed worksheet with example answers (rather than the ‘right’ answers). Please note that the styles of conversations will vary depending on the parent’s understanding, emotional status and the environment. Clinicians must use their emotional intelligence and situational awareness while counselling parents. Each family has to have a unique counselling that is suitable to them.

Below is a short guide to interpreting Positive Predictive and Negative Predictive Values.

The Worksheets follow on the next pages.

Interpreting Predictive Values

**Positive Predictive Value (PPV):** probability that a condition is present when the test is positive

**Negative Predictive Value (NPV):** probability that a condition is absent when the test is negative

A common example in this paper would be the ‘condition’ of ‘death or major disability from HIE’. The ‘test’ may be, for example, a cord gas, a need for resuscitation, an agpar score, a clinical examination, or an investigation such as an aEEG, cranial USS, or MR brain scan. These tests are then categorised as positive (if they predict the condition will be present) or negative (if they predict the condition will be absent). Positives and negatives can then be categorised as true or false, depending on if their predicted outcome was correct.

**PPV & NPV may be calculated thus:**

\[
\text{PPV} = \frac{\text{Number of true positives}}{\text{Number of true positives} + \text{Number of false positives}}
\]

\[
\text{NPV} = \frac{\text{Number of true negatives}}{\text{Number of true negatives} + \text{Number of false negatives}}
\]

PPV & NPV are relevant to the individual patient; specificity & sensitivity provide characteristics of the test itself.

**Example**

For aEEG, a positive test would be an abnormality; such as moderate or severely abnormal voltage criteria, or absence of sleep wake cycling. A negative test would be normal voltage, or the presence of sleep wake cycling.

As can be seen in figure 1, the sooner an aEEG normalises the higher the NPV. Similarly, the longer the aEEG remains abnormal, the higher the PPV. A similar pattern may be seen for clinical stage of encephalopathy.

One exception to these rules is present in figure 1:

**Normal MRI:**

\[
\text{PPV 91% / NPV 56% for Survival/IQ>70 by 6-7 years}
\]

In this example, the condition is **Survival/IQ>70 by 6-7 years**, a test positive is a normal MRI, and a test negative is an abnormal MRI. Thus a normal MRI gives a PPV of 91% for survival with an IQ>70 by 6-7 years.
Clinical Examples: (as detailed in Figure 2.)

Infants A, B & C all met identical entry criteria for cooling, their subsequent risk of severe disability may be estimated by the evolution of their encephalopathy, as assessed clinically and using aEEG.

In the spaces below, write in how and what you would say to parents in the delivery room, and following admission, for an infant who required resuscitation at birth and meets criteria for therapeutic hypothermia (Use Tables 3 & 4. & Figure 3. to help guide this).

**Immediate parental update in delivery room**

Write in how and what you would say to parents (Use Tables 3 & 4. & Figure 3. to help guide this).

**Parental update following admission and initiation of TH:**

Write in how and what you would say to parents (Use Tables 3 & 4. & Figure 3. to help guide this).
**Infant A**

Subsequent Clinical Details (As per Figure 2.) & Prognostic Value (As per Figure 1.)

- **Normalisation of aEEG voltage by 6 hours**
  Write in prognostic value in space below (Use figure 1. to help guide this):

- **Sleep-Wake Cycling at 24 hours**
  Write in prognostic value in space below (Use figure 1. to help guide this):

- **Grade 0 encephalopathy on day 4**
  Write in prognostic value in space below (Use figure 1. to help guide this):

**Updates day 1 – 3 (in TH centre, preferably as a multidisciplinary team with nurses, family worker & psychologist):**

Write in how and what you would say to parents (Use Tables 3 & 4. & Figure 3. to help guide this).

**Update day 4: rewarmed (in TH centre):**

Write in how and what you would say to parents (Use Tables 3 & 4. & Figure 3. to help guide this).
Worksheet: Infant B

Infant B
Subsequent Clinical Details (As per Figure 2.) & Prognostic Value (As per Figure 1.)

- Normalisation of aEEG voltage by 48 hours
  Write in prognostic value in space below (Use figure 1. to help guide this):

- Sleep-Wake Cycling by 60 hours
  Write in prognostic value in space below (Use figure 1. to help guide this):

- Grade 2 encephalopathy on day 4
  Write in prognostic value in space below (Use figure 1. to help guide this):

Updates day 1 – 3 (in TH centre, preferably as a multidisciplinary team with nurses, family worker & psychologist):
Write in how and what you would say to parents (Use Tables 3 & 4. & Figure 3. to help guide this).

Update day 4: rewarmed (in TH centre):
Write in how and what you would say to parents (Use Tables 3 & 4. & Figure 3. to help guide this).
Infant C
Subsequent Clinical Details (As per Figure 2.) & Prognostic Value (As per Figure 1.)

- Severely abnormal aEEG at 72 hours
  Write in prognostic value in space below (Use figure 1. to help guide this):

- Sleep-Wake Cycling not demonstrated by 72 hours
  Write in prognostic value in space below (Use figure 1. to help guide this):

- Grade 3 encephalopathy and seizures on day 4
  Write in prognostic value in space below (Use figure 1. to help guide this):

Updates day 1 – 3 (in TH centre, preferably as a multidisciplinary team with nurses, family worker & psychologist):
Write in how and what you would say to parents (Use Tables 3 & 4. & Figure 3. to help guide this).
Infant C

Update day 4: rewarmed (in TH centre) or prior to this if re-orientation of care discussions are being considered:
This infant has a severely abnormal aEEG with no recovery, seizures, grade III encephalopathy and the MR brain scan demonstrates severe brain injury. Write in what you think are the potential care options for this infant. Who should be involved in this decision making and how should communication be directed with the parents? (Use Tables 3 & 4. & Figure 3. to help guide this).
Clinical Examples: (as detailed in Figure 2.)

Infant A, B & C all met identical entry criteria for cooling, their subsequent risk of severe disability may be estimated by the evolution of their encephalopathy, as assessed clinically and using aEEG.

In the spaces below, write in how and what you would say to parents in the delivery room, and following admission, for an infant who required resuscitation at birth and meets criteria for therapeutic hypothermia (Use Tables 3 & 4. & Figure 3. to help guide this).

Immediate parental update in delivery room

As per Table 4, explain that:

- Baby has been unwell and has required resuscitation at birth
- It is possible that the baby has had a period of reduced blood flow and oxygen to the whole body. This may lead to injury to the baby’s brain and other vital organs including the kidney, liver and heart.
- It is too early to know how severely the baby has been affected
- The infant will be admitted to the neonatal unit for further assessment and may need a treatment called ‘Cooling’ to protect the brain from ongoing injury. You will update them once baby has been admitted and further assessed

The detail provided in this initial consultation will need to be adjusted according to available staff, medical condition of the mother and condition of the baby.

Example text:

Initial Consultation [Delete as appropriate]

Your baby needed resuscitation at birth, this included: help with the breathing | chest compressions due to a slow/absent heart beat | resuscitation medications.

He/she continues to need help including; use of a breathing machine | drip fluids | Sedation/ Pain relief | Medications to support the heart.

We are concerned that he/she is showing signs of having suffered lack of blood supply and oxygen around the time of birth. This can damage his/her vital organs, including the brain. It is too early to know if the baby has been severely affected and we are monitoring them closely. Although other organs including heart, liver, lungs and kidneys could be affected, they are very likely to fully recover. However, the brain may not fully recover. There is a risk of death or long-term disability. Therefore, we will be starting a special standard treatment called cooling therapy, where we carefully cool the baby, reducing his/her body temperature for 3 days. Cooling therapy has been shown to reduce brain injury and improve survival without disabilities.

We will monitor baby closely, ensuring they have appropriate medication for any discomfort. We will know more about the risk of long-term effects as we see how baby progresses over the next 4 days, and after a brain scan in approximately 1 week. Baby is at risk of seizures in the next 3 to 4 days which we may pick up on our monitoring equipment. If we are concerned that baby is becoming more unwell we will inform you.

Parental update following admission and initiation of TH:

- Ascertain parental understanding
- Provide explanation of general condition of baby (including multi-organ support if relevant) and re-iterate support they needed after birth (explain ventilation, chest compressions, medications)
- Explain what HIE is (including risk of death or major disability) “Babies may go on to encounter problems with their learning, thinking and speaking, and problems with their walking and movements.”
- Explain role and duration of TH & need for transfer to ‘cooling centre’ (if relevant)
- Explain TH improves survival and reduces the number of babies with severe long-term disability
- Explain prognosis is uncertain but that over the next week it will become clearer how severely the baby has been affected; as response to TH is observed and results of investigations are available
- Reassure infant will be kept comfortable and monitored by experienced staff
- When at cotside: briefly explain the role of monitoring leads connected to baby (Pulse-oximeter, ECG, aEEG)
- Summarise discussion at end, clarify parental understanding, offer time for questions and sign-post when next update is expected and what further information may be known at that time
- Ensure parents will be given tour of neonatal unit, and that visiting rules, parking and hospital facilities will be explained

Throughout all consultations, use baby's name if one is provided
Infant A
Subsequent Clinical Details (As per Figure 2.1) & Prognostic Value (As per Figure 1.)

- Normalisation of aEEG voltage by 6 hours
  A normal aEEG at 6 hours provides a NPV for death or major disability of 100%*. Caution is needed in interpreting this NPV; very few infants meeting trial criteria had a normal voltage pattern aEEG at 6 hours, no test will truly have a 100% NPV for death and disability. A normal aEEG at 6 hours cannot completely exclude subtle future physical or intellectual problems, but is highly reassuring.

- Sleep-Wake Cycling at 24 hours
  Sleep-wake cycling is a normal pattern of brain activity, early development of sleep-wake cycling is prognostically reassuring. The NPV for death or major disability, of achieving sleep-wake cycling at 24 hours of age is 100%*. Caution is needed, published data relating to sleep-wake cycling is available in only a small number of participants; no test will truly have a 100% NPV for death and disability.

- Grade 0 encephalopathy on day 4
  The PPV progressively reduces on day 4 as clinical stage of encephalopathy improves: Severe (Grade 3): PPV 89%, Moderate (Grade 2) : PPV 31%, to Mild (Grade 1) : PPV 29%. Absence of encephalopathy (‘Grade 0’) is thus reassuring, but cannot rule out subtle motor or intellectual difficulties.

Overall, whilst outcome is not certain, severe disability would be highly unlikely. MR brain scan & examination at discharge will still add prognostic value to infant’s assessment.

Updates day 1 – 3 (in TH centre, preferably as a multidisciplinary team with nurses, family worker & psychologist):
Update at least daily:
- Overall clinical condition (e.g. Lung/Heart/Kidney function)
- Level of encephalopathy & interpretation of aEEG if this aids with assessment of prognosis
  - “As we have discussed, we are monitoring your baby closely”. “As part of your baby’s monitoring we are continually assessing their brain activity.”. “Your baby’s brain activity normalised quickly which is a reassuring sign”. “we still need to continue to monitor closely during the remainder of your baby’s cooling and re-warming periods, in case any changes occur.”. “The chance of your baby developing serious disability is low”. “After re-warming we will arrange for a detailed Brain scan, which will also help to tell us about potential damage which may have occurred”
- Explain timeline for re-warming and pre-warned of risk of possible extension of duration of TH if complications occur
- Empathise with parents, clarify parental understanding, answer questions & signpost next planned update
- Ensure the junior medical team and nursing team caring for the family are in agreement with the information given to the family. Clear any misunderstandings within the team about prognosis to avoid parents being told confusing and variable information

Update day 4: rewarmed (in TH centre):
- Explain how baby has coped with re-warming and, following clinical assessment of the baby’s encephalopathy and aEEG, discuss what this may indicate for their prognosis
  - “I am pleased that your baby’s brain activity has remained normal during the re-warming period and that your baby now appears alert and well on examination”. “Babies whose brain activity normalises quickly are less likely to encounter problems with their learning, thinking and speaking, and are less likely to encounter problems with their walking and movements”. “However, it is important we will still arrange for a detailed brain scan in the coming days, and, when your baby is ready for discharge, we will ensure you have follow-up to ensure that if problems do occur in the future they are detected and supported early on”.
- Empathise with parents throughout, clarify understanding, answer questions & signpost next planned update
**Infant B**

Subsequent Clinical Details (As per Figure 2.) & Prognostic Value (As per Figure 1.)

- **Normalisation of aEEG voltage by 48 hours**
  A normal aEEG voltage at 48 hours carries a NPV for death or major disability of 92%. i.e 92% probability of survival without major disability, whereas 8% progress to death or major disability.

- **Sleep-Wake Cycling by 60 hours**
  Absence of sleep-wake cycling is pathological. Absence of sleep-wake cycling on aEEG is therefore a positive test for the diseased state of HIE, and is predictive of progression to death or major disability. Infants without sleep-wake cycling at 48 hours have a PPV for death or major disability of 65%. i.e 65% probability of death or major disability, whereas 35% survive without major disability. The NPV at 72 hours of an infant who tests negative (i.e have achieved sleep-wake cycling after 48 hours but by 72 hours) is 33%.

- **Grade 2 encephalopathy on day 4**
  The PPV for death or major disability for grade 2 encephalopathy (by Sarnat staging) on day 4 (post-warming) is 31%. i.e. 31% probability of death or major disability.

Overall, this infant has a moderate risk; whilst normalisation of aEEG by 48 hours is reassuring, the persistence of clinical grade 2 encephalopathy on day 4 highlights an ongoing risk. The effect of pharmacological sedation may be modifying both the infant’s aEEG and clinical presentation. Examination at discharge and MR brain scan will contribute to assessing this infant’s prognosis.

**Updates day 1 – 3 (in TH centre, preferably as a multidisciplinary team with nurses, family worker & psychologist):**

**Update at least daily:**

- **Overall clinical condition (e.g. Lung/Heart/Kidney function)**
- **Level of encephalopathy & interpretation of aEEG if this aids with assessment of prognosis**
- **Pre-48 hours:** "As we have discussed, we are monitoring your baby closely" / "No test that we have can be 100% certain of your baby’s future" / "No test can 100% predict or rule out the risk of disability". “As part of your baby’s monitoring we are continually assessing their brain activity.”. “At present your baby’s brain activity is suppressed, which means it is not functioning normally”, “It is still hard to know the significance of this as baby is still very young”, “we need to continue to monitor closely during the remainder of your baby’s cooling and re-warming periods for any changes which may occur.”
- **After 48 hours:** “Your baby’s brain activity has started to normalise.”. “It is still hard to know the significance of this as baby is still very young”, “It does offer some reassurance that recovery is beginning to occur but we still need to continue to monitor closely for any other changes which may occur.”, “Given that your baby’s brain activity has started to normalise, the risk of severe disability has come down, however a small risk still remains with this pattern of recovery”, “After re-warming we will re-assess your baby’s neurological examination and arrange for a detailed Brain scan, which will also help to tell us about potential damage which may have occurred”
- **Explain timeline for rewarming and pre-warn of risk of possible extension of duration of TH if complications occur**
- **Empathise with parents, clarify parental understanding, answer questions & signpost next planned update**
- **Ensure the junior medical team & nursing team are in agreement with the information given. Clear any misunderstandings within the team about prognosis to avoid parents being told confusing & variable information**

**Update day 4: rewarmed (in TH centre):**

- **Explain how baby has coped with re-warming and, following clinical assessment of the baby’s encephalopathy and aEEG, discuss what this may indicate for their prognosis**
  - “Baby is now rewarmed”, “Their neurological examination (how their brain and nerves are functioning) has not yet fully normalised”, “Whilst this is slow to recover, it is still hard to know the significance of this as baby may be recovering from the cooling process and the sedation they needed to stay comfortable”. “Putting all the information we have regarding your baby’s brain activity, and examination, we would expect a mild to moderate impact on your baby’s motor and intellectual skills”, “MRI brain scan can offer more information regarding the impact on your baby’s future physical and intellectual needs”. “We will arrange for this to occur in the next few days and continue to assess baby’s progress”
  - “When your baby is ready for discharge, we will ensure you have follow-up to ensure that if problems do occur in the future they are detected and supported early on”.
- **Empathise with parents throughout, clarify understanding, answer questions & signpost next planned update**
**Infant C**

**Subsequent Clinical Details (As per Figure 2.) & Prognostic Value (As per Figure 1.)**

- **Severely abnormal aEEG at 72 hours**
  
  An abnormal aEEG by voltage criteria at 72 hours carries a PPV of 96%; i.e a 96% probability of death or major disability.

- **Sleep-Wake Cycling not demonstrated by 72 hours**
  
  Absence of sleep-wake cycling is pathological. Absence of sleep-wake cycling on aEEG is therefore a positive test for the diseased state of HIE, and is predictive of progression to death or major disability. Infants without sleep-wake cycling at 72 hours have a PPV for death or major disability of 82%. i.e 82% probability of death or major disability.

- **Grade 3 encephalopathy and seizures on day 4**
  
  The PPV for death or major disability for grade 3 (severe) encephalopathy (by Sarnat staging) on day 4 (post-warming) is 89%. i.e. 89% probability of death or major disability.

Overall, this infant is at very high risk of death or severe disability. Whilst no test can be 100% certain of outcome, corroboratation of persistent severely abnormal findings across test modalities over time increases the definitiveness of outcome. In infant C, both clinical examination & aEEG indicate persistence of severe encephalopathy without recovery. Formal EEG, prompt MR brain scan and full consideration of differential diagnoses should be undertaken. Early MR brain scan at 48-72 hours of TH should be considered.

Within the short-term, consideration of feeding support and safety of swallow should be considered. Within the medium to long term, consideration of ongoing seizure risk; and early physiotherapy, occupational therapy and Speech & Language intervention is key. Parents must be prepared for risk of death, and the potential for palliative end of life care if ongoing intensive support is required, and clinical examination, aEEG interpretation and MR brain scan corroborate findings of severe impairment that require full consideration of whether life-sustaining treatment is in the infant’s best interests.

**Updates day 1 – 3 (in TH centre, preferably as a multidisciplinary team with nurses, family worker & psychologist):**

**Update at least daily:**

- **Overall clinical condition (e.g. Lung/Heart/Kidney function)**

- **Level of encephalopathy & interpretation of aEEG if this aids with assessment of prognosis**

  - **Pre-48 hours:** “As we have discussed, we are monitoring your baby closely” / “No test that we have can be 100% certain of your baby’s future” / “No test can 100% predict or rule out the risk of disability”. “As part of your baby’s monitoring we are continually assessing their brain activity.”. “At present your baby’s brain activity is suppressed, which means it is not functioning normally”. “It is still hard to know the significance of this as baby is still very young”, “we need to continue to monitor closely during the remainder of your baby’s cooling and re-warming periods for any changes which may occur.”

- **After 48 hours:**

  - Early MR brain scan should be considered in this scenario. Discussions relating to reorientation of care in the best interests of the baby may need to be approached if the aEEG, clinical examination and MRI brain scan indicate high risk of severe disability, or imminent or inevitable death is expected irrespective of treatment.

  - “We are concerned that baby’s brain activity remains suppressed and has not yet recovered.”. “We know that delayed or absent recovery significantly increases the baby’s risk of future problems; this includes problems with their walking and movements, and can also affect their learning, thinking and speaking”. **Ensure time and support for parents to mentally process this.** “I am also concerned that because your baby is unwell there is a risk that despite our intensive care support he/she may not be able to survive and is at risk of dying.”. **Ensure time and support for parents to mentally process this.** “We need to continue to monitor closely for any other changes which may occur.”, “We need to consider undertaking an early MRI brain scan to see the extent of brain injury. If the brain injury is extensive, then there is likely to be a high burden of disability and impairment for your baby.”. “Once we know the results of the brain scan, we should discuss together what this may mean for your baby, and what decisions relating to their intensive care you think are in their best interests”. “It may be too early to detect some changes and so we may have to repeat the brain scan later.”

- Emphasise with parents, explain timeline for MR brain scan and next discussion, clarify parental understanding, answer questions & signpost next planned update.

- When relevant, explain process of rewarming & pre-warn of risk of possible extension of TH if complications occur.

- Ensure the junior medical team & nursing team are in agreement with the information given. Clear any misunderstandings within the team about prognosis to avoid parents being told confusing & variable information.
Infant C

Update day 4: rewarmed (in TH centre) or prior to this if re-orientation of care discussions are being considered:
This infant has a severely abnormal aEEG with no recovery, seizures, grade III encephalopathy and the MR brain scan demonstrates severe brain injury. Write in what you think are the potential care options for this infant. Who should be involved in this decision making and how should communication be directed with the parents? (Use Tables 3 & 4. & Figure 3. to help guide this).

- This infant is at risk of death despite intensive medical support or survival with severe disability including intellectual and motor impairment.

- Multidisciplinary team involvement is vital. Multidisciplinary support may include neonatologists, neuroradiologists, neurologists, developmental care physicians, physiotherapists with expertise in outcome data of cooled infants and the senior nurse and perinatal psychology member looking after the family.

- The multidisciplinary team should discuss the present and potential future burden of the infant’s condition and treatment, as well as the infant’s future prospects of benefiting from living, when considering their best interests. If re-orientation of life-sustaining care is felt to be appropriate for the infant, then this should be sensitively discussed with the parents. Subsequent parental and family involvement in decision making and deliberating the infant’s best interests is essential. Available options should be explained clearly. The process should follow national ethical and legal frameworks. Parents should be adequately supported and ample time be provided. Parental support with perinatal psychology team should be offered.

- Each stage may need to be adapted if infant condition is critical, worsening and death is anticipated.

- Following death of an infant, ongoing perinatal psychological and bereavement support should be provided

- Following discharge of an infant at high risk of severe disability, ongoing support should be provided by the neonatal team, and should include early follow up with community nursing or health-visitor support, and the developmental care team