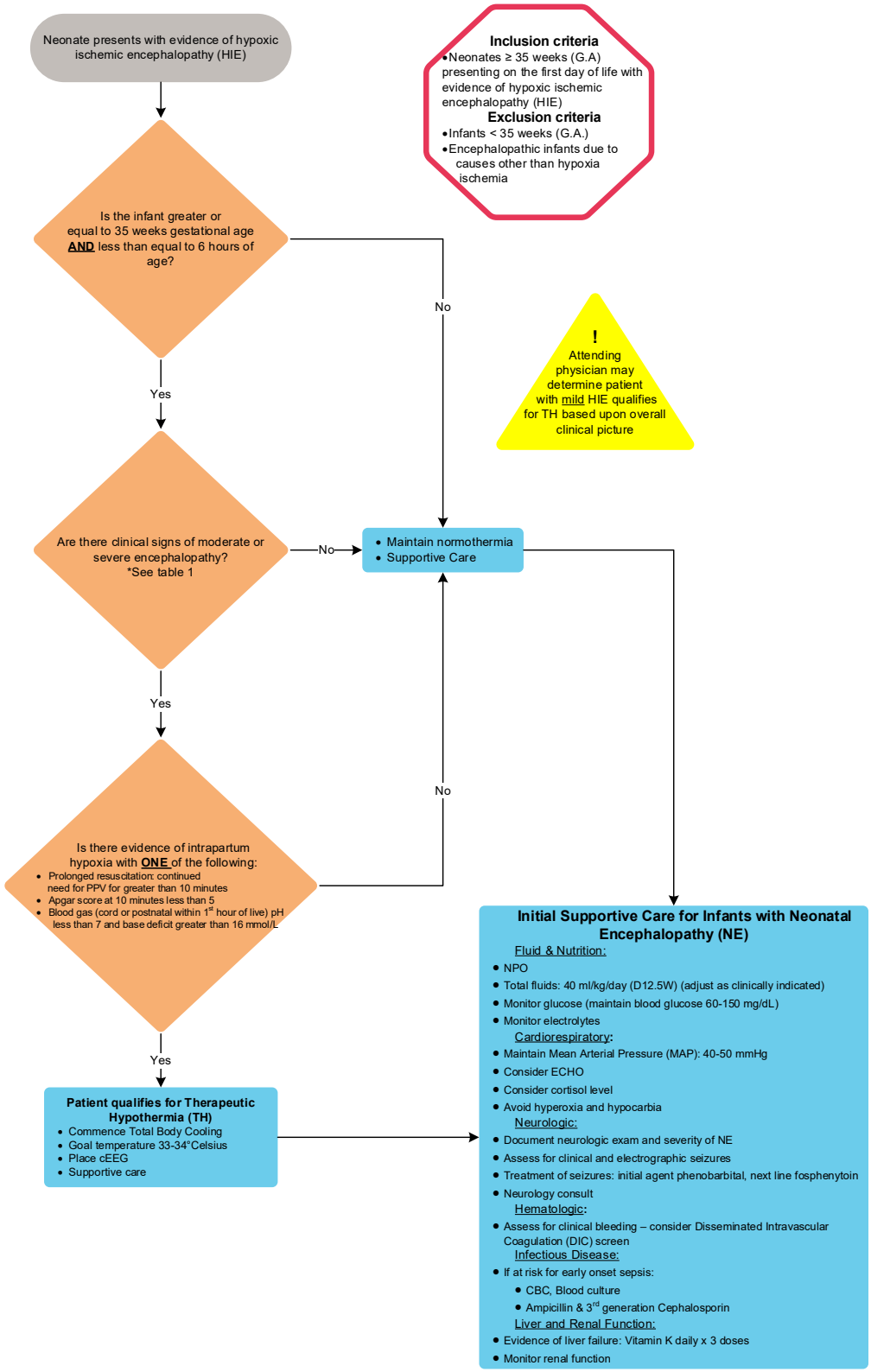
HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE)

ALGORITHM



Therapeutic Hypothermia Policy

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TARGET POPULATION

Inclusion Criteria:

- Intended for neonates ≥ 35 weeks (G.A) presenting on the first day of life with evidence of hypoxic ischemic encephalopathy (HIE)

Exclusion Criteria:

- Infants < 35 weeks (G.A.)
- Encephalopathic infants due to causes other than hypoxia ischemia

BACKGROUND | DEFINITIONS

Hypoxic-ischemic encephalopathy (HIE) is a clinically defined syndrome of disturbed neurologic function in the first day of life in an infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, sub normal level of consciousness and often seizures.

This condition occurs in 1-2/1000 newborns and is a significant cause of neonatal mortality and morbidity. The risk of death or severe disability in survivors of moderate-severe HIE is 60%.

Induced moderate therapeutic hypothermia (33-34 °C) has been shown to be safe and decrease the incidence of death and disability with HIE.[1, 2, 3]

INITIAL EVALUATION

Eligibility Criteria for Therapeutic Hypothermia[1, 2, 3]

1. Gestational Age **≥ 35 weeks** **AND**
2. Infant **less than 6 hours** of age (The decision to start hypothermia after 6 hours will be at the discretion of the neonatology attending) **AND**
3. Clinical signs consistent with **encephalopathy** (moderate, severe *– Table 1) **AND**
4. Evidence of intrapartum hypoxia including **one of the following**:

- Prolonged resuscitation: continued need for positive pressure ventilation; required at birth and continued for greater than or equal to 10 minutes.
- Apgar score at 10 minutes ≤ to 5.
- *Blood gas [arterial cord gas, venous cord gas, or postnatal (within 60 min) arterial blood gas pH ≤ 7 and base deficit ≥ 16 mmol/L].

* **Note:** aEEG may be additional tool to determine degree of encephalopathy.

* Attending physician may decide to initiate therapeutic hypothermia for infants with mild HIE based upon complete clinical picture.[4]

Sarnat Staging of Encephalopathy

Moderate/Severe Encephalopathy will be defined as **either clinical seizures or the presence of 3 of 6 categories from moderate or severe column in Table 1 below**.

Table 1. Stages of Encephalopathy

	Stage 1/Mild	Stage 2/Moderate	Stage 3/Severe
Level of Consciousness *	Normal	Lethargic/Obtunded (Reduced response to stimulation)	Stuper or coma (Absent response to stimulation)
Spontaneous Activity *	Normal	Decreased Activity	No Activity
Muscle Tone *	Hypertonia	Hypotonia (focal or general)	Flaccid
Posture *	Normal	Distal flexion, or complete extension or frog-legged	Decerebrate
Reflexes **Moro** **Suck**	Exaggerated moro	Weak/incomplete Weak	Absent Absent
Autonomic system * **Pupils** **Respirations** **Heart Rate**		Constricted Periodic Breathing Bradycardia	Deviated, dilated, NR Apnea Variable
Seizures	Absent	May be present	May be present

* May be affected by hypothermia, narcotics, and/or sedatives.

CLINICAL MANAGEMENT

Management at Birth Hospital and During Transport

1. Start Passive Cooling Immediately
   - Advise referring provider to turn off exogenous heat source (turn off radiant warmer, with close monitoring of temperature).[5]
   - Earlier cooling is associated with better outcomes.[6]
   - We **do not** recommend that **active** cooling commence before the arrival of the transport team.
2. Continuous Temperature Monitoring

- Continuous temperature monitoring (rectal probe) is preferred. Intermittent axillary temperatures are acceptable if skills and/or equipment are not available for continuous rectal temperature.
- Target core body temperature of 33.5° C (range 33-34° C) (Usually achieved by turning off exogenous heat source).

3. Assess severity of HIE (prior to sedatives/narcotics; see Table 1)
4. Obtain a blood gas and glucose
   - Avoid Hypoglycemia: Glucose target: 50-150 mg/dL[7]
   - Avoid hyperoxemia[8, 9] and hypocarbia[10, 11]
5. NPO, start IVF with D10W at 60ml/kg/day, adjust as clinically indicated
6. Maintain adequate circulating volume and blood pressure (MAP target 40-50mmHg)
7. Consider CBC, LFTs and DIC panel if bleeding present
   - Elevated AST/ALT shortly after birth may reflect insult hours before birth
8. Seizure Management – phenobarbital 20mg/kg x 1 for clinical seizures, repeat 10mg/kg up to 2 times if still seizing
9. On transport:
   - Cooling: Children'sOne Flight Team has protocol for active and passive cooling[12]
     - Use of Servo-controlled cooling blanket during transport is recommended
   - Ventilation: Avoid hyperoxemia[8, 9] and hypocarbia[10, 11]
   - Ionotropic support as indicated
10. Request for referring provider to send placenta to pathology for review if available the referring institution

Initial NICU Management

- Cardiorespiratory stabilization:
  - Alterations in heart rate and blood pressure are common during cooling – hypothermia decreases cardiac output and HR
  - Usual heart rate with core temperature 33-34° C, can be as low as 70-80 bpm
  - Attempt to maintain MAP between 40-50mmHg
    a. Loss of cerebral autoregulation makes hypertension and hypotension hazardous
  - Treatment with volume replacement and/or inotropes should be considered if MAP < 40 mmHg
  - With persistent shock, consider adrenal insufficiency and obtain cortisol level: if low (< 10-15 mmol/L), treat with hydrocortisone 2mg/kg q 8 IV.
  - Consider echocardiogram which may identify poor cardiac contractility or under perfusion for etiology of refractory shock.
  - Avoid hyperoxemia[8, 9] and hypocarbia[10, 11]
- Commence Total Body Cooling: Target core temperature 33-34° C
- Assess neurologic status:
  - Determine Sarnat score – Document in H&P (neurological exam to include features listed in Table 1).
  - Place on continuous EEG (cEEG) with aEEG capabilities: Assess and Document aEEG findings.
  - Continue cEEG with aEEG recording during treatment and through rewarming*: assess occurrence of seizures and monitor severity of encephalopathy (Refer to bedside card for basics of aEEG).

    - * Consider discontinuing conventional EEG (cEEG) in patients with mild HIE with normal tracing and no evidence of seizures after 24 hours
  - IV antiepileptic drugs (AEDs) (phenobarbital) may cause transient suppression of EEG activity. Ideally aEEG should be performed before administering AEDs.
  - Neurology consult
- Laboratory tests to consider:
  - CBC if bleeding or concern for sepsis
  - CMP to assess renal function, evidence of transaminitis and electrolytes
  - ABG to assess for adequate ventilation and presence of acidosis
  - Lactate: consider for refractory metabolic acidosis
  - Blood culture if concern for sepsis, if not yet obtained
- Sepsis management:
  - Antibiotics are not indicated in all cases of HIE. For those with concern for infection in addition to HIE, evaluation and treatment of infection per standard of care is warranted, with the following considerations:
    - Avoidance of aminoglycoside is suggested due to increased risk of ototoxicity and potential for nephrotoxicity. Gentamicin can be substituted with ceftazidime.
    - Discontinuation of antibiotics at 36 hours if culture negative should be considered to avoid untoward effects of antibiotics.
    - Refer to LexiComp for antibiotic dosing information.
- Fluid & acid/base management:
  - NPO; IVF: D12.5W at 40ml/kg/day.
  - Frequent monitoring of urine output and serum sodium trends and adjust fluids as clinically indicated.
  - If urine output < 1ml/kg/hour obtain electrolytes q4- 6 hours and consider decreasing IVF to <40ml/kg/day while maintaining sufficient glucose infusion rate (GIR).
  - Consider diuretics to facilitate adequate urine output if volume overload is contributing to organ dysfunction.
  - Consider sodium bicarbonate for refractory acidosis in adequately ventilating infant with shock and/or coagulopathy. No evidence to support long term benefit of sodium bicarbonate in this population.
- Electrolyte management:
  - Risk of hyponatremia: decreased urine output due to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) and acute tubular necrosis (ATN)
  - Frequent glucose monitoring (risk of hypo or hyperglycemia).
  - Magnesium-should be maintained within normal range (1.7-2.2 mg/dL).[14]
- Seizure management:
    - Refer to Neonatal Seizures after Acquired Brain Injury clinical pathway
- Pain/sedation management:
  - Pain/stress may have adverse effects in infants with HIE.
  - Initial Fentanyl drip at 0.5-1mcg/kg/hour in ventilated infants; 0.5mcg/kg/hour in non-ventilated infants. Titrate to effect.
  - "Normal" heart rate may reflect stress or hypovolemia.

Subsequent ICU Management

Cardio-Respiratory Management:

- Per ICU [at risk for primary pulmonary hypertension (PPHN), and or hypoxic respiratory failure]
- Consider echocardiogram
- See above section on cardiorespiratory management

Renal:

- Acute tubular necrosis and or SIADH may affect urine output. Close monitoring of urine output is essential to avoid fluid overload and cerebral edema.

Fluid/Nutrition:

- Dextrose to keep blood glucose within normal range
- Total fluids to maintain adequate circulating volume, glucose and sodium
- Hypoxia ischemia may impair gut function and increase risk for necrotizing enterocolitis, cautious advancement in feedings recommended
- NPO except rare instances in non-ventilated, alert, infant who is able to PO feed limited volumes

Neurology:

- Continued Seizure Management: prompt treatment of seizures is indicated
- The clinical features of HIE evolves over days, perform daily neurologic exam and document changes in neurologic exam
- Neurology consult

Hematology:

- Risk for disseminated intravascular coagulation (DIC), if bleeding or petechiae present, measure platelets, hematocrit and bleeding times

Liver failure:

- Risk for liver failure
- Consider repeat dose of Vitamin K on DOL 2 & 3
- Check transaminases 12-24 hours after birth, if abnormal consider repeating in 12 to 24 hours
- Access: Consider arterial and venous access as clinically indicated

Rewarming:

- Commences at 72 hours
- Warm 0.5° C every hour to goal of 36.5° C
- Peripheral vasodilation during this time may drop CO and BP
- Continue aEEG or cEEG during rewarming phase

Occupational and Physical Therapy:

- Consult once appropriate

Monitoring and Assessment of aEEG:

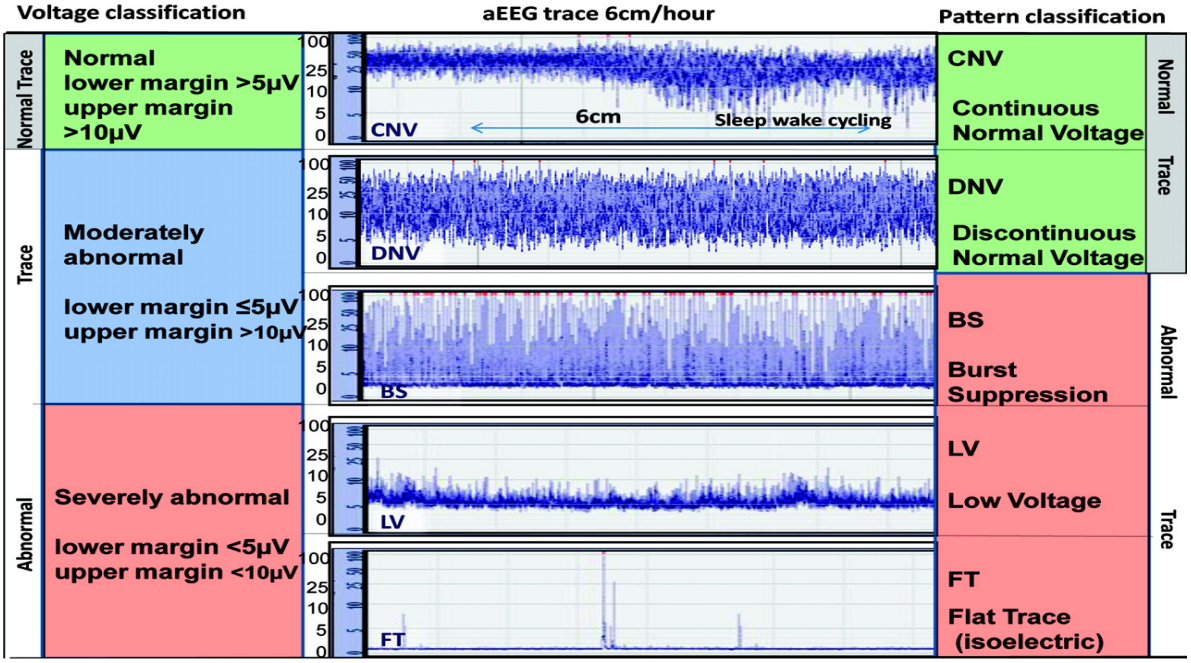
1. Monitor general neurologic status: background pattern
2. Monitor for seizures

3. Background at 48 hours correlates with long term neurologic outcome[15, 16]
4. Can be performed simultaneously with cEEG
5. Document at admission and daily

Basics of reading aEEG[17]:

1. **Background Pattern**: Describes the dominant type of electrical activity in the aEEG trace.
    - Continuous: Lower (minimum) amplitude around 7 to 10 mcV and maximum amplitude of 10 to 25 (to 50) mcV.
    - Discontinuous: Background minimum amplitude variable, but below 5 mcV, and maximum amplitude above 10 mcV.
    - Burst-suppression: Discontinuous background with minimum amplitude without variability at 0 to 1 (2) mcV and bursts with amplitude >25 mcV.
2. **Seizures:** Epileptic seizure activity in the aEEG usually is seen as an abrupt rise in the minimum amplitude and a simultaneous rise in the maximum amplitude, often followed by a short period of decreased amplitude.
    - Single seizure: A solitary seizure.
    - Repetitive seizures: Single seizures appearing more frequently than at 30 minute intervals.
    - Status epilepticus: Continuously ongoing seizure activity for >30 minutes.

Figure 1. Amplitude Integrated EEG Tracings[18]



LABORATORY STUDIES | IMAGING

Radiographic and Electrographic Evaluation:

1. Neuro Imaging: MRI
    - Day 4-5 depending upon clinical stability
    - Earlier MRI may be considered to make decisions about withdraw of intensive care
    - Use of total body cooling will improve feasibility of earlier imaging if indicated

2. EEG: continuous 1-3 hour
    - Ideally should be performed 24 hours after cooling is terminated to determine background activity for prognostication.

FOLLOW UP

- Neurology/Neonatal Brain Injury Clinic (located in the Hemophilia & Thrombosis Center).
    - Brain injury clinic coordinator will track the patient for discharge and arrange follow-up (no need to alert anyone).
- First follow-up with Neurology at 4-6 weeks after discharge.

RELATED DOCUMENTS

Therapeutic Hypothermia: Body Cooling for the Neonate

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Antimicrobial Stewardship – March 17, 2021
Pharmacy & Therapeutics Committee – February 4, 2021
Clinical Pathways and Measures Review Committee – January 19, 2021

MANUAL/DEPARTMENT	Clinical Pathways/Quality
ORIGINATION DATE	November 29, 2016
LAST DATE OF REVIEW OR REVISION	March 17, 2021
COLORADO SPRINGS REVIEW BY	 Michael DiStefano, MD Chief Medical Officer, Colorado Springs
APPROVED BY	 Lalit Bajaj, MD, MPH Medical Director, Clinical Effectiveness

REVIEW | REVISION SCHEDULE

Scheduled for full review on March 17, 2025

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