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Hypoxic Ischemic Encephalopathy (HIE) Clinical Care Pathway

Version: 8

Content

1.0 Introduction

Hypoxic ischemic encephalopathy (HIE) is defined as an abnormal neurologic state that occurs during the neonatal period following a hypoxic-ischemic insult. There is evidence from both animal and human studies that therapeutic hypothermia provides neuroprotection by reducing the severity of brain injury and resulting in an improved neurological outcome (1–4). All infants with HIE should be assessed for eligibility to receive therapeutic hypothermia. Evidence suggests that hypothermia in neonates with moderate to severe HIE reduces the severity of brain injury and leads to improved neurological outcomes (3). Therapeutic hypothermia (TH) is considered the standard of care in newborns with HIE.

2.0 Target Patient Population

- The commencement of therapeutic hypothermia **within 6 hours of birth**, for eligible patients, is the desired target (1,3,5). Recent data showed that the time to reach target temperature (i.e., therapeutic hypothermia initiated before or after 4 hours of age) demonstrated no significant effect on mortality, short-term outcomes, brain injury on MRI, and neurodevelopmental impairment at 2 years of age in infants with HIE (6).

- All term or late-preterm infants ≥ 35 weeks gestation with moderate or severe HIE should be considered for therapeutic hypothermia.
- Therapeutic hypothermia is not recommended for preterm infants and infants with mild HIE as there is currently no evidence that cooling is beneficial (3). Studies have shown that therapeutic hypothermia in preterm infants less than 35 weeks gestation was associated with adverse effects (7) and hypothermia is associated with increased mortality and morbidity in very preterm infants (8). Similarly, there is insufficient evidence to recommend therapeutic hypothermia for infants with mild HIE (3). The benefits of therapeutic hypothermia in preterm infants and infants with mild HIE may not outweigh the risks, therefore therapeutic hypothermia is currently not recommended for these infants until more evidence is available.
- In the presence of profound encephalopathy where the risk of death or adverse neurodevelopmental outcome is high, the responsible physician may choose not to offer hypothermia treatment if there is no plan to pursue aggressive treatment.
- Initiation of hypothermia does not preclude a decision to withdraw life-sustaining therapy.

3.0 Therapeutic Hypothermia Criteria

Inclusion Criteria: Infant should <u>fulfill all 4 criteria</u>:	
1.	Gestational age (GA) greater than or equal to 35 weeks.
2.	Less than 6 hours post-delivery.
3.	Evidence of intrapartum hypoxia is defined as: a. Cord or postnatal blood gas within one hour of birth with pH less than or equal to 7.00 **OR** base excess (BE) of greater than or equal to – 16. b. If pH between 7.01 – 7.15 or BE – 10 to – 15.9 and Apgar score is 5 or less at 10 minutes **OR** need for continued ventilation or resuscitation at 10 minutes. c. If there is no blood gas available then must have evidence of an acute perinatal event, i.e., placental abruption, uterine rupture, maternal trauma or cardiopulmonary arrest, late or persistent variable decelerations in an encephalopathy newborn.
4.	Signs of moderate or severe encephalopathy are defined as presence of clinical seizures **OR** 3 or more of the items in the moderate or severe categories using the modified Sarnat score.

Exclusion Criteria	
1.	Preterm infants born less than 35 weeks gestation.
2.	Neonates with mild encephalopathy on Sarnat Scoring.
3.	Neonates with a weight less than 1.8 kg.
4.	Clinically significant refractory coagulopathy despite treatment.
5.	Moribund neonates, or neonates with major congenital or genetic abnormalities, in whom no further aggressive treatment is planned.

4.0 Neurological Assessment

Standardized neurological examination must be performed by a physician or nurse practitioner skilled in neurological assessment within the first hour of life to determine the degree of encephalopathy. The gold standard in the encephalopathy assessment is the modified Sarnat Score; however, it is recommended to also perform the Thompson score as an additional tool to trend clinical evolution numerically. Of note, cerebral function monitoring using amplitude-integrated EEG (aEEG) can assist in screening infants for eligibility for therapeutic hypothermia, although this should not be used to exclude otherwise eligible neonates as per Newborn Brain Society Guidelines (9).

4.1 Modified Sarnat Score

	Normal	Mild	Moderate	Severe
Level of consciousness	☐ Alert and responsive	☐ Hyperalert, jittery, exaggerated responses	☐ Lethargic	☐ Stupor or coma
Spontaneous activity	☐ Normal	☐ Decreased ± periods of hyperactivity	☐ Decreased	☐ No activity
Posture	☐ Predominantly flexed posture	☐ Mild distal flexion	☐ Strong distal flexion or complete extension	☐ Intermittently decerebrate
Tonus	☐ Flexor tone in extremities	☐ Slightly increased peripheral tone	☐ Hypotonia or hypertonia	☐ Flaccid or rigid
Primitive reflexes **1) Suck** **2) Moro**	 ☐ Strong ☐ Strong	 ☐ Weak, poor ☐ Low threshold to elicit	 ☐ Weak or bites only ☐ Incomplete	 ☐ Absent ☐ Absent
Autonomic function **1) Pupils** **2) Heart Rate** **3) Respirations**	 ☐ Normal size, reactive ☐ Normal heart rate ☐ Normal	 ☐ Mydriasis ☐ Tachycardia (>160/min) ☐ Hyperventilation	 ☐ Miosis ☐ Bradycardia (<100/min) ☐ Periodic breathing	 ☐ Skewed/Non-reactive ☐ Variable ☐ Apnea/On ventilator

4.2 Thompson Score

Score	0	1	2	3
Tone	Normal	Hypertonic	Hypotonic	Flaccid
Level of consciousness	Normal	Hyper alert stare	Lethargic	Comatose
Seizures	None	Infrequent < 3/day	Frequent > 2/day	
Posture	Normal	Fisting, cycling	Distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent ± bites	
Respiration	Normal	Hyperventilation	Brief apnea	IPPV (apnea)
Fontanel	Normal	Full, not tense	Tense	
TOTAL SCORE				

5.0 Clinical and Neurophysiologic Monitoring during Therapeutic Hypothermia

- The modified Sarnat score and Thompson score should be administered daily and documented in the Electronic Health Record (EHR) in all newborns undergoing TH until the end of rewarming.
- Newborns receiving therapeutic hypothermia should receive aEEG monitoring during the cooling and rewarming periods.
- Continuous EEG should be considered if there is a concern for seizures or suppressed background patterns 0n aEEG (discontinuous normal voltage, burst-suppression, continuous low voltage, isoelectric trace) (10).
- Near-infrared spectroscopy (NIRS) should be connected to newborns undergoing therapeutic hypothermia to assess brain hemodynamics (11). Refer to Near-Infrared Spectrometry (NIRS) Use in the NICU.
- A medical order for specific alarm limits is to be placed for patients requiring alarm limits to be set outside the standard parameters.

5.1 Laboratory Monitoring

The following **laboratory monitoring** is recommended as a minimum and is to be ordered by the medical team. Additional laboratory tests may be ordered as needed.

Timing	Lab Testing
POCT glucose	Every 6 hours throughout the cooling process
On admission	Gas, lactate, CBC, coagulation, electrolytes, ALT, AST, urea, creatinine, ammonia, calcium, glucose
12 hours after initiation of cooling	Gas, lactate, electrolytes, C-reactive protein
24 hours after initiation of cooling	- Gas, lactate, CBC, coagulation, electrolytes, LFTs, bilirubin, urea, creatinine, ammonia, calcium, phosphate. - Ensure newborn screen (NBS) is collected.
48 hours after initiation of cooling	Electrolytes, urea and creatinine, bilirubin
72 hours after initiation of cooling	Glucose, electrolytes, bilirubin, CBC
24 hours after rewarming has been completed	Glucose, electrolytes, calcium, bilirubin

Infants Without a Clear Sentinel Event

- For infants presenting without a clear sentinel event, other causes of neonatal encephalopathy should also be considered and investigated appropriately.
- The possibility of a systemic and/or central nervous system infection should be ruled out.
- Placental pathology should be sent, and pathology results should be monitored closely.
- Neurometabolic disorders are a frequent cause of neonatal encephalopathy, so a metabolic/genetic consultation for further testing with whole exome sequencing is strongly advised in these infants in consultation with the neonatal neurology team.

6.0 Patient Considerations

- **Venous and Arterial Access**
  - Consider venous and arterial access needs for patient monitoring prior to the cooling process as difficulties in obtaining access may occur due to hypothermia-associated decreased perfusion.

- **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.

- **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 – refer to NICU Enteral Feeding and Gastroesophageal Reflux Management Guideline for 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. Refer to Subcutaneous Fat Necrosis guideline.

- **Analgesia and Sedation Management**
  - Indications for sedation include agitation or a shivering response.
  - Shivering leads to increased peripheral muscle oxygenation consumption. Neonates with excessive shivering should be considered for treatment with dexmedetomidine as per e-formulary (12) and refer to NICU Sedation Guidelines.
  - 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 greater than 10 micrograms/kg per hour (13).

- **Concurrent Use of Anti-Seizure Medications (ASM) 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.
  - Refer to the SickKids Neonatal Seizure Management Guidelines for the management of seizures and consult Neonatal Neurology service for further guidance.

- **Holding during Therapeutic Hypothermia**

- Patients MAY be eligible for holding during cooling. Refer to Infant Holding in the NICU guideline for eligibility and procedure.

- **Rewarming**
  - Rewarming should occur no faster than 0.5 degrees Celsius per hour, even if rewarming is occurring for other clinical indications such as hemodynamic instability or persistent coagulopathy. Refer to Thermal Regulating System Use in NICU for rewarming procedure.

7.0 Process for Management of HIE in NICU

1. Refer to the Hypoxic Ischemic Encephalopathy (HIE) Care Pathway.
2. Refer to Thermal Regulating System Use in the NICU (i.e., CritiCool® MINI, Blanketrol®) guideline for how to provide therapeutic hypothermia.

8.0 References

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9.0 Guideline Group and Reviewers

- The guideline was reviewed and updated December 2025.
- This guideline was critically reviewed and revised by SickKids Neonatal Neurocritical Care Team in May 2023.
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