JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Therapeutic Hypothermia for Perinatal Hypoxic Encephalopathy Clinical Pathway

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Brain temperature reduction can provide neuroprotection. Brain cooling is effective in reducing the extent of brain injury when initiated within a certain time after the hypoxic ischemic event. This results in improved neurodevelopmental outcomes in neonates who have suffered hypoxic-ischemic encephalopathy (HIE) from acute perinatal asphyxia. Brain temperature reduction can be accomplished by therapeutic hypothermia (TH) through total body cooling.

This clinical pathway was developed by a consensus group of Johns Hopkins All Children's Hospital (JHACH) physicians, advanced practice providers, nurses, and pharmacists to identify those neonates who have suffered acute perinatal asphyxia resulting in HIE, and meet the historical, biochemical, and neurologic criteria consistent with moderate to severe encephalopathy using a Modified Sarnat Score. These neonates will undergo TH by total body cooling. Before the neonate undergoes TH, they will be screened for exclusions to undergo therapy.

Background / Published Data and Levels of Evidence:

The landmark study of whole-body hypothermia showed that the primary outcome for death or moderate or severe disability occurred in 44% of the group who underwent therapeutic hypothermia, and 62% in the non-cooled group. There was no increase in major disability among survivors who have undergone TH. Cerebral palsy (CP) occurred in 19% of the therapeutic hypothermia group as compared to 30% in the non-cooled group [Shankaran 2005].

Perinatal hypoxia-ischemia is commonly used to denote neonates who experience an impairment of placental gas exchange proximate to birth. Asphyxia is a more accurate term for this event, and it is important to recognize that asphyxia and hypoxia-ischemia are not physiologically equivalent. However, the term asphyxia carries far greater medical-legal implications than hypoxia-ischemia, and unfortunately, these concerns are often inappropriate. Given that asphyxia, hypoxia-ischemia, and ischemia are often used interchangeably in the literature, it is best that discussions and charting be limited to the use of the term hypoxia-ischemia.

Neonatal encephalopathy (NE) is characterized by difficulty initiating respirations at birth and is accompanied by subnormal levels of activity, tone, reflexes, and consciousness, and possibly seizures. It is a diagnosis of near-term and term neonates and is usually not considered for preterm neonates since the neurological features of prematurity can be similar to encephalopathy. Recognition is typically at birth or shortly thereafter, although symptoms may evolve over the first few days. Encephalopathy is a non-specific response to different events, of which intrapartum hypoxia-ischemia represents one specific type. Based on population studies,

NE may be attributable in part or in total to hypoxia-ischemia in up to 30% of cases [Badawi 1998].

The challenge for “diagnosing” perinatal HIE is twofold; first, biochemical abnormalities of placental gas exchange, as evidenced by fetal acidemia, do not correlate well with clinically important problems [King 1998], and second, perinatal HIE has etiologic links to neurodevelopmental outcomes such as CP [Nelson 1989]. Thus, it is difficult to translate a simple physiological concept of hypoxia-ischemia into an easily characterized clinical diagnosis. Essential criteria have been formulated by the American College of Obstetricians and Gynecologists (ACOG) and the International Cerebral Palsy Task Force to define an acute intrapartum event that is sufficient to cause CP [Hankins 2003]. These criteria include a) fetal acidemia with a prominent metabolic component (pH < 7, base excess (BE) > -12 mmol/L), b) moderate or severe encephalopathy, c) CP of the spastic quadriplegic or dyskinetic type, and d) exclusion of other identifiable etiologies. Outcomes such as CP can only be linked to perinatal events if moderate or severe encephalopathy has occurred.

These criteria, however, are focused on establishing links between perinatal events and long-term outcomes. Previously published criteria by both ACOG and the American Academy of Pediatrics (AAP) are probably better suited for evaluation and clinical management in the immediate neonatal period. These criteria include a) profound fetal acidemia (pH < 7), b) depression at birth with an Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score of 0-3 for more than 5 minutes, c) evidence of encephalopathy, and d) multi-system organ dysfunction [Eds 2002]. These criteria provide links to outcomes accounting for the severity of the parameters. More modest alterations within these categories (e.g., umbilical artery pH of 7 – 7.1, 10-minute APGAR of 5 with consequent need for ventilation at birth) can be accompanied by organ dysfunction that may impact neonatal management. Organ dysfunction may not be apparent immediately after birth, and the diagnosis is sometimes only established 48 – 72 hours after birth, after the evolution of neurological findings and exclusion of other causes of encephalopathy. Thus, a reasonable approach to diagnosis is a stepwise sequence in which the history is suggestive of an acute peripartum event, followed by the presence of birth depression with fetal acidemia, and accompanied by organ system dysfunction noted in the first 48 hours following birth. The latter may be non-central nervous system (CNS) alone, but if encephalopathy is present, there will inevitably be other organ system dysfunctions. Finally, the exclusion of other causes of encephalopathy is essential.

Clinical Management:

Indications:
Induced hypothermia or total body cooling is to be utilized on term or near-term neonates with encephalopathy following an acute perinatal hypoxic-ischemic event. This induced hypothermia is to be initiated as soon as possible after delivery and maintained for 72 hours.

Patient population:
All term and near-term neonates (≥ 35 weeks' gestational age (GA)) will be screened for possible treatment with induced hypothermia if they are admitted to the Neonatal Intensive Care Unit (NICU) with a diagnosis of neonatal depression, acute perinatal asphyxia, or encephalopathy.

Inclusion criteria:
Neonates will be evaluated in two steps: STEP A – evaluation by clinical and biochemical criteria, followed by STEP B – neurological examination.

The presence of biochemical criteria A1, A2, or A3 AND neurological examination criteria B (EITHER B1 – seizures alone OR B2 – one or more signs in 3 of 6 categories on neurological examination consistent with encephalopathy) AND does not meet exclusion criteria, the neonate qualifies for hypothermia treatment.

If the neonate does not qualify for cooling on initial assessment (i.e., does not meet the neurologic criteria), continue hourly assessments until the neonate meets the criteria, then start TH within the 6-hour window from the time of birth.

STEP A: All neonates will be evaluated for the following:

1. History of an acute perinatal event, including placental abruption, cord prolapse, cord rupture, uterine rupture, maternal trauma (e.g., hemorrhage or cardiorespiratory arrest), severe fetal heart rate (HR) abnormality, like variable or late decelerations
2. An APGAR score < 5 at 10 minutes
3. Cord pH or first postnatal blood gas pH within 1 hour after birth, less than or equal to 7
4. Base deficit on cord gas or first postnatal blood gas within 1 hour after birth, more negative than (-)16 mEq/L
5. Continued need for ventilation initiated at birth and continued for at least 10 minutes

Table 1: Biochemical and clinical criteria

If blood gas is available	**If blood gas or one-hour postnatal blood gas is available, but pH is between 7.01 – 7.15 and base deficit is (-) 10 – 15.9**	**If cord blood gas or one-hour postnatal blood gas is NOT available**
A1 A sentinel event may not always be identifiable	A2 One of the following 2 additional criteria is needed	A3 One of the following 2 additional criteria is needed
pH ≤ 7 on cord gas or any postnatal gas WITHIN 60 MINUTES AFTER BIRTH OR base deficit ≥ 16 mEq/L on cord gas or any postnatal blood gas WITHIN 60 MINUTES AFTER BIRTH	1. Acute perinatal event* AND an APGAR score < 5 at 10 minutes OR 2. Acute perinatal event * AND assisted ventilation was initiated at birth and continued for at least 10 minutes	1. Acute perinatal event* AND an APGAR score < 5 at 10 minutes OR 2. Acute perinatal event * AND assisted ventilation was initiated at birth and continued for at least 10 minutes
NOTE: Once the neonate meets either A1, A2, or A3, proceed to the neurologic examination		

*Acute perinatal events may include late or variable decelerations, cord prolapse, cord rupture, uterine rupture, placental abruption, maternal trauma (e.g., hemorrhage or cardiorespiratory arrest)

Neurological examination:

Performance of the examination: The neurological examination should be performed by the Attending Neonatologist. In cases where the decision to use TH is unclear, either due to the findings of the examination or specific issues related to the neonate, consultations with other available Attendings should be pursued. Repeated hourly exams should be performed on neonates who do not initially meet the neurological examination criteria for moderate to severe HIE within 6 hours right after birth.

Timing of the examination: In general, there is a decreasing efficacy of neuroprotective treatments further into the therapeutic window. Initial management needs to prioritize airway stabilization, ventilator support adjustment, intravenous (IV) and/or arterial vascular access, correction of acid-base disturbances, maintenance of adequate perfusion pressure, and maintenance of normal blood glucose (BG) concentrations. Categorizing neurological findings after birth is complex, given the transitional physiology, maternal medications, evolving neurological abnormalities, and other non-CNS conditions. If examinations are performed too early after birth, more neonates may be needlessly exposed to treatment. The decision to cool a neonate based on the neurological examination is best done at least an hour after birth, especially if the neonate is showing progressive improvement within the first hour after birth. Given the uncertainty of the duration of the therapeutic window, neurological examinations and a decision to initiate cooling must be made by 6 hours after birth.

STEP B (NEUROLOGICAL EXAMINATION CRITERIA):

1. The presence of moderate/severe encephalopathy, defined as *seizures*

OR

2. The presence of one or more signs in 3 of the 6 categories below

	Moderate Encephalopathy	Severe Encephalopathy
1. Level of consciousness	Lethargy	Stupor/coma
2. Spontaneous activity	Decreased	No activity
3. Posture	Distal flexion, full extension Frog leg posture	Decerebrate
4. Tone	Hypotonia (focal or general) Hypertonia (focal or truncal)	Flaccid
5. Primitive reflexes:		
• Suck	Weak	Absent
• Moro	Incomplete	Absent
6. Autonomic system:		
• Pupils	Constricted	Skew deviation/dilated/ non-reactive to light
• HR	Bradycardia	Variable HR
• Respirations	Periodic breathing	Apnea

The presence of biochemical criteria A1, A2, or A3 AND neurological examination criteria B (EITHER B1 – seizures alone OR B2 – one or more signs in 3 of 6 categories on neurological examination consistent with encephalopathy) AND does not meet exclusion criteria, the neonate qualifies for hypothermia treatment.

Depending on the circumstances, TH may be initiated at the discretion of the Neonatologist, even if the patient has not strictly met the criteria.

Brain-specific therapies:

1. *Modest brain cooling*: The National Institute of Child Health and Human Development (NICHD) Neonatal Network randomized trial of modest hypothermia demonstrated that whole body cooling (esophageal temperature of 33.5°C) reduced the incidence of death and disability (moderate to severe in extent) in near-term and term neonates suffering from moderate or severe encephalopathy [Shankaran 2005]. The benefits of this therapy were not associated with an increase in predefined serious adverse events.
2. *Other therapies*: Currently, there is no data to justify the implementation of other potential neuroprotective therapies (e.g., high-dose barbiturates, magnesium (Mg), and allopurinol).

Neonate with mild HIE: Evidence indicates that some neonates with mild HIE experience adverse neurodevelopmental outcomes. Currently, there are no established criteria for initiating therapeutic hypothermia (TH) in neonates with mild HIE. Amplitude-integrated electroencephalography (aEEG) may be helpful, in conjunction with clinical history and biochemical data, in guiding individualized decisions regarding TH in this population.

Guidelines for monitoring a neonate with mild HIE:

If a neonate has a:

1. GA greater than or equal to 35 weeks
2. Birth weight (BW) greater than or equal to 1800 g
3. Less than or equal to 6 hours since the insult occurred

AND has biochemical evidence of a possible hypoxic-ischemic insult as evidenced by:

a. pH less than or equal to 7 with a base deficit of greater than or equal to 16 mEq/L on arterial blood gas (ABG) determination (BE more negative than -16 mmol/L)
b. pH 7.01 – 7.15, base deficit (-)10 to (-)15.9 mEq/L or no blood gas available, and acute perinatal event (e.g., cord prolapse, HR decelerations, uterine rupture), and either:
    a. APGAR less than or equal to 5 at 10 minutes or assisted ventilation at birth required for greater than or equal to 10 minutes
c. Difficult birth or resuscitation

If the neonate does not have seizures or meets 3 of the 6 neurological examination criteria for entry into TH, then the provider should consider:

1. Serial neurological examinations for the first 6 hours of life
2. Monitoring temperature closely; preventing temperatures above 37 °C
3. If the provider is concerned about possible injury, i.e., there was a sentinel event such as an abruption, the pH was less than 7 on a cord gas, the provider may consider:
    a. Liver function tests (LFTs) (abnormal with an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) above 100 units/L)
    b. Cardiac enzymes (troponin T (greater than 0.1 ng/mL) or I and CK-MB total and CK-MB (greater than 25 units/L)
    c. Lactic acid (greater than 7.5 mmol/L)
    d. Coagulation studies
    e. May consider aEEG monitoring for the first 6 hours after birth to determine the background pattern

Labs should be drawn at 1 hour of age [Shah 2004].

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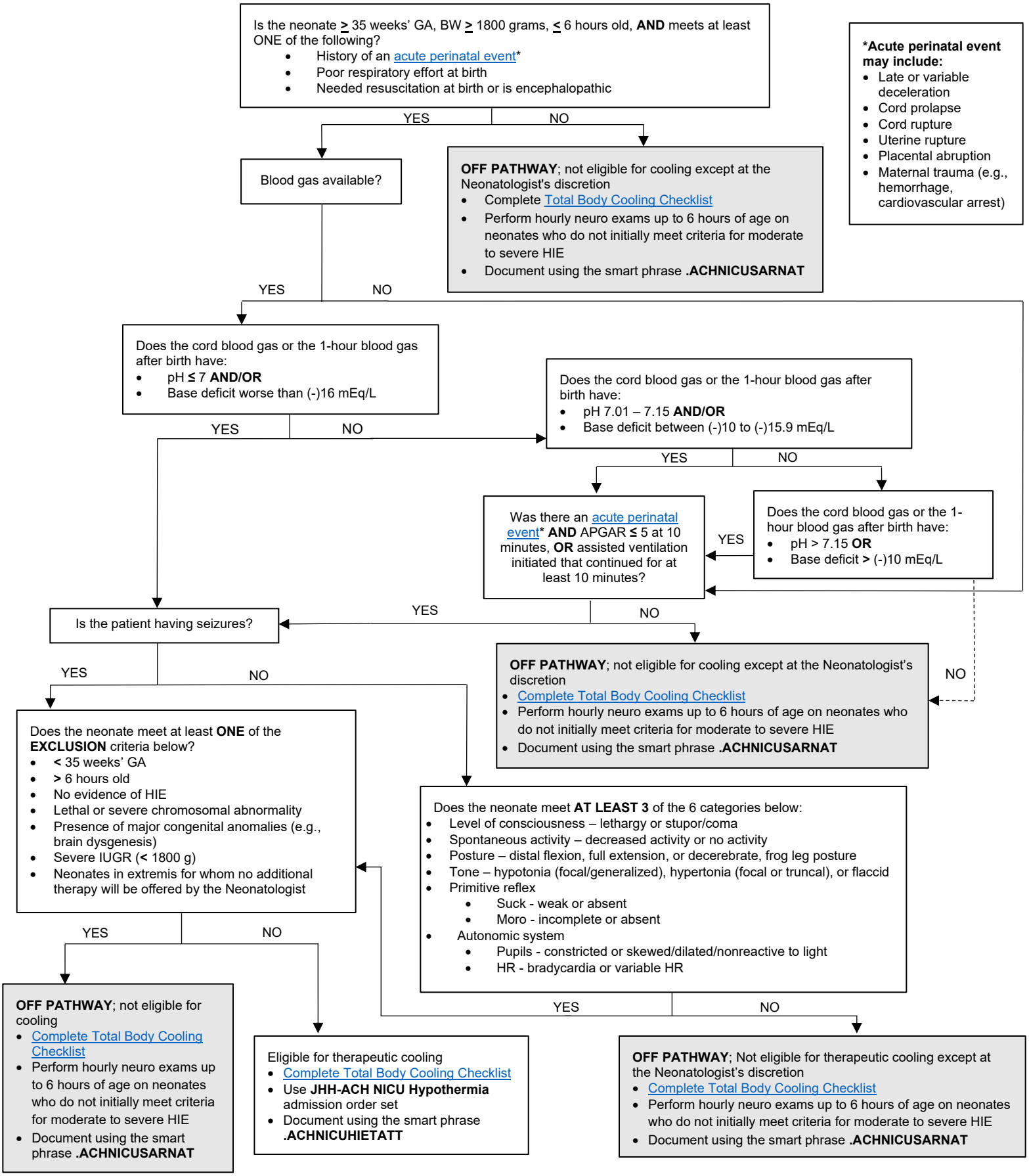

Exclusion criteria:

a. Inability to complete the neurological examination or initiate cooling by 6 hours of age
b. Presence of lethal chromosomal anomaly or major congenital anomalies (e.g., brain dysgenesis)
c. Severe intrauterine growth restriction (IUGR) (BW < 1800 g)
d. GA < 35 weeks
e. Significant intracranial hemorrhage (ICH) with a large ICH (Grade III or intraparenchymal echodensity (Grade IV))
    a. Note, may start hypothermia without obtaining a head ultrasound (HUS) if not immediately available, but should be obtained as soon as possible after the start of hypothermia
f. Without evidence of HIE
g. Neonates in extremis for whom no additional therapy will be offered

Overview of management:

- *Vital signs (VS)*:
    - VS, including esophageal probe and skin temperatures, should begin upon initiation of therapy and every 15 minutes times 4 occurrences, then hourly for the next 68 hours with continuous pulse oximetry monitoring
    - During rewarming, VS are collected every 1 hour or with every temperature change (every 30 minutes) on the machine
    - The external length of internal temperature probes is measured every 6 hours with hands-on care

- *Fluids and nutrition*:
    - Record strict ins and outs (I&O): In general, fluids should be administered judiciously for neonates with hypoxia-ischemia once perfusion and blood pressure (BP) are stabilized
        - This approach is based on the associated renal and CNS morbidities that may be exacerbated with excess free water administration
        - Consideration can be given to the placement of an umbilical venous catheter (UVC) to facilitate fluid restriction
            - This will also allow the simultaneous provision of high glucose concentrations to meet glucose requirements with restricted fluids
    - Consider placing a Foley catheter if urine output (UOP) is low; may remove if UOP is deemed adequate
    - Nothing by mouth (NPO) or consider low volume feeds (trophic) depending on the clinical condition of the neonate; may consider oral care with maternal colostrum
        - *Fluids*: An initial fluid intake of 60 – 70 mL/kg/day as appropriate for neonates on the first day of life (DOL) may be considered, but fluid management should be individualized to the patient's needs

- *Feeds**:
  - After the 1st 24 hours of TH, if there is no cardiovascular instability or need for pressors, minimal enteral nutrition may be provided at up to 20 mL/kg/day of mother's milk or donor milk with no advance until fully rewarmed
  - Feedings may be increased to 40 mL/kg/day after being fully rewarmed, on DOL 4
  - Further advances on DOL 5 onwards may be made at 30 – 40 mL/kg/day

*****Recent studies suggest that enteral feeding is safe [Kunar 2023]. Feeding during TH was also associated with higher survival to discharge. Neonates in the enteral feeding group achieved full enteral feeding earlier, had higher breastfeeding rates at discharge, received parenteral nutrition (PN) for a shorter duration, and had shorter hospital stays than the control group. Enteral feeding during TH is safe and does not increase the risk of necrotizing enterocolitis (NEC), hypoglycemia, or feed intolerance. It may reduce the incidence of sepsis and all-cause mortality until discharge.

- *Cardiovascular*:
  - Set lower HR limit at 70 beats per minute (bpm)
    - Neonates receiving therapeutic hypothermia at temperatures of 33 – 34°C have mild bradycardia of around 100 bpm. An HR consistently above 110 bpm in cooled neonates with temperatures of 33 – 34°C suggests that the neonate may be distressed or have volume loss. The provider may consider increasing sedation if appropriate. If sedation is increased and the HR continues to remain elevated, it is recommended to evaluate potential sources of bleeding, such as intracranial or intra-abdominal. Conversely, an HR below 70 bpm may lead to decreased cardiac output. Consider decreasing sedation or increasing the temperature set point by 0.2 – 0.3°C increments to a maximum of 35°C.
    - An echocardiogram (ECHO) may be considered for neonates with HIE due to the increased risk of cardiac dysfunction requiring pressor support and the association between HIE and pulmonary hypertension. Adverse myocardial effects are uncommon but may include tricuspid insufficiency or global ischemia. Suspicion for myocardial dysfunction may present as an inability to maintain perfusion pressure or as a more subtle difficulty in resolving metabolic acidemia.
  - *Correct hypotension/hypoperfusion*: Usual management guidelines of volume expansion followed by pressor support should be used judiciously in these patients, and only when assessments support hypoperfusion. There is one small, randomized trial comparing low-dose dopamine (2.5 mcg/kg/minute) to placebo in neonates with suspected hypoxia-ischemia [DiSessa 1981]. There was no difference in mortality or outcome, but the numbers were small. Consideration can be given to obtaining an ECHO to assess myocardial function and fluid status.

- *Medications used to treat systemic hypotension include*:
    - Although dopamine is commonly used, it is predominantly a vasopressor and, in neonatal animal studies, has been shown to increase pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR), which has the potential to increase afterload, decrease left-to-right shunting, and compromise systemic oxygen delivery
    - Epinephrine may be an appropriate inotrope due to its action on α1, α2, β1, and β2 receptors and its favorable impact on PVR/SVR ratio
    - The action of dobutamine via α and β receptors, decreasing SVR, may have advantages as an inotrope in the context of persistent pulmonary hypertension of the newborn (PPHN) and myocardial dysfunction

- *Neurological*: Consult Pediatric Neurology and obtain an electroencephalography (EEG)
    1. *Physiological monitoring*:
        a. Placement of near-infrared spectroscopy (NIRS) for cerebral oximetry to monitor cerebral perfusion and aid in optimization of BP. Apply to the abdominal area to help assess the adequacy of splanchnic perfusions and oxygenation [Toet 2006, Chock 2009].
        b. Place a cerebral function monitor (aEEG) on the patient and obtain continuous video EEG monitoring. Monitor for 72 hours and during rewarming. The aEEG and EEG background activity may provide helpful prognostic information.
    2. *Neuroimaging*:
        a. Cranial Ultrasound (US): Obtain a cerebral US with Doppler flow to evaluate for alternative causes of encephalopathy and to assess the severity of hypoxic-ischemic injury. If a Grade I–II intraventricular hemorrhage (IVH) is identified, repeat imaging may be performed at the discretion of the neonatologist if there are concerns for hemorrhage progression.
        b. Magnetic resonance imaging (MRI): should be carried out, if possible, on DOL 4 – 5. Follow-up MRI on DOL 10 – 21 or before discharge if earlier. Images should be obtained in the transverse plane with T1-weighted spin echo, T2-weighted spin echo, age-related inversion recovery sequences, and spectroscopy.
    3. *Sedation*:
        a. The management of sedation in the term neonate with NE undergoing TH is an important element of optimal neonatal neurocritical care. Preventing stress can be seen as a component to limit further injury in a vulnerable brain.
        b. Intermittent dosing for sedation should be tried first; if adequate sedation cannot be achieved, then a low-dose infusion should be started, and efforts to wean regularly.

c. Morphine represents the current standard of care with a history of utilization and extensive pharmacokinetic data to guide safe and effective dosing.
    i. Dose:
        1. Intermittent IV dosing:
            a. 0.03 mg/kg/dose IV every 3 – 4 hours as needed (PRN) if patient is breathing spontaneously
            b. 0.03 to 0.05 mg/kg/dose IV every 3 – 4 hours PRN for intubated patients
        2. Continuous IV infusion:
            a. Loading dose (LD): 0.03 – 0.05 mg/kg/dose IV (repeat PRN times 1 dose for shivering, severe irritability, tachycardia with HR > 120 bpm)
            b. Start continuous IV infusion: 0.01 mg/kg/hour
                i. DO NOT INCREASE THE INFUSION RATE
                ii. Reduce the rate to 0.005 mg/kg/hour after 12 hours
d. Dexmedetomidine: In clinical studies to date, dexmedetomidine has been found to lower the shivering threshold. Dexmedetomidine has been evaluated retrospectively in term neonates with NE receiving TH. Dexmedetomidine eliminated the need for open-label boluses of opioids for pain/agitation perceived by the provider, shivering, or tachycardia. It also facilitates weaning off opioids. Dexmedetomidine may act as a neuroprotective agent based on preclinical data, which is in direct contrast to opioids and benzodiazepines
    i. Low-dose dexmedetomidine infusion: 0.2 – 0.5 mcg/kg/hour
    ii. Dexmedetomidine may be weaned during rewarming by 0.1 mcg/kg/hour every 6 hours to a minimum dose of 0.2 mcg/kg/hour before discontinuation
    iii. Obtain appropriate monitoring for bradycardia and hypotension
e. Benzodiazepines should be avoided for sedation, due to a high risk for hemodynamic adverse effects and the potential to augment aberrant neuronal and synaptic development in the setting of hypoxic injury.

4. *Seizure control*:
    a. About half of neonates treated with TH for NE have EEG-confirmed seizures. The potential of seizures exacerbating brain injury remains a concern. This concern drives the practice of treating clinically detectable seizures. Studies show that aggressive treatment of seizures decreases neurologic sequelae. Phenobarbital and fosphenytoin are the most used antiepileptics in neonates and have been evaluated more than other agents for effectiveness [Painter 1999]. Recent studies have demonstrated levetiracetam as safe and effective with potential for neuroprotection [Abend 2011; Khan 2011; Ramantani 2011].

b. Medications:
    i. Phenobarbital:
        1. Loading dose (LD): 20 mg/kg/dose IV (max dose: 40 mg/kg/dose)
        2. Maintenance: 3 – 5 mg/kg/DAY divided every 12 hours, starting 12 hours after the LD
        3. Target serum level: 25 – 40 mcg/mL
    ii. Fosphenytoin:
        1. LD: 20 mg/kg/dose IV (max dose: 30 mg/kg/dose)
        2. Maintenance: 8 – 10 mg/kg/DAY divided every 8 hours, starting 8 hours after the LD
        3. Target serum level: 15 – 25 mcg/mL
    iii. Levetiracetam:
        1. LD: 40 mg/kg/dose IV (max dose: 60 mg/kg/dose)
        2. Maintenance: 40 – 60 mg/kg/DAY divided every 8 hours, starting 8 hours after the LD
        3. Target serum level: 12 – 46 mcg/mL
    iv. Lorazepam or midazolam:
        1. Indication: Refractory seizure, status epilepticus

- *Infectious disease*:
    - Evaluate for sepsis – Obtain complete blood count (CBC), blood culture
    - Start antimicrobials – ampicillin 100 mg/kg/dose every 8 hours and gentamicin 4 mg/kg/dose every 36 hours
        - Gentamicin metabolism and clearance are affected in neonates with HIE undergoing TH
        - If continuing gentamicin beyond 48 hours, obtain gentamicin trough before administering 2nd dose
            - Do not give gentamicin until the level is < 1 mcg/mL
    - Discontinue antimicrobials after 48 hours if there is no evidence of sepsis

- *Skin*:
    - Reposition the neonate every 30 minutes to prevent pressure injury
    - Monitor for fat necrosis

- *Laboratory*:
    - Labs: CBC with differential, comprehensive metabolic panel (CMP), Mg, phosphorus (Phos), prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), and fibrinogen will be monitored at the beginning of cooling, and at 24, 48, and 72 hours
    - Follow BG closely with minimum glucose > 47 mg/dL (target 60 - 150 mg/dL)
    - Blood gases: ABG with ionized calcium (iCa+) and lactate every 6 hours
        - Temperature correct blood gases while neonates are undergoing whole body cooling
        - During hypothermia, consider continuous CO_2 monitoring
            - Results of ABGs can be used to calibrate CO_2 monitors

- Hepatic dysfunction: Biochemical abnormalities supportive of hepatic injury can occur in response to hypoxia-ischemia, but clinical manifestations are rare

- Gastrointestinal dysfunction: Evidence of bowel hypoxia-ischemia is difficult to assess due to the absence of easily monitored laboratory parameters

- Metabolic abnormalities:
    - Changes in glucose concentrations are most common immediately after birth
    - Hypoglycemia and hyperglycemia in neonates with NE are associated with worse neurodevelopmental outcomes
        - Minimum glucose > 47 mg/dL

- Electrolyte disturbances:
    - Sodium (Na+):
        - Hyponatremia can occur and may reflect excess free water administration or syndrome of inappropriate anti-diuretic hormone (SIADH)
        - Hypernatremia secondary to diabetes insipidus (DI) is rare
        - Neonates with NE are at risk for hyponatremia
            - In most neonates with NE, hyponatremia results from free water excess, and not sodium depletion, and thus requires restriction of free water administration, often to estimated insensible water loss plus UOP
    - Potassium (K+):
        - 42% of neonates with NE experience hypokalemia
            - Judicious K+ replacement is recommended, maintaining serum K+ greater than 3.5 mEq/L
        - However, during the rewarming phase, as K+ shifts to the extracellular space, it places the neonate at risk for hyperkalemia
    - Calcium (Ca+) and Mg:
        - Changes in Ca+ and Mg are more characteristically found between 12 – 24 hours after birth
        - Hypocalcemia and hypomagnesemia are commonly seen in neonates with NE
        - Monitor levels closely
    - Acidosis: Avoid base replacement therapy if circulation is reestablished and the patient can correct over time

- Treat hypovolemia with volume administration as needed
    - Normal saline (NS) – 10 mL/kg/dose IV
    - Packed red blood cells (pRBC) (+/- plasma) – if blood loss is the etiology

Documentation:

1. *aEEG*:
    a. Complete report on admission, daily during cooling, and 24 hours after rewarming
    b. Use the smart phrase .ACHNICUAEEG, to document the aEEG result

2. *Statement of eligibility*:
    a. Use the smart phrase .ACHNICUHIETATT – "The infant has hypoxic ischemic encephalopathy. The infant has met the historical, biochemical, and neurological criteria for initiating therapeutic hypothermia."

3. *Neurological examination*:
    a. Use the smart phrase .ACHNICUSARNAT for the neurological examination on admission and hourly for the next 6 hours after birth if the neonate does not initially qualify on admission

Expectations during body cooling:

- Decreased HR
    - Cooled neonates at temperatures of 33 – 34°C have mild bradycardia of around 100 bpm and a mean BP greater than 40 mmHg
    - A HR consistently above 110 bpm in cooled neonates with temperatures of 33 – 34°C suggests that the neonate is distressed
        - Consider sedation or increase sedation if appropriate
    - The metabolic rate is reduced during hypothermia, and this results in bradycardia and prolonged PR and QT intervals
        - Watch closely for arrhythmia
            - If these are suspected or develop, obtain an electrocardiogram (EKG)
            - Slowly rewarm the neonate following the rewarming protocol (see below)
    - If the HR is < 70 bpm, increase the target temperature by 0.3°C increments to a maximum of 35°C
        - If the HR continues to fall despite this, consider starting low-dose dobutamine 3 – 5 mcg/kg/minute
            - If there is still no improvement, then start rewarming the patient following the rewarming protocol (see below)
- Increased BP initially due to increases in peripheral vasoconstriction
- Increase in UOP initially due to shunting of blood to the internal organs, cold, and diuresis
- Decrease in Ca+, Mg, Phos, and K+
- Labile glucose due to relative insulin resistance and decreased metabolic rate
- Stress may have adverse effects in asphyxiated neonates and may influence the therapeutic effect of hypothermia

- In addition, NICU procedures may cause considerable stress to neonates, and cooling may also be associated with stress
- Signs of distress include tachycardia, facial grimacing, and irritability
    - An HR consistently above 110 bpm in cooled neonates suggests that the neonate is distressed

Potential adverse events risk:

1. BP changes, either hypotension or hypertension
2. Cardiac arrhythmias
3. Abnormal clot formation – major vessel thrombosis
4. Bleeding
5. Skin breakdown
6. Persistent metabolic acidosis

Discontinuing cooling treatment: (cooling may be discontinued if the following occur)

1. Caregiver's request that cooling be stopped before 72 hours
2. Attending stops cooling; reasons for early discontinuation of cooling might include clinical, EEG, and imaging evidence of severe, irreversible brain injury, or inability to maintain esophageal/rectal temperature in the desired range
3. Uncontrollable adverse effects of cooling
4. If the caregivers or the Attending elect to discontinue cooling, then rewarming will commence
    1. The steps in the "Rewarming guidelines" section below will be followed, with the exception that the neonate would not have completed the full 72 hours of cooling

Rewarming guidelines: (after 72 hours of induced TH)

- *Check electrolyte panel with iCa+, Mg, and Phos before rewarming, and do not rewarm until electrolyte abnormalities are resolved*
- Rewarm the neonate by gradually increasing the core body temperature (at the rate of 0.5°C per hour for 6 hours) to increase the neonate's temperature from 33.5 to 36.5°C
- Check VS making sure HR < 120 bpm and BP mean $\geq$ 40 mmHg
    - Expect an increase in HR, a decrease in BP (due to a decrease in PVR and vasodilation)
- Potential decrease in UOP due to increases in third spacing and shunting of blood to the periphery
- May have electrolyte shifts as renal and liver clearance rates change
- After rewarming is completed, manage the radiant warmer per unit protocols
- Diffusion weighted MRI with spectroscopy at DOL 4 – 5 and again at DOL 10 – 21
    - If only one MRI can be obtained, it should occur during DOL 4 – 5
    - These recommendations may need to be adjusted in critically ill neonates who will be compromised in obtaining the MRI (consider at DOL 7 – 14)
    - Diffusion weighted MRI (performed with all studies) and spectroscopy (needs to be ordered separately) are adjuncts in determining prognosis

Follow-up of neonates with perinatal hypoxia-ischemia:

Given the potential link between perinatal hypoxia-ischemia and early childhood adverse neurodevelopmental outcomes, it is recommended that all neonates with a moderate or severe encephalopathy of any duration should be followed up in the NICU Follow-up Clinic in addition to routine pediatric health maintenance. This recommendation applies regardless of imaging findings, the absence of seizures, or a normal evaluation at the time of discharge. Neonates with no CNS involvement or encephalopathy limited to stage I Sarnat (mild encephalopathy) do not require follow-up in the NICU Follow-up Clinic unless unusual findings are noted (e.g., abnormalities on MRI imaging). Recommend referral to the Early Steps Program.

Summary:

Acute perinatal asphyxia can cause HIE, resulting in death or disability. TH reduces the risk of death or disability in neonates with moderate or severe HIE. It is essential to identify neonates with moderate or severe HIE and meet the criteria for cooling early, as there is a short window of opportunity for cooling to be initiated for it to be effective

Outcome Measures:

1. Neurologic outcomes:
    a. Measure: Percentage of cooled neonates who survive to discharge with normal or mildly abnormal neuroimaging findings (MRI)
    b. Rationale: MRI at DOL 5 – 10 is a validated surrogate for long-term neurologic outcome
        i. This measure reflects both the timeliness and effectiveness of TH
    c. Target: ≥ 80% of cooled neonates have normal or only mild MRI abnormalities

2. Timeliness of initiation:
    a. Measure: Percentage of eligible neonates who have TH initiated within 6 hours of birth
    b. Rationale: Early initiation is crucial for neuroprotection
        i. This process evaluates pathway adherence and team coordination between delivery, transport, and NICU teams
    c. Target: ≥ 90% of eligible neonates cooled within 6 hours

3. Adherence and complication rate:
    a. Measure: Rate of adverse events (e.g., overcooling < 32 °C, coagulopathy requiring transfusion, arrhythmia, electrolyte derangements) during cooling
    b. Rationale: Ensures patient safety and pathway compliance
        i. Balanced measures to monitor potential harm while achieving therapeutic targets
    c. Target: ≤ 10% of cooled neonates experience significant cooling-related complications

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Therapeutic Hypothermia for Perinatal Hypoxic Encephalopathy

Clinical Pathway

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Disclaimer:

Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners, and other healthcare providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The ultimate judgment regarding care of a particular patient must be made by the physician considering the individual circumstances presented by the patient.

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Appendix A: Total Body Cooling Checklist

Patient label:

Date/Time: _____

Gestational Age: _____ (must be ≥ 35 weeks)

Hours of Life: _____

Diagnosis: _____

Eligibility Criteria for Therapeutic Hypothermia
The neonate is ≥ 35 weeks GA, less than 6 hours old, and had poor respiratory effort at birth, requiring resuscitation, or is encephalopathic.

Biochemical and clinical criteria

If blood gas is available	**If blood gas or one-hour postnatal blood gas is available, but pH is between 7.01 – 7.15 and base deficit is (-) 10 – 15.9**	**If cord blood gas or one-hour postnatal blood gas is NOT available**
A1 A sentinel event may not always be identifiable	A2 One of the following 2 additional criteria is needed	A3 One of the following 2 additional criteria is needed
pH ≤ 7 on cord gas or any postnatal gas WITHIN 60 MINUTES AFTER BIRTH OR base deficit ≥ 16 mEq/L on cord gas or any postnatal blood gas WITHIN 60 MINUTES AFTER BIRTH	1. Acute perinatal event* AND an APGAR score < 5 at 10 minutes OR 2. Acute perinatal event * AND assisted ventilation was initiated at birth and continued for at least 10 minutes	1. Acute perinatal event* AND an APGAR score < 5 at 10 minutes OR 2. Acute perinatal event * AND assisted ventilation was initiated at birth and continued for at least 10 minutes
NOTE: Once the neonate meets either A1, A2, or A3, proceed to the neurologic examination		

*Acute perinatal events may include late or variable decelerations, cord prolapse, cord rupture, uterine rupture, placental abruption, maternal trauma (e.g., hemorrhage or cardiorespiratory arrest)

The presence of biochemical criteria A1, A2, or A3 AND neurological examination criteria B (EITHER B1 – seizures alone OR B2 – one or more signs in 3 of 6 categories on neurological examination consistent with encephalopathy) AND does not meet exclusion criteria, the neonate qualifies for hypothermia treatment.

STEP B (NEUROLOGICAL EXAMINATION CRITERIA):

1. The presence of moderate/severe encephalopathy, defined as ***seizures***

OR

2. The presence of one or more signs in 3 of the 6 categories below

	Moderate Encephalopathy	**Severe Encephalopathy**
1. Level of consciousness	Lethargy	Stupor/coma
2. Spontaneous activity	Decreased	No activity
3. Posture	Distal flexion, full extension Frog leg posture	Decerebrate
4. Tone	Hypotonia (focal or general) Hypertonia (focal or truncal)	Flaccid
5. Primitive reflexes: • Suck • Moro	 Weak Incomplete	 Absent Absent
6. Autonomic system: • Pupils • HR • Respirations	 Constricted Bradycardia Periodic breathing	 Skew deviation/dilated/ non-reactive to light Variable HR Apnea

The presence of biochemical criteria A1, A2, or A3 AND neurological examination criteria B (EITHER B1 – seizures alone OR B2 – one or more signs in 3 of 6 categories on neurological examination consistent with encephalopathy) AND does not meet exclusion criteria, the neonate qualifies for hypothermia treatment.

Depending on the circumstances, TH may be initiated at the discretion of the Neonatologist, even if the patient has not strictly met the criteria.

Exclusion criteria: Circle any of the below if applicable
Any one of the following criteria makes the neonate ineligible for total body cooling.

1. Inability to complete the neurological examination or initiate cooling by 6 hours of age
2. Presence of lethal chromosomal anomaly or major congenital anomalies (e.g., brain dysgenesis)
3. Severe IUGR (BW < 1,800 g)
4. GA < 35 weeks
5. Significant ICH with a large ICH (Grade III or intraparenchymal echodensity (Grade IV))
    a. Note, may start hypothermia without obtaining a HUS if not immediately available, but should be obtained as soon as possible after the start of hypothermia
6. Without evidence of HIE
7. Neonates in extremis for whom no additional therapy will be offered

FINAL REVIEW OF CRITERIA FOR TOTAL BODY COOLING*

1. ____YES ____NO Met criteria for total body cooling above
2. ____YES ____NO Met exclusion criteria above (TAKES PRECEDENCE OVER ELIGIBILITY CRITERIA)

*If an neonate meets criteria A1, A2, or A3 and criteria B and does not meet exclusion criteria, the neonate is eligible for whole-body cooling

3. ____YES ____NO Neonate did not meet strict criteria, but the Neonatologist determines the neonate will benefit from therapeutic hypothermia. Obtain a second opinion from another Neonatologist.

Reason for initiating therapeutic hypothermia:

_____

FINAL DECISION FOR TOTAL BODY COOLING

____ YES Proceed with total body cooling

____ NO Do not proceed with total body cooling:
_____The neonate met exclusion criteria that take precedence over total body cooling eligibility criteria
_____The neonate did not meet cooling criteria