GUIDELINE

Hypoxic Ischaemic Encephalopathy (HIE) and Therapeutic Hypothermia

Scope (Staff): Nursing and Medical Staff
Scope (Area): NICU KEMH, NICU PCH, NETS WA

Child Safe Organisation Statement of Commitment
CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

This document should be read in conjunction with this disclaimer

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Please refer to NETS WA Guidelines for the retrieval of neonates with suspected HIE and instructions on Therapeutic Hypothermia.

Aim
Outline the criteria and process for Therapeutic hypothermia for infants with Hypoxic Ischaemic Encephalopathy.
Background

Hypoxic ischaemic encephalopathy (HIE) is suppression of brain activity with possible brain injury due to inadequate oxygen or perfusion to the brain. The brain injury may occur immediately (primary neuronal death) due to primary energy failure; or during the secondary phase (latent period, 6-100 hours) due to cytotoxic oedema, mitochondrial failure or build-up of excitotoxins leading to cell death.

HIE contributes significantly to neonatal mortality and morbidity with adverse neurodevelopmental outcomes seen in up to 25-60% of survivors. Evidence from high quality RCTs indicates that therapeutic hypothermia (TH), using whole body or targeted head methods, of neonates with moderate to severe HIE is relatively safe and reduces the risk of death or disability at 18 to 22 months of age.

Criteria for Therapeutic Hypothermia

Key Points

- This guideline is only for newborn infants >35 weeks GA with moderate to severe HIE.
- The positive effects of TH are optimised when started prior to 6 hours of age.
- Avoid hyperthermia (>37.5°C).
- Complete TH Eligibility and Monitoring Chart (MR461.00) if HIE suspected.
- If a neonate meets eligibility criteria 1, 3, and 4 but is 6-12 hours of age, delayed initiation of TH may be considered at the discretion of the attending neonatologists.

Inclusion Criteria

Essential: the following four inclusion criteria should be met to be eligible for TH

1. > 35 weeks gestational age.
2. < 6 hours post birth.
3. Evidence of asphyxia as defined by the presence of at least two of the following four criteria:
   - Any acute perinatal event that may result in HIE (e.g. abruption of placenta, cord prolapse, severe FHR abnormality).
   - Apgar < 6 at 10 minutes or continued need for resuscitation with positive pressure ventilation +/- chest compressions at 10 minutes of age.
   - Cord pH < 7.0 or base deficit of 12 or more.
   - If cord pH is not available, arterial pH < 7.0 or BE > 12 mmol/L within 60 minutes of birth (if able to do gas).
4. Moderate or severe HIE defined by at least one of the following 3 criteria:
Hypoxic Ischaemic Encephalopathy (HIE) and Therapeutic Hypothermia

- >=3 criteria in moderate/severe category based on modified Sarnat Classification (see table 1 below).
- Seizures
- Abnormal aEEG (low voltage discontinuous, burst suppression)

Table 1. Clinical features of HIE based on the Sarnat Classification (Sarnat 1976)

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Stage 1 (mild)</th>
<th>Stage 2 (moderate)</th>
<th>Stage 3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Alert</td>
<td>Lethargic</td>
<td>Comatose</td>
</tr>
<tr>
<td>Spontaneous activity</td>
<td>Normal</td>
<td>Decreased</td>
<td>No activity</td>
</tr>
<tr>
<td>Neuromuscular control (A)</td>
<td>Normal or hypertonic</td>
<td>Hypotonic</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Muscle tone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuromuscular control (B)</td>
<td>Normal or mild flexion</td>
<td>Distal flexion</td>
<td>Decerebrate, thumb adduction</td>
</tr>
<tr>
<td>Posture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic function</td>
<td>Dilated, reactive</td>
<td>Small, reactive Bradycardia</td>
<td>Variable/fixed Ataxic, apnoeic Bradycardia</td>
</tr>
<tr>
<td>Pupils</td>
<td>Regular</td>
<td>Periodic</td>
<td></td>
</tr>
<tr>
<td>Respiration</td>
<td>Normal/tachycardia</td>
<td>Bradycardia</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primitive reflexes</td>
<td>Active</td>
<td>Weak</td>
<td>Absent</td>
</tr>
<tr>
<td>Suck</td>
<td>Exaggerated</td>
<td>Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>Normal/exaggerated</td>
<td>Exaggerated Overactive</td>
<td>Absent</td>
</tr>
<tr>
<td>Grasp</td>
<td>Normal</td>
<td>Overactive</td>
<td>Reduced/absent</td>
</tr>
<tr>
<td>Oculocephalic</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

Relative contra-indications to Therapeutic Hypothermia

- Passive partial cooling might be considered (to keep axillary or rectal temperatures at 34.5°C) prior to receiving result of the coagulation profile (O'Reilly, Labrecque et al. 2013).
- Persistent pulmonary hypertension (PPHN)
  - Pulmonary hypertension itself is NOT a contraindication (Thoresen 2008, Jacobs, Berg et al. 2013).
Hypoxic Ischaemic Encephalopathy (HIE) and Therapeutic Hypothermia

- Refractory hypoxaemia despite maximal medical therapy (due to the shift in the oxyhaemoglobin dissociation curve to the left with hypothermia), e.g. Oxygen requirement greater than 80% (Dyson 2017, Yum, Seo et al. 2018).
- Cooling might worsen PPHN and meconium aspiration syndrome (need to be guided by clinical condition and echocardiography).

Implementing Therapeutic Hypothermia

Key Points

- Aim of TH is the achieve target range of 33-34°C (rectal temperature) within 1 hour.

- TH is divided into:
  - Active phase: 72 hours from initiation of TH
  - Rewarming phase: 12 hours of rewarming, aiming to increase rectal temperature by 0.5°C every 2 hours with a target of 37°C +/- 0.5.

- Equipment:
  - Automated options: Medi-Therm III, Cincinnati 3, Arctic Sun.
  - Cool gel packs if automated options are unavailable
  - Rectal temperature probe

Initiation of Therapeutic Hypothermia

For further information regarding automated options or cool gel packs, refer to Appendix 1:

Monitoring of Newborn Receiving Therapeutic Hypothermia

General Monitoring

- Continuous intensive care monitoring (ECG, BP, SaO₂, ETCO₂).
- Continuous aEEG monitoring during active and rewarming phase.
- Document neurological observations on Neonatal Neurological Observation Chart MR494.00.
- Document HIE stage daily on Therapeutic Hypothermia Eligibility and Monitoring Form MR461.00.

Temperature Monitoring

- Rectal probe inserted to depth of 5cm.
- Set temperature alarm limits at 33 (low) to 34 (high).
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aEEG Monitoring
- aEEG monitoring should be applied after stabilisation of the newborn.
- It is used for early decision making and monitoring of cerebral activity.
- Up to 50% of infants may develop seizures as a result of HIE.

Investigations
1. Complete “HIE bloods” daily during the active and rewarming phase
   - FBP, UE&C, calcium, magnesium, LFT, coagulation profile, blood gas monitoring
     - TH may decrease platelet function and counts.
2. Formal EEG to be arranged (usually post rewarming phase).
3. MRI to be arranged usually post rewarming phase between day 4-8 of age.

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloods</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>Neurological assessment</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>aEEG Monitoring (Brainz Monitor)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EEG (usually at 72hr)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Y</td>
<td>-</td>
</tr>
<tr>
<td>MRI (before day 8, ideally on day 4 or 5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Y</td>
</tr>
</tbody>
</table>

Management of Newborn Receiving Therapeutic Hypothermia

General Management Points
- Asphyxia may lead to multi-organ failure (Monitor hepatic, renal, respiratory and cardiac systems regularly).
- TH may lead to reduced platelet function and counts, immune dysfunction.

Cardiac Support
- Volume expansion or Inotrope may be required.
- The infant should remain normotensive to assist in cerebral perfusion.
- If cardiac function is depressed consider dobutamine or low dose adrenaline.

Fluid and Electrolyte Management
- Total fluid intake early is usually 40-60mL/kg/day.
- Maintain normal electrolyte levels especially sodium to reduce risk of cerebral oedema.
• Strict fluid balance as asphyxia and TH may lead to reduce urine output.

**Glucose Homeostasis**

• Hypoglycaemia may worsen neurodevelopmental outcomes of infants with HIE.
• Aim for blood glucose levels between 3.5-6 mmol/L.
• Provide 6-8 mg/kg/min of glucose infusion IV.
• Increase concentration of dextrose if fluid restriction required.

**Sedation**

• Sedation may be required to assist in reducing metabolic rate in infants that have become agitated.

**Skin**

• Frequent repositioning and monitoring of dependent areas. Documentation of NSCS and GS as per Neonatal Skin Care guideline.
• Increased risk of subcutaneous fat necrosis
  o This may lead to hypercalcaemia, hyperlipidaemia and thrombocytopenia.

**Seizure Control**

• Higher seizure burden is known to be associated with worse outcomes in HIE (Kharoshankaya 2016).
• Identify and treat seizures early guided by aEEG and clinical examination.
• Suggested management (Refer to Seizures: Neonatal):
  o 1st line: phenobarbital.
  o 2nd and/or 3rd line: Leviteracetam, midazolam.
  o 4th line: lignocaine infusion or phenytoin.
• For resistant seizures discuss with neurologist.

**Feeding**

• Unit practice is to keep the infant nil by mouth during TH and rewarming phase.
• If clinicians would like to give enteral feeds, use expressed breast milk and minimal volumes (5-10 ml/kg/day).
• A recent retrospective study found that administration of minimal enteral feeds is safe in infants undergoing therapeutic hypothermia for HIE (Thyagarajan 2015).
Follow-Up

- All infants that received TH require developmental follow-up with Griffiths Scales at one year and Bayley Scales at two years of age.
Hypoxic Ischaemic Encephalopathy (HIE) and Therapeutic Hypothermia

Related CAHS internal policies, procedures and guidelines

Neonatology Clinical Guidelines
- Hypoglycaemia
- Seizures: Neonatal
- Sepsis: Neonatal

Neonatal Medication Protocols

References


This document can be made available in alternative formats on request.

<table>
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<th>Neonatology</th>
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<td>Reviewer / Team:</td>
<td>Neonatology Coordinating Group</td>
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<td>Date First Issued:</td>
<td>July 2018</td>
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<td>Date:</td>
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<tr>
<td>Standards Applicable:</td>
<td>NSQHS Standards:</td>
</tr>
</tbody>
</table>

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Appendix 1: Active Cooling Phase

Maintenance of Target Rectal Temperature for 72 Hours using the Cincinnati 3 or Meditherm III Servo Controlled Cooling and Warming Machine

- Place the gel neonatal mattress underneath the baby. A single sheet can be used over the mattress if required.
  - Consider the use of a pressure mattress.
- Nurse the infant on a radiant warmer with the warmer off.
- Do not dress the infant.
- Leave the nappy unfastened.
- Insert a rectal probe and tape the 10 cm mark to the upper inner aspect of the thigh. This depth will give an accurate core temperature. The probe remains in situ for the duration of the cooling period.
- Full cardiopulmonary monitoring including invasive blood pressure if possible.
- If the infant is ventilated, leave ventilation humidity at normal temperature.
- When hypothermia has been achieved and temperature range is stable, apply BRAINZ Monitor.
- Therapeutic hypothermia should not be stopped earlier than the 72-hour period unless attending neonatal consultant decides to cease earlier. The reason for stopping must be documented in the medical records.
- All other documentation/care/treatment should be as per NICU routine care of infant requiring intensive care.
- Advise/reassure parents re: appearance, cool to touch.
## Appendix 2: Cooling and Warming Machines

<table>
<thead>
<tr>
<th>CINCINNATI 3</th>
<th>MEDITHERM III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connect the tubes to the black insulated hose from the machine.</td>
<td>Connect the tubes to the grey insulated hose from the machine.</td>
</tr>
<tr>
<td>Make sure the hoses and gel roll are not kinked. Check the water level at the back of the machine. Water level must be visible at the bottom of the water fill opening.</td>
<td>Make sure all clamps are in the open position, both on the grey hose and on the neonatal mattress. Press the on switch, located at the front lower left of the Medi-therm III machine. Select the centre square button, THE AUTOMATIC MODE. Tab to select the speed - choose the middle speed.</td>
</tr>
<tr>
<td>Press the on switch, located at the front lower left of the machine.</td>
<td>Set the target temperature of the patient with the far lower right hand side square button. To cool below 36˚C, keep the button depressed to confirm and set the new patient cooling set temperature to 33.5˚C.</td>
</tr>
<tr>
<td>Press TEMP SET and use the UP &amp; DOWN buttons to select desired temperature to 33.5°C.</td>
<td>Cooling will now commence.</td>
</tr>
<tr>
<td>Select the GRADIENT 10°C and the select SMART MODE.</td>
<td>When the infant temperature is approaching the target temp the machine will slow down automatically to prevent significant undershooting and will maintain the target temperature.</td>
</tr>
<tr>
<td>Ensure that paddle wheel is turning. If paddle is not turning check for obstruction such as kinked hose.</td>
<td>Cooling will now commence.</td>
</tr>
<tr>
<td>When the infant temperature is approaching the target temp the machine will slow down automatically to prevent significant undershooting and will maintain the target temperature.</td>
<td>When the infant temperature is approaching the target temp the machine will slow down automatically to prevent significant undershooting and will maintain the target temperature.</td>
</tr>
</tbody>
</table>

### REWARMING PHASE - THIS PHASE WILL TAKE UP TO 12 HRS.

<table>
<thead>
<tr>
<th>After the period of cooling, to rewarm the infant, press the TEMP SET button.</th>
<th>After the period of cooling, to rewarm the infant, set the target temperature to the desired temperature 37°C (Core).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use the ↑ button to increase the set temperature by 0.3°C every hour until the infants temperature is 36.5°C over 12 hours.</td>
<td>Continue with the MODERATE rate setting which will rewarm the patient at 0.33°C per hour, i.e. from 33.5 to 36.5°C over 12 hours.</td>
</tr>
<tr>
<td>Every time the TEMP SET is adjusted the GRADIENT 10°C/GRADIENT VARIABLE &amp; SMART button must be pressed to accept the change and to start the unit again.</td>
<td>Once the infants core temperature reaches 36.5°C at 12 hours the mattress is removed and the machine is turned off. The rectal probe is removed.</td>
</tr>
<tr>
<td>Once the infants core temperature reaches 36.5°C at 12 hours the mattress is removed and the machine is turned off. The rectal probe is removed.</td>
<td>Monitor neurological status closely during the rewarming phase</td>
</tr>
</tbody>
</table>

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**Hypoxic Ischaemic Encephalopathy (HIE) and Therapeutic Hypothermia**

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Appendix 3: Active Cooling Phase with Cool Packs

TH using cool packs should only be done when automated machines are unavailable. TH should not be delayed or withheld because of unavailability of automated machines.

Nursing care is as above under **Active cooling phase**

- Set alarm limits for rectal temp at 33.0-34.0°C.
- Use cold packs from the fridge, **never** frozen.
- Always put cold packs in cotton bags.

<table>
<thead>
<tr>
<th>Temperature algorithm</th>
<th>Number of cool packs to be applied</th>
<th>Areas to apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 37.0</td>
<td>4</td>
<td>Head, shoulders, neck, trunk</td>
</tr>
<tr>
<td>36.1 - 37.0</td>
<td>3</td>
<td>Shoulders, neck, trunk</td>
</tr>
<tr>
<td>35.1 - 36.0</td>
<td>2</td>
<td>Shoulders, trunk</td>
</tr>
<tr>
<td>34.1 - 35.0</td>
<td>1</td>
<td>Trunk</td>
</tr>
<tr>
<td>33.0 - 34.0</td>
<td>0</td>
<td>Nil</td>
</tr>
</tbody>
</table>

- When rectal temp < 33.0, set radiant warmer on manual and gradually adjust heater output to maintain rectal temp at 33.0-34.0°C. Turn off the heater once temperature reaches 33.5.
- Caution: watch temperature range more closely in infants treated with anticonvulsants or muscle relaxants as they may cool much quicker.

Rewarming Phase after use of cool packs

**This Phase will take up to 12 Hours**

- Apply skin temperature probe and turn radiant warmer on if switched off.
- Set servo at 34.0°C.
- Increase servo temp by 0.5 every 2 hours until rectal temperature is 36.5°C.
- Adjust alarm limits accordingly on rectal temp range as temp increases.
- Record both skin and rectal temp hourly.
- When normothermia has been achieved, **pay attention to avoid overheating the infant above 37°C.**