SLHD: Royal Prince Alfred Hospital Guideline

Therapeutic Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy

<table>
<thead>
<tr>
<th>TRIM Document No</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy Reference</td>
<td></td>
</tr>
<tr>
<td>Related MOH/SLHD Policy</td>
<td>Infant newborn, Hypoxia ischaemia, therapeutic hypothermia, neonatal encephalopathy</td>
</tr>
<tr>
<td>Keywords</td>
<td></td>
</tr>
<tr>
<td>Applies to</td>
<td>RPA Newborn Care</td>
</tr>
<tr>
<td>Clinical Stream(s)</td>
<td>(Delete those that do not apply/ or write 'N/A' if non-clinical)</td>
</tr>
<tr>
<td></td>
<td>Women's Health, Neonatology</td>
</tr>
<tr>
<td>Date approved GM, RPA</td>
<td></td>
</tr>
<tr>
<td>Date approved by RPA Policy Committee</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Dr Amanda Dyson, Neonatal Fellow, A/Prof Nicholas Evans, Neonatal Staff Specialist.</td>
</tr>
<tr>
<td>Status</td>
<td>Draft/Active/Under Review/Rescinded</td>
</tr>
<tr>
<td>Review Date</td>
<td>5 years</td>
</tr>
<tr>
<td>Risk Rating</td>
<td>(At time of publication)</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Replaces</td>
<td>Moderate systemic hypothermia for the treatment of neonatal hypoxic ischaemic encephalopathy (HIE). November 2007</td>
</tr>
</tbody>
</table>

Version History

| Date | September 2017 |
Therapeutic Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy

Contents


9. Guideline

9.1 Background, Evidence and Epidemiology Page 4
9.2 Criteria for Therapeutic Hypothermia Page 5
9.3 Contraindications to Therapeutic Hypothermia Page 7
9.4 Procedure for Therapeutic Hypothermia Page 8
9.5 Supportive Care during Therapeutic Hypothermia Page 9
9.6 Predicting Outcome Page 11
9.7 Key Points Page 13

Appendix: Modified Sarnat Staging Page 14

10. 11. Consultation and References Page 15
1. **Introduction**
   - Therapeutic hypothermia to 33-34°C within 6 hours of birth and continued for 72 hours has been shown to reduce the risk of death and disability after neonatal hypoxic ischaemic injury.

2. **The Aims / Expected Outcome of this Policy/Procedure/Guideline**
   - Procedure will be performed safely and for appropriate indications.

3. **Risk Statement**
   - Risk of missed opportunity of not implementing therapeutic hypothermia in a baby with hypoxic ischaemic encephalopathy

4. **Policy Statement (delete if standalone Procedure or Guideline)**
   - This guideline provides direction for clinicians at RPAH Centre for Newborn Care in providing whole body hypothermia for newborns ≥35 weeks gestation with hypoxic ischaemic encephalopathy.

5. **Scope**
   - Medical and nursing staff in RPA Newborn Care

6. **Resources**
   - None, all resources already available

7. **Implementation**
   - None, this guideline replaces the previous guideline and reflects current clinical practice in a lowering of the threshold for starting hypothermia to include not only those with established moderate or severe encephalopathy but those deemed to be at risk of an evolving encephalopathy.

8. **Key Performance Indicators and Service Measures**
   - Department audit and follow up of HIE babies and those given therapeutic hypothermia.
9. Guideline

9.1 EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE)

The incidence of HIE is estimated to be between 1.3 and 1.7 per 1000 live births with a combined point estimate of 1.5 per 1000 live births(1). It is a problem that causes significant mortality and morbidity in the neonatal population. The brain requires both oxygen and glucose to maintain its usual metabolic functions. When there is a reversible hypoxic-ischemic global insult, neuronal cell death occurs by a number of mechanisms in distinct phases depending on the both the severity of the insult and its nature (2-5). When the brain is acutely deprived of oxygen, it undergoes primary energy failure during which ATP production decreases, lactic acid is produced and neuronal excitotoxicity occurs, leading to necrosis and cell death.

The acute phase of injury is following by a latent period starting around 30-60 minutes after the primary injury that can last for up to 6 hours. This period is characterised by a return of aerobic metabolism and ongoing inflammation and ongoing cell death. The secondary phase of injury which occurs after the latent phase lasting for hours to days is characterised by cytotoxic oedema as well as energy failure related to mitochondrial failure and excitotoxicity. It is clinical characterised by encephalopathy.

OUR EXPERIENCE AT RPAH

Between 2006 and 2016, 120 newborn required therapeutic hypothermia at RPA Centre for Newborn care. This equates to approximately one newborn being cooled each month.

EVIDENCE FOR THERAPEUTIC HYPOTHERMIA

There are a number of mechanisms by which it is thought that hypothermia is neuro-protective including altering the course of apoptosis, decreasing the cellular metabolic rate in the brain and reducing the release of neuro-excitatory amino acids and free radicals(2)

There is strong evidence from a Cochrane Systematic Review including 1505 newborns with moderate/severe encephalopathy and evidence of perinatal asphyxia (11 randomised controlled trials) that therapeutic hypothermia reduces the combined outcome of mortality or major neuro-developmental disability at 18 months of age (typical RR 0.75 (95% CI 0.68 to 0.83); NNTB 7 (95% CI 5 to 10) (6). The 6-7 year neuro-developmental outcomes from some of the large RCTs included in this meta-analysis have become available including those from the Coolcap trial, NICHD trial and TOBY trials.

Reassuringly these results have shown no increase in disability amongst survivors (7). The TOBY trial follow up at 6-7 years has shown that the frequency of survival with an IQ of 85 or greater was higher in the hypothermia group compared to the control group (52% vs 39%, RR 1.31 (1.01 to 1.71) P = 0.04, NNT 8). Survival without neurological abnormality is also improved (44.8% vs 28%, RR 1.60 (1.15-2.22), P=0.004). Therapeutic hypothermia has now become a standard of care in neonatal practice.
3.2 CRITERIA FOR THERAPEUTIC HYPOTHERMIA:

Therapeutic hypothermia should be considered if the following four criteria are met:

1. **Gestation at birth** should be 35 weeks or older
2. **Age** should be less than 6 hours since birth
3. **Evidence of asphyxia** as defined by at least 2 of the following
   a. Apgar <6 at 10 minutes or ongoing need for resuscitation
   b. Any acute perinatal event that may cause HIE (i.e. fetal heart rate abnormalities, placental abruption, cord prolapsed)
   c. Cord arterial pH <7.0 or cord arterial BE ≤-12mmol or cord arterial lactate ≥9.5mmol/L(8)
   d. If no cord pH is available an arterial pH taken within 60 minutes of birth can be used with the same lactic acidosis thresholds.
4. **The presence of moderate or severe HIE;** defined as:
   a. Seizures or,
   b. Signs in at least 3 of the 6 categories in the table below or,
   c. Neonatologist concern that a moderate or severe encephalopathy may evolve.

| Table 1: Encephalopathy criteria for initiating therapeutic hypothermia |
|-----------------------------------------------------|-----------------|-----------------|
| Category                                             | Moderate encephalopathy   | Severe encephalopathy |
| Level of consciousness                              | Lethargy               | Stupor/coma       |
| Spontaneous activity                                 | Decreased activity      | No activity       |
| Posture                                              | Decorticate(arms flexed, legs extended) | Decerebrate (arms and legs extended) |
| Tone                                                 | Hypotonia               | Flaccid           |
| Primitive reflexes                                   | Weak suck, incomplete Moro | Absent suck/Moro |
| Autonomic (any of)                                   | Constricted             | Dilated/non-reactive |
| Pupils                                               | Bradycardia             | Variable heart rate |
| Heart Rate                                           | Period breathing        | Apnoea            |
| Respiration                                          |                            |                  |

For more details of the Sarnat staging see Table in the appendix.

**Start hypothermia within 6 hours in borderline or uncertain cases as this decision could be reversed if it becomes apparent that the infant does not have moderate or severe HIE.**

**Timing of starting hypothermia**

The evidence from animal studies is that the earlier hypothermia can be started after the hypoxic ischemic insult, the better the potential neuronal rescue (9, 10). Earlier hypothermia (<3 hours) when
compared with hypothermia at 3-6 hours showed better motor outcomes in survivors of moderate/severe HIE at 18-22 months (11). Unless there is a sentinel obstetric event, we will not know the timing of the hypoxia that caused the brain injury. It may have preceded delivery by some time, thus increasing the imperative to try and commence hypothermia as soon as possible after birth. This creates the clinical need for early postnatal prediction of babies likely to develop moderate or severe encephalopathy which remains challenging.

While there is a suggestion that initiating hypothermia at >12 hours may be harmful in neonatal rats (12) this has not been proven in humans. There are reports of neonates who begin hypothermia after the recommended 6 hours with one group in France reporting that 22% of babies recording on their national database fell into this category without any apparent increase in the complications of hypothermia (13, 14). This group have not reported their long term neurodevelopmental outcomes and it is unknown whether hypothermia is effective beyond 6 hours. A review of the UK TOBY Hypothermia register found that 2.2% of infants were cooled >12 hours (15). The results of an RCT “Late hypothermia for HIE” are awaited (NCT00614744) which may help resolve this issue.

**At present the evidence supports starting hypothermia as early as possible and definitely before 6 hours. While there is currently no evidence to support starting hypothermia after 6 hours of life, it appears to be safe and could be considered at the discretion of the consultant on call pending the results of ongoing trials.**

**Duration and depth of therapeutic hypothermia**

Despite animal data suggesting that longer or deeper hypothermia may be beneficial, an RCT comparing hypothermia newborns (n=364) at 33.5°C for 72 hours, 32.0°C for 72 hours, 33.5°C for 120 hours, and 32.0°C for 120 hours was stopped early due to safety concerns as well as concerns about futility (16). Their longer duration group had more arrhythmia, anuria and a longer hospital stay, while those cooled to 32 degrees had a trend towards more inhaled nitric oxide therapy, ECMO, more days of oxygen, and a higher incidence of bradycardia (16).

Newborns eligible for therapeutic hypothermia should be cooled to between 33-34 degrees for 72 hours.

**Therapeutic hypothermia during transport**

Given the importance of starting hypothermia as early as possible, consideration needs to be given to starting therapeutic hypothermia at the referral hospital and during transport. A recent RCT (n=100) examined the benefits of active servo-regulated hypothermia in transport and found that newborns randomised to the device (compared with passive hypothermia or using cool gel packs) were cooled more quickly and reliably (17). Those cooled using servo-control reached target temperatures during transport more frequently (80% vs 49%, P <.001) and more quickly (44 +/- 31 minutes vs. 63 +/- 37 minutes, P = 0.04) than those receiving passive hypothermia (17). The use of active hypothermia also reduced the risk of over-cooling (18) which is associated with arrhythmias and pulmonary hypertension (17).

For ex-utero transfers hypothermia should begin at the referral hospital and during transport, this could be performed with cool-packs as in the ICE trial or using servo-control when this is available.

**Adjuncts to therapeutic hypothermia**

Although therapeutic hypothermia improves outcomes in HIE, this condition continues to be associated with significant morbidity and mortality. This has led to a number of adjuncts agents including erythropoietin, noble gases, N-acetylcysteine, melatonin, magnesium phenobarbitone and
allopurinol being investigated(19, 20). At present there is insufficient evidence to support the use of any adjunct however a number of trials investigating the use of erythropoietin, darbopoietin, magnesium and xenon are underway.(21) The results of the TOBYxe RCT examining the use of xenon as an adjunct to hypothermia has not shown any apparent benefit when using fractional anisotropy (mean difference $-0.01$, 95% CI $-0.03$ to $0.02$) in the posterior limb of the internal capsule as a primary outcome. RPA newborn care is currently participating in the PAEAN trial examining the use of erythropoietin as an adjunct to hypothermia in asphyxiated newborn.

Are there other babies who may benefit from therapeutic hypothermia?

There has been speculation about whether there is a population that could benefit from hypothermia who don’t meet the hypothermia criteria used by the large RCTs (22). A prospective cohort study comparing newborns cooled outside of CoolCap/TOBY criteria (n=36) with those who met usual criteria (n=129) found no difference in the complications of hypothermia or developmental outcome between groups, however their population was small (14). The subgroups included those cooled >6 h of age (median 7.8 hrs), moderately preterm infants (34-35 weeks of gestation), and infants with postnatal collapse, major cranial haemorrhage, congenital cardiac disease and surgical conditions. Those with major intracranial haemorrhage had worse bleeding outcomes and the authors concluded that this population should not receive therapeutic hypothermia (14). There are reports from hypothermia registers that therapeutic hypothermia is being used in mild HIE (23) however there is no data to support its efficacy. There are ongoing studies investigating the effect and safety of selective head hypothermia in preterm infants between 33 and 35 weeks gestation and >1200g (NCT00620711) and of whole body hypothermia in infants 33-35 weeks >1500g. (NCT01793129). There is insufficient evidence at this time to support therapeutic hypothermia for preterm infants <35 weeks gestation. Further research is required to determine if any of these groups benefit from therapeutic hypothermia.

9.3 CONTRAINDICATIONS TO THERAPEUTIC HYPOTHERMIA

Absolute contraindications:

- Birthweight less than 1800g which was an exclusion criterion in the CoolCap and TOBY trials. The Coolcap trial found better outcomes in newborns >25th percentile (24)

- Less than 35 weeks gestation (A clinical trial examining the effects of hypothermia at 33-35 weeks gestation is ongoing (NCT01793129))

- Refractory hypoxaemia despite maximal medical therapy (due to the shift in the oxyhaemoglobin dissociation curve to the left with hypothermia) Persistent pulmonary hypertension in itself is not a contraindication to hypothermia (25)

- Coagulopathy with active bleeding despite treatment.

There is lack of evidence of benefit for therapeutic hypothermia in the following circumstances:

1. If therapeutic hypothermia cannot be commenced before 6 hours of age – there is some observational evidence in the literature that hypothermia initiated between 6 and 12 hours is not associated with worse short term or long term outcomes than standard hypothermia practice, however the numbers in this study are small (14). The results of an RCT investigating later initiation of hypothermia are awaited (NCT00614744).

2. Major congenital abnormalities including: Suspected neuromuscular disorders, suspected significant chromosomal abnormalities or life threatening abnormalities of the cardiovascular or respiratory systems.

3. Infants in extremis and not expected to survive.
9.4 DESCRIPTION OF PROCEDURE

THERAPEUTIC HYPOTHERMIA - HOW TO GUIDE

The goal of active hypothermia is to target a rectal temperature of 33.5°C (acceptable range 33-34°C) for 72 hours starting as soon as possible after birth and within 6 hours. The target temperature should be reached within an hour of starting hypothermia.

| Table 2: Process for therapeutic hypothermia |
| Aspect | Considerations |
| Clinical standard | • Commence hypothermia within 6 hours of birth before secondary reperfusion injury begins  
• Hypothermia is continued for 72 hours  
• Achieve core temperature between 33.0 and 34.0 °C by 1 hours from commencement |
| Clinical practice | • Active hypothermia: Use the Tecotherm servo-controlled hypothermia and rewarming mattress. (see Tecotherm Guideline)  
• If the baby is ventilated maintain the humidifier temperature at the temperature recommended by the manufacturer. |
| Blood Tests | • Blood gas, EUC, FBC, LFT, Cardiac Troponin T and Coagulation screen.  
• Further testing as indicated by the clinical situation. |
| Monitor | • Rectal Temperature continuously  
• Blood pressure invasively or non-invasively.  
• Other vital signs  
• BRAINZ aEEG monitor |
| Re-warming before 72 hours | Indications to consider ceasing hypothermia prior to 72 hours include:  
• Encephalopathy has not evolved as predicted.  
• Bleeding due to coagulopathy unresponsive to treatment.  
• Resistant hypoxia due to pulmonary hypertension.  
• A cardiac arrhythmia requiring treatment. |
| Sedation/pain relief | • If the baby shows any signs of distress or there is excessive shivering causing difficulties maintaining the desired baby temperature, consider low dose morphine infusion (5-10mg/kg/hr)  
• Metabolism of most drugs, including analgesics and sedatives, is altered by hypothermia and NICU-specific guidelines or consultation with a neonatal pharmacist is advised. |
| Feeding | • Be aware of the risk of gut compromise and/or necrotising enterocolitis.  
• Do not feed in first 24 hours.  
• Consider cautious introduction of breast milk after this depending on the clinical situation. |
Therapeutic hypothermia does not appear to affect the incidence or severity of most typical multi-organ system complications found in asphyxiated babies. Risks may include:

- Subcutaneous fat necrosis
- Thrombocytopenia
- Sinus bradycardia
- Due to the potential for drug accumulation and toxicity, carefully administer all pharmacological agents according to clinical need.

<table>
<thead>
<tr>
<th>Risks</th>
<th>Therapeutic hypothermia does not appear to affect the incidence or severity of most typical multi-organ system complications found in asphyxiated babies. Risks may include:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Subcutaneous fat necrosis</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>• Sinus bradycardia</td>
</tr>
<tr>
<td></td>
<td>• Due to the potential for drug accumulation and toxicity, carefully administer all pharmacological agents according to clinical need.</td>
</tr>
</tbody>
</table>

Rewarming

- Re-warm after 72 hours of hypothermia and aim to return body temperature to normal over 12 hours.
- Some infants experience increased seizure frequency during rewarming.
- May become hypotensive if they are do not have adequate cardiac preload(26)

9.5 SUPPORTIVE CARE FOLLOWING ASPHYXIA AND DURING HYPOTHERMIA

The goal of supportive care following asphyxia is to optimise the chance of cerebral recovery by avoiding hypovolaemia, hypoxia/hyperoxia, hypoglycaemia or hypcapnia (2). Particular care should be taken to avoid cerebral oedema from fluid overload.

Table 3: Supportive care following asphyxia and during hypothermia

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Goals</th>
<th>Reasoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>• Aim for normal PaO2/saturations and PCO2 (pCO2 35-45 mmHg)</td>
<td>Hyperoxia (paO2&gt;100mmHg) and severe hypcapnia (PaCo2&lt;35mmHg) in the first 120minutes of life in newborns with HIE have been shown to been associated with worse outcomes at 24 months(27)</td>
</tr>
<tr>
<td></td>
<td>• Avoid hyperoxia and hypocapnia (PCO2 &lt;35mmHg)</td>
<td>The aim is to restore a circulating volume that provides a return of cerebral perfusion and to optimise the chance of cerebral recovery.</td>
</tr>
<tr>
<td>CVS</td>
<td>• Perform a clinician performed ultrasound to identify low flow states and support the cardiovascular system with inotropes as required (refer to circulatory support guideline)</td>
<td>Acute renal failure/oliguria/anuria (often secondary to acute tubular necrosis) may occur as may SIADH. The injured brain may be vulnerable to low blood glucose concentrations, maintain a BGL of &gt;2.6 mmol/L(26)</td>
</tr>
<tr>
<td>Renal/Metabolic</td>
<td>• Fluid restrict to 40-60ml/kg/day of IV fluids until good urine output is established and keep strict fluid balance.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hypoglycaemia monitoring and prompt treatment of hypoglycaemia (see hypoglycaemia protocol).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• If early BSL is &lt;1.0mmol/L, treat</td>
<td></td>
</tr>
</tbody>
</table>
with repeat boluses of 5mls/kg 10%D with rapid BSL checks till BSL >2.6 mmol/L.
  • If there is ongoing severe metabolic acidosis consider giving a half correction of bicarbonate (providing ventilation is adequate).

| Haematology                                                                                                                                                                                                 | Hypoxic liver injury can lead to coagulopathy(26). Thrombocytopenia is more common in infants undergoing therapeutic hypothermia(26) however meta-analyses have not shown any worsening in bleeding complications in therapeutic hypothermia. (6) |
| ---                                                                                                                                                                                                                                                             |
| • Monitor for thrombocytopenia/bleeding                                                                                                                                                    |                                                                                                                                                                                                                 |
| • Monitor coagulation if hypothermia or if clinical bruising, petechiae or bleeding.                                                                                                               |                                                                                                                                                                                                                 |
| • Ensure vitamin K given and consider FFP/blood products as required                                                                                                                         |                                                                                                                                                                                                                 |

| Neurology                                                                                                                                                                                                                                                   | Hyperthermia is associated with adverse outcome at 6-7 years in infants not meeting hypothermia criteria(28).                                                                                           |
| ---                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                 |
| • Avoid hyperthermia.                                                                                                                                                                               |                                                                                                                                                                                                                 |
| • Treat seizures as per seizures guideline.                                                                                                                                                       |                                                                                                                                                                                                                 |
| • BRAINZ aEEG monitoring.                                                                                                                                                                        |                                                                                                                                                                                                                 |

| Infection                                                                                                                                                                                                                                                   | Infection is a possible cause of perinatal asphyxia.                                                                                                                                                        |
| ---                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                 |
| • Consider co-existing infection and treat as required.                                                                                                                                           |                                                                                                                                                                                                                 |

| Gastro-intestinal                                                                                                                                                                                | The hypothermia trails withheld feeds during hypothermia. There is some observational evidence that enteral feeds can be tolerated during hypothermia(29). Some feeds may be introduced cautiously at the discretion of the neonatologist on call. Evidence is this area is limited. |
| ---                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                 |
| • Be aware of increased risk of NEC and feed intolerance.                                                                                                                                     |                                                                                                                                                                                                                 |
| • Initially keep the infant nil by mouth during therapeutic hypothermia.                                                                                                                         |                                                                                                                                                                                                                 |
| • Can consider introducing feeds cautiously (preference for breastmilk).                                                                                                                         |                                                                                                                                                                                                                 |

**PHARMACOKINETIC CONSIDERATIONS DURING HYPOTHERMIA**

Therapeutic hypothermia can alter the pharmacodynamics and pharmacokinetics of drugs. The function of cytochrome P450 decreases during hypothermia as does the volume of distribution, due to peripheral vasoconstriction (30). Altered organ perfusion may also impact on drug metabolism and clearance.(30) Drugs that are excreted unchanged in the kidneys may be less impacted by therapeutic hypothermia providing that renal function is maintained (25). It seems sensible to start drug infusions (such as morphine or fentanyl) at the lower end of the range for the normal starting dose and titrate to response. Other medications should be given at their usual neonatal doses (please refer to individual drug protocols). There is ongoing research in this area the results of which are awaited (NTR2529) (31).

**TOLERANCE OF HYPOTHERMIA:**

In general babies tolerate hypothermia well. In our experience, the babies that don’t tolerate it well tend to be those in whom the encephalopathy has not progressed as expected or has improved faster than expected. In such babies, particularly if they are not ventilated, consideration should be given to ceasing the hypothermia early. If the babies are ventilated and have not been given anticonvulsants but appear uncomfortable and require sedation, then morphine should be used. You could consider using a low dose morphine infusion in infants who are not ventilated.
9.6 PREDICTING OUTCOME

Many of the tools used to predict outcome were developed in the pre-hypothermia era and have been found to be less predictive of long term outcome following the introduction of hypothermia(32). A lack of return to a normal background aEEG (discontinuous or continuous normal voltage pattern) on aEEG by 48 hours has been shown to be predictive of death and poor long term outcome (33).

If you extrapolate the outcomes of newborns following hypothermia from the subgroup analysis of the Cochrane meta-analysis “hypothermia for newborns with hypoxic ischaemic encephalopathy” the following percentages are obtained(6).

<table>
<thead>
<tr>
<th>Sarnat staging group</th>
<th>Outcome</th>
<th>Percentage of cooled group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate</strong></td>
<td>Death and severe disability</td>
<td>37*</td>
</tr>
<tr>
<td></td>
<td>Death alone</td>
<td>14*</td>
</tr>
<tr>
<td></td>
<td>Major disability in survivors</td>
<td>26*</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>Death and severe disability</td>
<td>70*</td>
</tr>
<tr>
<td></td>
<td>Death alone</td>
<td>52*</td>
</tr>
<tr>
<td></td>
<td>Major disability in survivors</td>
<td>38</td>
</tr>
</tbody>
</table>

Table 4: Sarnat Encephalopathy Stage and Outcome

Figure 3: Outcomes of cooled group by staging of encephalopathy (subgroup analysis) of Cochrane meta-analysis 2013(6) Severe disability = CP, developmental delay (Bayley or Griffith assessment more than two standard deviations (SD) below the mean) or intellectual impairment (intelligence quotient (IQ) more than two SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification.

* Significant difference between hypothermia and non-hypothermia groups

Table 5: Other Prognostic Markers

<table>
<thead>
<tr>
<th>Apgar Score</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>In a cohort (n=85) of both cooled and non-cooled babies with Apgar scores of 0-3 at 10 minutes 75% had death or neurodisability compared to 45% of those with scores &gt;3(34).</td>
</tr>
<tr>
<td>•</td>
<td>An Apgar score of 0 at 10 minutes has been associated with death or abnormal neurodevelopment at 18–24 months in 73% cooled and 79.5% normothermic infants (p=0.61)(35).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cord pH</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>A low cord pH has been associated with an overall increased risk of death and neurodisability (36) There has been debate about what constitutes a low cord pH in the literature. The international consensus is that a cord pH &lt;7.0 with a BE of -12 is associated with cerebral palsy. A large cohort study of babies who met criteria for cord gas testing at birth found that a pH&lt;7.1 was associated with higher prevalence of encephalopathy (37). There is no good data about using cord pH to predict long term outcome.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>aEEG</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Therapeutic hypothermia alters the prognostic value of aEEG within 72 hours of delivery and decreases the predictive value of aEEG in the first 6 hours of life (33).</td>
</tr>
<tr>
<td>•</td>
<td>A quick recovery of aEEG to normal background within 24 hours is associated with an excellent prognosis(33, 38)</td>
</tr>
<tr>
<td>•</td>
<td>If an abnormal (low voltage, burst suppression or flat trace) aEEG recovers to either a discontinuous or continuous normal voltage pattern by 24 hours this is associated with a good prognosis. Non recovery of an aEEG trace to a...</td>
</tr>
</tbody>
</table>
discontinuous or continuous pattern by 48 hours is associated with a universally poor outcome(33)
- Not having a return of sleep wake cycling during the period of aEEG monitoring is associated with death/disability at 18-22 months(33)

**MRI**
- Conventional MRI at >1 week of life has a sensitivity of 0.91 of and a specificity 0.56 of for detecting death/moderate to severe disability at 12 months (39)
- MRI should be performed between 5 and 7 days to confirm diagnosis and assist in prognostication

**General Movements Assessment**
- General movement assessment has high sensitivity (88%) for abnormal outcome but low specificity (56%) on initial assessment. The specificity improves with serial examination.(40)

**Magnetic resonance imaging (MRI)**

The timing of MRI is important. If an MRI is done too soon after a brain injury it can underestimate the degree of injury. Diffusion weighted imaging shows changes earlier than conventional MRI and are best shown between days 2 and 5 post injury in non-cooled populations, returning to normal (pseudonormalisation) by 6-8 days (41). Pseudonormalisation may occur later in cooled infants(41). In non-cooled populations T1 and T2 weighted MRI changes become visible from day 3 but more apparent at around 1 week of age. A large pooled meta-analysis has shown that the sensitivity of conventional MRI at >1 week of life has a sensitivity of 0.91 of and a specificity 0.56 of for detecting death/moderate to severe disability at 12 months however there was significant heterogeneity between pooled studies (39).

There are two common pattern of injury seen following hypoxic ischaemic encephalopathy; the basal ganglia pattern where there is an abnormal signal intensity in the basal ganglia, thalami, corticospinal tracts and a watershed pattern where there are abnormalities in the white matter and cortex(38, 41). Abnormalities in the posterior limb of the internal capsule on conventional MRI have been particularly associated with abnormal neurodevelopmental outcomes (42)

**Magnetic resonance spectroscopy (MRS)**

The potential benefit of MRS over MRI is that is an absolute measure of metabolites in the brain rather than an image that requires subjective interpretation. Lactate (Lac) increases in the first 24 hours following brain injury while N-acetylaspartate (NAA) decreases over the subsequent 3 days. Studies evaluating the use of MRS have measures Lac/NAA ratios(41). A pooled meta-analysis of 10 studies found that Lac/NAA ratio in the basal ganglia had a sensitivity of 0.82 and specificity of 0.95 in predicting death/disability at 12 months(39). This is an area of ongoing research.

MRI should be performed ideally between day 5 and 7. While MRI adds information that is relevant for prognostication, it must be remembered that it has a limited sensitivity and specificity for predicting abnormal neurological outcome

**RISKS AND COMPLICATIONS**

Sub-cutaneous fat necrosis has been reported in asphyxiated infants and can be associated with hypercalcaemia(43). The Cochrane meta-analysis of hypothermia found that the risk bradycardia was significantly increased in cooled infants relative to non-cooled infants RR 11.59 (4.94, 27.17) P<0.0001 but without any increase in hypotension(6). There was also an increased risk of
thrombocytopenia 1.21 (1.05, 1.40) P=0.007 without an increased risk of bleeding in the cooled group.

**Risk Minimisation.** During therapeutic hypothermia newborns should have continuous rectal temperature monitoring and invasive or non-invasive arterial blood pressure monitoring.

**9.7 Key Points**

<table>
<thead>
<tr>
<th>Table 6: Key Points</th>
<th>LOE</th>
<th>GOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia is indicated in newborns of 35 weeks gestation or higher weighing &gt;1800g who have evidence of an asphyxial insult that has led to encephalopathy.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Moderate hypothermia to between 33-34 degrees should be continued for 72 hours.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Therapeutic hypothermia should be commenced as early as possible and within 6 hours of birth</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>The Tecotherm mattress should be used in preference to cool packs when initiating hypothermia in RPA newborn care</td>
<td>III-2</td>
<td>B</td>
</tr>
<tr>
<td>The target hypothermia temperature should be reached within 1 hour of starting active hypothermia.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Rewarming should occur slowly over 12 hours avoiding hyperthermia</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>MRI should be performed between 5 and 7 days to confirm diagnosis and assist in prognostication. While MRI adds information that is relevant for prognostication, it must be remembered that it has a limited sensitivity and specificity for predicting abnormal neurological outcome</td>
<td>III-1</td>
<td>B</td>
</tr>
</tbody>
</table>
### Modified staging of HIE

<table>
<thead>
<tr>
<th>Stage of HIE</th>
<th>Features</th>
</tr>
</thead>
</table>
| Mild (Stage 1) | - Muscle tone may be increased slightly and deep tendon reflexes may be brisk during the first few days  
- Transient behavioural abnormalities, such as poor feeding, irritability, or excessive crying or sleepiness, may be observed  
- By 3–4 days of life, the central nervous system examination findings become normal |
| Moderate (Stage 2) | - The baby is lethargic, with significant hypotonia and diminished deep tendon reflexes  
- The grasping, Moro, and sucking reflexes may be sluggish or absent  
- The baby may experience occasional periods of apnoea  
- Seizures may occur within the first 24 hours of life  
- Full recovery within 1–2 weeks is possible and is associated with a better long-term outcome  
- An initial period of well-being or mild HIE may be followed by sudden deterioration, suggesting ongoing brain cell dysfunction, injury, and death:  
- During this period, seizure intensity might increase |
| Severe (Stage 3) | - Stupor or coma is typical.  
- The baby may not respond to any physical stimulus  
- Breathing may be irregular and the baby often requires ventilator support.  
- Generalised hypotonia and depressed deep tendon reflexes are common  
- Neonatal reflexes (e.g. sucking, swallowing, grasping, Moro) are absent.  
- Disturbances of ocular motion (e.g. skewed deviation of the eyes, nystagmus, bobbing, and loss of "doll's eye" i.e. conjugate movements) may be revealed by cranial nerve examination.  
- Pupils may be dilated, fixed or poorly reactive to light.  
- Seizures occur early and often and may be initially resistant to conventional treatments  
- The seizures are usually generalised, and their frequency may increase during the 24–48 hours after onset, correlating with the phase of reperfusion injury.  
- As the injury progresses, seizures subside and the EEG becomes isoelectric or shows a burst suppression pattern.  
- At that time, wakefulness may deteriorate further, and the fontanelle may bulge, suggesting increasing cerebral oedema  
- Irregularities of heart rate (HR) and blood pressure (BP) are common during the period of reperfusion injury, as is death from cardiorespiratory failure. |
| Clinical interpretation | - In Stage 1, the baby will usually require minimal support with a normal neurological examination within 3–4 days  
- In Stage 2 and 3, the baby will be significantly more unwell and the |
10. Consultation

- Multi-disciplinary team of senior neonatal medical and nursing staff.

11. References

11.1 NSW Health Policies

11.2 National Standard