1.0 Introduction

Hypoxic ischemic encephalopathy (HIE) is defined as an abnormal neurologic state in the neonatal period arising as a result of a hypoxic-ischemic insult. The long-term neurodevelopmental outcome for neonates who have suffered brain injury from a birth related hypoxic-ischemic insult is often poor. There is evidence from both animal and human studies that induced hypothermia provides a mechanism for neuroprotection reducing the severity of brain injury leading to an improved neurological outcome in many patients. All infants with HIE should be assessed for eligibility to receive total body cooling. Evidence suggests that hypothermia in neonates with moderate to severe HIE reduces the severity of brain injury and leads to improved neurological outcome. Therapeutic hypothermia is considered the standard of care treatment in perinatal asphyxia of the term newborn.

Target Patient Population

- The commencement of hypothermia within 6 hours of birth, for eligible patients, is the desirable target. Ideally this should be initiated as soon as possible as earlier cooling can improve its effectiveness. However due to challenges with clinical assessment of encephalopathy within the first 6 hours of life ALL babies with HIE irrespective of the inclusion and exclusion criteria, who are referred to SickKids within 12 hours of birth, should be considered as potentially eligible for therapeutic hypothermia, in consultation with the staff neonatologist.
- In the presence of severe encephalopathy where the risk of death or adverse neurodevelopmental outcome is assessed to be high, the responsible physician(s) may choose to not offer hypothermia treatment if the plan is not to pursue aggressive treatment.
- Initiation of hypothermia does not preclude a decision to withdraw life-sustaining therapy.

Inclusion Criteria:
Infant should fulfill all 4 criteria:
1. GA greater than or equal to 35 weeks
2. Less than 6 hours post-delivery
3. Evidence of intrapartum hypoxia defined as:
   EITHER:
   Cord or postnatal blood gas within one hour of birth with pH less than or equal to 7.00 OR base deficit of greater than or equal to -16 OR if pH 7.01-7.15 or BD -10 to 15.9, and Apgar score 5 or less at 10 minutes or need for continued ventilation or resuscitation at 10 minutes.
   (if no blood gas available then must have evidence of an acute perinatal event ie abruption, uterine rupture, maternal trauma or cardiopulmonary arrest, late or variable decelerations)
4. Signs of moderate or severe encephalopathy defined as presence of clinical seizures or 3 or more of the items in the moderate or severe categories using the modified Sarnat score or a Thompson score of >7.

Therapeutic Hypothermia Criteria
- **Exclusion Criteria**
  1. Neonate less than 1.8 kg
  2. Clinically significant coagulopathy despite treatment
  3. Moribund neonates, or neonates with major congenital or genetic abnormalities, in whom no further aggressive treatment is planned

**Neurological Assessment**

The neurological examination must be performed by a physician/NP skilled in neurological assessment to determine the degree of encephalopathy.

### Modified Sarnat Score

<table>
<thead>
<tr>
<th>Category</th>
<th>Mild Encephalopathy</th>
<th>Moderate Encephalopathy</th>
<th>Severe Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Level of consciousness</td>
<td>Hyperalert</td>
<td>Lethargic</td>
<td>Stupor/coma</td>
</tr>
<tr>
<td>2. Spontaneous activity</td>
<td>Normal</td>
<td>Decreased</td>
<td>No activity</td>
</tr>
<tr>
<td>3. Posture</td>
<td>Mild distal flexion</td>
<td>Strong distal flexion</td>
<td>Decerebrate (arms extended and internally rotated, legs extended with feet in forced plantar flexion)</td>
</tr>
<tr>
<td>4. Tone</td>
<td>Normal</td>
<td>Mild hypotonia</td>
<td>Flaccid tone</td>
</tr>
<tr>
<td>5. Primitive reflexes Suck</td>
<td>Weak</td>
<td>Weak</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>Strong</td>
<td>Incomplete</td>
<td>Absent</td>
</tr>
<tr>
<td>6. Autonomic system</td>
<td>Dilated, responsive Tachycardia</td>
<td>Constricted Bradycardia</td>
<td>Skew deviation, dilated/non-reactive to light</td>
</tr>
<tr>
<td>Pupils</td>
<td>Heart rate</td>
<td>Periodic breathing</td>
<td>Variable HR</td>
</tr>
<tr>
<td>Respirations</td>
<td>Normal</td>
<td>Normal</td>
<td>Apnea</td>
</tr>
</tbody>
</table>

### Thompson Score

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tone</td>
<td>__ Normal</td>
<td>__ Hypertonic</td>
<td>__ Hypotonic</td>
<td>__ Flaccid</td>
</tr>
<tr>
<td>LOC</td>
<td>__ Normal</td>
<td>__ Hyper alert stare</td>
<td>__ Lethargic</td>
<td>__ Comatose</td>
</tr>
<tr>
<td>Seizures</td>
<td>__ None</td>
<td>__ Infrequent &lt; 3/day</td>
<td>__ Frequent &gt; 2/day</td>
<td></td>
</tr>
<tr>
<td>Posture</td>
<td>__ Normal</td>
<td>__ Fisting, cycling</td>
<td>__ Strong distal flexion</td>
<td>__ Decerebrate</td>
</tr>
<tr>
<td>Moro</td>
<td>__ Normal</td>
<td>__ Partial</td>
<td>__ Absent</td>
<td></td>
</tr>
</tbody>
</table>
## 2.0 Ancillary monitoring during Whole Body Cooling

- Cooled patients should receive a\textbf{EEG} (amplitude integrated electroencephalography) monitoring during the cooled period.
- Continuous EEG monitoring should be considered if there is discontinuity on the aEEG or seizures.
- Adjustments to alarm limits for continuous cardiorespiratory monitoring should be documented in the doctor’s orders (i.e low resting heart rates).
- The following \textbf{laboratory monitoring} is recommended as a minimum to be ordered by the medical team. Additional laboratory tests may be ordered as needed.

<table>
<thead>
<tr>
<th>Laboratory Monitoring</th>
<th>On admission</th>
<th>12 hours after initiation of cooling</th>
<th>24 hours after initiation of cooling</th>
<th>48 hours after initiation of cooling</th>
<th>72 hours after initiation of cooling</th>
<th>24 hours after rewarming</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POCT glucose</strong></td>
<td>Every 6 hours throughout the cooling process</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>Gas, lactate, CBC, coagulation, electrolytes, ALT, AST, urea, creatinine, ammonia, calcium, glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 hours</td>
<td>Gas, lactate, electrolytes, C-reactive protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hours</td>
<td>Gas, lactate, CBC, coagulation, electrolytes, LFTs, bilirubin, urea &amp; creatinine, ammonia, calcium, phosphate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 hours</td>
<td>Electrolytes, urea and creatinine, bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 hours</td>
<td>Glucose, electrolytes, bilirubin, CBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hours after rewarming</td>
<td>Glucose, electrolytes, calcium, bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.0 Patient Considerations

- **Rewarming**: Rewarming should occur no faster than 0.5 degrees Celsius/hour, even if rewarming is occurring for other clinical indications such as hemodynamic instability or persistent coagulopathy. – see rewarming section.

- **Venous/arterial Access**
  Consider venous/arterial access needs for patient monitoring prior to the cooling process as difficulties in obtaining access may occur related to decreased perfusion secondary to hypothermia.

- **Fluid and Nutritional Requirements**
  Fluid and nutritional requirements should be assessed daily and when there are changes to the level of patient sedation. Hypothermia, sedation, and the effects of a hypoxic ischemic insult have an additive effect on the infant's metabolic activity. Fluid and nutritional requirements may need modification, as metabolic activity is likely to be significantly reduced.

- **Enteral feeding during therapeutic hypothermia**
  - Patients with moderate-severe HIE will remain NPO during cooling.
  - Patients with milder HIE may be eligible for tropic feeds – Enteral Feeding During Therapeutic Hypothermia

- **Minimizing the risk of subcutaneous fat necrosis**
  - Once target temperature has been reached do not use additional ice packs on the skin as this increases the risk for subcutaneous fat necrosis (see 5.3 #10, below) – Subcutaneous Fat Necrosis

- **Analgesia and sedation management**
  - Indications for sedation include agitation or shivering response. Shivering leads to increased peripheral muscle oxygenation consumption. Neonates with excessive shivering should be considered for treatment with dexmedetomidine (please see formulary for dosing details).
  - Analgesia may be used instead of a sedative in the case of patients who have pain due to trauma at delivery, with low dose morphine infusion. Infants with hypoxic ischemic encephalopathy have reduced morphine clearance and elevated serum morphine concentrations.
  - Potentially toxic serum concentrations of morphine may occur with moderate hypothermia and infusion rates >5 micrograms/kg per hour 12.

- **Concurrent use of anti-epileptic drugs (AED) and sedative medications**
  Caution should be used in patients who are receiving anticonvulsants in addition to sedative or opioid agents. Please discontinue sedatives for patients receiving Phenobarbital or midazolam infusions for seizures.

- **Holding during therapeutic hypothermia**
  Patients MAY be eligible for holding during cooling. Refer to NICU Holding Guidelines for eligibility and procedure.
### 4.0 Process for Management of HIE in NICU

#### Hypoxic Ischemic Encephalopathy (HIE)  
**Expected Date of Discharge:** 8 days post admission

<table>
<thead>
<tr>
<th>DAY OF ADMISSION (0-24 HOURS POST BIRTH)</th>
<th>1-2 DAYS POST ADMISSION (24-48 HOURS POST BIRTH)</th>
<th>DAY 3-4 HOURS POST BIRTH</th>
<th>DAY 4 &amp; 5 POST BIRTH</th>
</tr>
</thead>
</table>
| 1. Complete HIE admission order (HIE order set)  
2. Complete baseline labs and blood work  
3. Ensure neonate is monitored closely for seizure activity  
4. If intubated, assess for ongoing respiratory support  
5. Initiate seizure cooling protocol (if indicated)  | 1. Monitor I & O.  
2. Ensure neonate is responding to temperatures  
3. Hypothyroidism  
4. Control seizures as needed  
5. If intubated, complete sleep monitor breathing trial  
6. Start MRI for day 4-5 post rewarming  
7. Book family meeting with both parents.  | 1. Refer to neurosurgery if coded  
2. Prepare for MRI  
3. Complete seizure plan for day 4-5 post rewarming  
4. Review partial nutrition status  
5. Continue to assess for readiness for extubation.  | 1. MRI on day 4/5  
2. Discontinue propofol/paralytics  
3. Decrease prone position time  
4. Discontinue diuretics and diuretics  |

<table>
<thead>
<tr>
<th>DAY 5 POST BIRTH</th>
<th>DAY 6 POST BIRTH</th>
<th>DAY 7 POST BIRTH</th>
<th>DAY 8 POST BIRTH</th>
</tr>
</thead>
</table>
| 6. Continue to assess for readiness for extubation  
7. Start enteral feeds  
8. Review feeding tolerances  | 1. MRI on day 4/5  
2. Review mood status  
3. Discontinue prone position  
4. Discontinue diuretics  | 1. MRI on day 4/5  
2. Review mood status  
3. Discontinue prone position  
4. Discontinue diuretics  | 1. MRI on day 4/5  
2. Review mood status  
3. Discontinue prone position  
4. Discontinue diuretics  |

#### Printable Version of Process for Care Coordination

### 5.0 Procedure

#### 5.1 Equipment

- **Blanketrol III unit** (located in the link room)  
  - Hypo/hyperthermia blanket – should be attached to Unit (do not remove unless leak/defect)
- **Disposable rectal probe** – supply room (special order item – inventory monitored by Patient Information coordinator)

#### 5.2 Preparing Blanketrol III unit

<table>
<thead>
<tr>
<th>Important Steps</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Check the level of distilled water in the reservoir. To do so, lift cover of the water fill opening and check if the water is visibly touching the strainer. If needed, carefully add distilled water.</td>
<td>Low water indication/warning message will alarm if water level is too low. If in operation and this alarm occurs press</td>
</tr>
</tbody>
</table>
### Important Steps | Key Points
--- | ---
1. **SILENCE ALARM** button. Pour distilled water into reservoir in until it is visible touching the strainer. The status display will change to show CHECK SET PT. All parameters will need to be reset to proceed (see below).

2. Lay the hypo/hyperthermia (rubber blanket) flat on the Overbed warmer with the hoses lying without kinks, towards the Blanketrol III unit. **Ensure hoses are not twisted to allow for unrestricted circulation of water through the unit to the hypo/hyperthermia blanket.**

3. If hoses from hypo/hyperthermia blanket are not connected attach return and outlet couplings to Blanketrol III unit. **Do not disconnect hoses from Blanketrol III after use.**

4. Check that the power switch is **OFF** prior to inserting the electrical plug into a properly grounded hospital grade receptacle (red electrical outlet).

5. Turn power switch **ON**. Water will be circulated through the blanket. Check that there are no leaks in the blankets or hoses. **Water leaks present a risk of infection to the patient and should not be used. Obtain alternate blanket from another Blanketrol III supply box.**

6. **Set the Celsius/Fahrenheit switch so that Celsius is displayed.**

7. **Pre-cool the blanket to 33°C** by first operating in the Manual Control Mode.  
   - Press the **MANUAL CONTROL** button.  
   - Press the **TEMP SET** button
   **Allow 15 minutes to pre-cool the hypo/hyperthermia blanket prior to use.**

### 5.3 Cooling the Infant

<table>
<thead>
<tr>
<th>Important Steps</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> Place infant on a radiant over-bed warmer.</td>
<td>Allows for easy access to the infant.</td>
</tr>
</tbody>
</table>

| **2.** Ensure radiant warmer on over-bed is OFF. Monitor skin temperature with skin temperature probe. | Exposure to the environment assists in maintaining hypothermic state. Skin temperature should be monitored as a safety measure, in case the rectal thermometer becomes dislodged. |

| **3.** Insert the rectal/esophageal temperature probe to the appropriate depth.  
  a. **Rectal insertion:**  
     i. Lubricate probe with water-based lubricant. Gently insert temperature probe to 3 cm into infant’s rectum. Secure probe to infant’s leg to avoid probe dislodgement. | Utilize esophageal placement for infants with anorectal malformations/injuries. |

  b. **Esophageal insertion:**  
     i. Submerging probe in warm water will make probe more pliable.  
     ii. Measure distance from the tip of the nose to the earlobe to the xyphoid process then **subtract** 2 cm from the length to approximate distance to lower esophagus.  
     iii. Lubricate probe with sterile water or infant’s saliva. |
### Important Steps

| **iv.** Insert esophageal probe into nare. Do not push past resistance. Attempt opposite nare or insert orally and secure probe with tape. | **Key Points**
| **v.** Confirm placement with a 2 view x-ray. | This exposes the greatest amount of body surface area of the infant to the hypo/hyperthermia blanket. The Blanketrol III system is used either: to lower or to raise a patient's temperature and/or maintain a desired patient temperature through conductive heat transfer. An infant’s body temperature is more responsive to surface heating and cooling than adults related to their higher ratio of skin contact area to body mass. Prevent excessive and/or prolonged tissue pressure and shearing forces, especially over bony prominences, to prevent skin damage. |
| **vi.** Secure probe to infant’s face to avoid dislodgement. |

| 4. Insert temperature probe plug into Blanketrol III unit patient probe jack on the right side of the unit. |
| 5. Position the pre-cooled hypo/hyperthermia blanket fully unfolded under the infant such that the infant is supine with the occiput resting on the blanket. |

| 6. Active cooling will be reduced when the rectal/esophageal temperature falls below or meets 34.5 °C. |
| - Press TEMP SET button. |
| - Use the up/down arrows to change the SETPT temperature to **33.5°C**. |
| - Press the GRADIENT 10C* button, then press the SMART MODE button. |

The target rectal/esophageal temperature is **33.0°C-34.0°C** which is consistent with published trials of whole body hypothermia. 10; 11

*In GRADIENT 10C MODE the unit monitors the patient’s temperature and maintains the circulating water temperature at a maximum of 10°C different from the patient’s temperature in order to gradually adjust the patient's temperature to a set point determined by the operator. When the patient reaches set point, the unit continues to circulate the water but the water is not heated or cooled. If the patient’s temperature falls outside the set point range, the unit resumes operation in GRADIENT 10C MODE. Therefore, if the patient temperature is set for 33.5°C the blanket temperature will not fall below 23.5°C. If a 10°C gradient is not maintaining the patient’s temperature at the desired level a variable gradient can be Commencement of 72 hour cooling period begins when target temperature is reached. Notify physician immediately if temperature increases or decreases outside of the **33.0°C-34.0°C** target. Once you activate the SMART Mode function, the unit will evaluate whether or not the patient's current temperature is the same as their target temperature every 30 minutes. If they are not the same then the unit will respond by adjusting the water temperature by 5 degrees (warmer or cooler) until the patient reaches their target temperature. Once the patient reaches the target temperature the SMART Mode will turn off and the Blanketrol III will default back to the original Gradient setting. If the patient's temperature...
selected using the GRADIENT VARIABLE MODE, whereby a gradient value can be set (range from 0 to 20 degrees Celsius gradient).

To set GRADIENT VARIABLE MODE:
- Press TEMP SET button.
- Use the up/down arrows to change the SET PT temperature to desired patient temperature.
- Press GRADIENT VARIABLE button.
- Use the up/down arrows to change the gradient to the desired value (0 to 20).
- Press GRADIENT VARIABLE button.

deviates by 0.2 degrees C (+/-) the SMART Mode will be activated.

---

7. Rectal/esophageal, skin and blanket/water temperatures are to be assessed and recorded at specified frequencies:

<table>
<thead>
<tr>
<th></th>
<th>Rectal/esophageal</th>
<th>Skin</th>
<th>Blanket</th>
</tr>
</thead>
<tbody>
<tr>
<td>q15min</td>
<td>x4hrs</td>
<td>x4hrs</td>
<td>x4hrs</td>
</tr>
<tr>
<td>then q1hr</td>
<td>x12hrs</td>
<td>x12hrs</td>
<td>x12hrs</td>
</tr>
<tr>
<td>then q2hr</td>
<td>x72hrs (until cooling completed)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The probe used to record skin temperature should be placed on the abdomen, not the extremities.

Monitor the skin temperature as follows:
- Insert skin temp module into bedside monitor
- Insert metal end of skin temp probe into module
- Secure pt end of probe onto infant’s abdomen (over liver).
- Apply silver dot over probe to hold probe in place
- Skin temp should appear on VS monitoring screen

An infant’s body temperature is more responsive to surface heating and cooling than adults related to their higher ratio of skin contact area to body mass. Prevent excessive and/or prolonged tissue pressure and shearing forces, especially over bony prominences, to prevent skin damage. Frequent skin assessments should be conducted (manufacturer’s recommendations indicate as frequently as q20 minutes and more frequently for pediatric patients) of areas in contact with the hypo/hyperthermia blanket for skin damage. Neonates are at risk for developing fat necrosis.

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8. Notify physician immediately if:

Under physician’s order active cooling will be reduced if:
- Oxygen requirements increase by more than 20%
- The infant is treated with anticonvulsants or muscle relaxants.

Under physician’s order cooling will be stopped if:
- Persistent hypoxemia despite 100% oxygen and pulmonary vasodilator treatment.
- Life threatening coagulopathy.
- Arrhythmia requiring medical treatment (not sinus bradycardia).
- Decision made by responsible physician to withdraw intensive care support on the basis of poor neurodevelopmental outcome.

Notify physician/nurse practitioner immediately of any changes in the infant’s condition.

*The infant’s rectal/esophageal temperature will begin to decrease soon after initiation of the cooling therapy. Within the first 30-45 minutes on the blanket, it is expected for the infant’s esophageal temperature to drop below the eventual desired temperature of 33.5°C. The Blanketrol system adjusts quickly and will warm the blanket water to raise the infant’s temperature to 33.5°C by approximately 90-120 minutes from initiation of the cooling therapy. While maintaining the infant’s temperature at 33.5°C, the blanket...*
9. During cooling therapy there should only be a thin sheet between the infant and the hypothermia blanket. Rolled cloth blankets and other positioning aids may be used but should be placed under the cooling blanket.
   - Hats, socks, and a thin sheet ON TOP of the patient are acceptable as long as the core temperature is within expected range.
   - In some infants there is difficulty maintaining the target temperature. For those infants ensure serum magnesium levels are in the normal range, try lowering the gradient temperature to 15 degrees Celsius, Do not use additional ice packs on the skin-this may pose an additional risk for subcutaneous fat necrosis, try warming the infants hands and feet to reduce shivering.

10. Monitor skin for signs of Subcutaneous Fat Necrosis

### 6.0 Rewarming of Infants Following Body Cooling

Upon completion of the 72-hour period of cooling, the infant will be re-warmed gradually, increasing the core body temperature at the rate of 0.5°C per hour over a 6-hour period.

<table>
<thead>
<tr>
<th>Important Steps</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> Rewarming of Infants Following Body Cooling</td>
<td>Re-warming the infant’s temperature should not exceed at the rate of 0.5°C per hour over a 6-hour period.</td>
</tr>
<tr>
<td>Each hour increase the Blanketrol III Set point temperature:</td>
<td></td>
</tr>
<tr>
<td>• Press the TEMP SET switch.</td>
<td></td>
</tr>
<tr>
<td>• Press the Up arrow to increase the SETPOINT by 0.5°C.</td>
<td></td>
</tr>
<tr>
<td>• Press the GRADIENT 10C button.</td>
<td></td>
</tr>
</tbody>
</table>

| **2.** At the end of the 6-hour re-warming period, the infant’s thermoregulation will be returned to the Overbed warmer servo-control with skin probe placed on the infant’s abdomen; set the initial radiant warmer set point (skin/control) temperature 0.5°C higher than the infant’s current skin temperature. Press the Blanketrol III TEMP SET switch, remove the blanket from under the infant, remove the esophageal probe, and turn the Blanketrol III unit power switch to OFF. The radiant warmer set point temperature should be increased by 0.5°C every hour until a set point of 36.5°C is reached, or until the infant has achieved an axillary temperature of 36.5°C. | |

### 7.0 References

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8.0 Guideline Group and Reviewers

Guideline Group Membership:
1. Diane Wilson, NP, NICU
2. Amr El-Shahed, MD
3. Linh Ly, MD
4. NICU Neurological Interest Group
5. Kyong Soon Lee, MD
6. NICU NiQ Committee
7. Quality Management

Internal Reviewers:

1. Christine Elliott
2. Christopher Tomlinson

Attachments:

HIE Pathway_April 25_2018.docx

HIE Pathway_April 25_2018.pdf