Hypoxic Ischemic Encephalopathy (HIE)-Neonatal - Inpatient Consensus Care Guideline

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Introduction

Hypoxic-ischemic encephalopathy (HIE) occurs in 1-3 per 1000 term births and accounts for 22% of neonatal deaths worldwide.[1-3] Infants with HIE suffer a high rate of morbidity and mortality. Therapeutic hypothermia is a neuroprotective strategy which has become a standard of care for neonatal HIE and can improve outcomes in death and disability. Given the timing constraints needed to initiate therapeutic hypothermia, it is important that clinicians be aware of recommended protocols and practices. This guideline serves as a compendium on the medical management and care of infants with hypoxic-ischemic encephalopathy.

Scope

Intended User(s): Physicians, Advanced Practice Providers, Registered Nurses, Pharmacists

Objective(s): To provide guidance on the medical management of neonates with suspected hypoxic ischemic encephalopathy

Target Population: Neonatal infants with suspected or confirmed diagnosis of HIE in the inpatient setting/Neonatal Intensive Care Unit (NICU)

Clinical Questions Considered:

- Which infants (i.e., inclusion criteria) should undergo therapeutic hypothermia?
- When should amplitude electroencephalography (aEEG) be initiated?
- What labs should be obtained to monitor neonates with HIE?
- What imaging studies should be obtained upon admission and subsequently to assess neurologic injury?
- What supportive care measures are recommended for infants with HIE?

Recommendations:

Therapeutic hypothermia

Since 2005, therapeutic hypothermia has become a standard neuroprotective strategy used in the management of infants with hypoxic ischemic encephalopathy as a result of the improved clinical outcomes demonstrated in randomized controlled trials.[4,5]

Inclusion and Exclusion criteria

Infants with HIE must meet all of the following 3 criteria within 6 hrs of life to be considered for therapeutic hypothermia: [5-12] *(UW Health Moderate quality evidence, strong recommendation)*

1. Gestational age ≥ 36 and 0/7 weeks

2. One of the following clinical scenarios:
    a) pH ≤ 7.0 or base deficit ≥16 (cord gas* or baby gas within 1hr of life)
    b) If blood gas not available <u>or</u> pH is 7.01-7.15 <u>or</u> base deficit is 10-15.9, then patient must have:
        i. Acute perinatal event (i.e., uterine rupture, placental abruption, umbilical cord prolapse/avulsion, or severe fetal heart rate abnormality)
        <u>AND</u>
        ii. Either Apgar ≤ 5 at 10 min <u>or</u> need for prolonged resuscitation (CPR, CPAP, PPV) for ≥ 10 min

3. Evidence of moderate or severe encephalopathy on clinical exam <u>or</u> seizures HealthLink dotphrases (e.g. .HIE or .HIEexam) are available to be used in clinical documentation.

    <u>*Cord Gas (Only applies to Meriter)</u>
    - All cord gases will be run by RT in the NICU
    - RT to report the following blood gas to neonatology provider:
        - pH ≤ 7.15 and/or base deficit of ≥10
    - Neonatology provider follow-up:
        - If patient in NICU, determine cooling eligibility
        - If patient in Newborn Nursery
            - Daytime: NICU to notify/voicera Newborn Nursery Provider
            - Evening: NICU to determine cooling eligibility

Therapeutic hypothermia for neonatal HIE is NOT recommended for patients who meet the following **exclusion criteria:**

- Presence of major congenital anomalies
- Infants for whom no additional intensive therapy will be offered, as determined by attending neonatologist

The following are considered **relative contraindications**, in which case the potential risks and benefits will be evaluated by the neonatologist to determine eligibility:[6-10] *(UW Health Moderate quality evidence, conditional recommendation)*

- Infant > 6 hours of life at time of initial referral/evaluation[4,13]
- Birth weight < 1800 grams
- Severe hemodynamic compromise

  - Consult the pediatric intensivist when considering therapeutic hypothermia for an infant with critical congenital heart disease
- Severe coagulopathy with active bleeding
- Confirmed venous sinus thrombosis

Serial Exams

If cooling criteria are not met on the initial exam (at 30-60 min of life), a second exam should be performed at 4–5 hours of life (or sooner), with at least one exam performed by or directly supervised by newborn/neonatology attending.

Outside referral for therapeutic hypothermia

Eligibility for therapeutic hypothermia for patients born outside of the UW Health system will be determined in conjunction with the referring provider and admitting neonatologist.

Therapeutic strategy

It is recommended that therapeutic hypothermia (i.e., active or passive cooling) be initiated within 6 hours of life with a targeted esophageal temperature of 33.5-34.5°C and once targeted temperature is reached it should be maintained for 72 hours.[5-10] *(UW Health Moderate quality evidence, strong recommendation)*

For further information on conducting cooling on transport, passive cooling and cooling in the Neonatal Intensive Care Unit, refer to UW Health Neonatal Whole Body Cooling Procedure.

Re-warming strategy

It is recommended to begin re-warming 72 hours after the first esophageal temperature between 33.5-34.5°C was reached.[6-9] *(UW Health Moderate quality evidence, strong recommendation)*

Slow rewarming of the patient is preferred and is recommended at the rate of 0.5°C per hour to a core body temperature of 36.5°C (approximately 6 hours).[6,8,9,14,15] *(UW Health Moderate quality evidence, strong recommendation)*

For additional information on how to re-warm patients, refer to UW Health Neonatal Whole Body Cooling Procedure

Management of HIE

Monitoring

Imaging studies

A babygram is recommended upon admission. *(UW Health Good Practice Statement)* It is also important to confirm esophageal probe placement.

HIE patients should also have a cranial ultrasound with Doppler conducted upon admission.[16,17] *(UW Health Low quality of evidence, strong recommendation)*

In infants undergoing therapeutic hypothermia, a non-sedated (feed & swaddle) brain MRI and MRS is recommended on Day of Life 4-5.[10,17-21] *(UW Health Moderate quality of evidence, strong recommendation).*

Remarks:

- If the patient is unable to undergo brain MRI within the recommended time frame, postponing the brain MRI until Day of Life 10 – 14 should be considered. While a non-sedated brain MRI/MRS may be performed at any other timepoint as clinically indicated, imaging between Day of Life 7 – 10 may have a greater risk of a failing to show brain injury (false negative scan).

Consider obtaining a follow-up MRI and MRS in patient on Day of Life 10-14, particularly in those cases with discrepant clinical-imaging findings or those infants with an earlier abnormal MRI/MRS examination.[18-21] *(UW Health Low quality of evidence, conditional recommendation)*

Note: When ordering cranial ultrasound or brain MRI it is important to note "HIE Protocol" in the comment section of order to ensure the appropriate imaging study is performed.

If the patient appears severely encephalopathic and the family is considering withdrawing support, consider obtaining brain MRI at 24-28 hours of life (or when clinically appropriate).[17] *(UW Health Very low quality of evidence, conditional recommendation)*

Near-infrared spectroscopy (NIRS)

Cerebral and renal NIRS monitoring is recommended for all HIE patients.[15,22] *(UW Health Low quality of evidence, strong recommendation)*

Labs

Table 1 outlines suggested labs to obtain when monitoring HIE infants during therapeutic hypothermia.[15,18,23] *(UW Health Low quality evidence, strong recommendation)*

Table 1. Therapeutic Hypothermia- Labs for monitoring

Lab (Normal Range)	Suggested frequency
Temperature corrected blood[13] gas, lactate, ionized calcium (iCa) (4.5-5.3 mg/dL which equals: 1.12-1.32 mmol/L; 2.25-2.65 mEq/L)	Every 6-12 hours (based on infant acuity) for first 24 hours then every 12-24 hours **Note:** Temperature corrected blood gases are available on the NICU ABL 90 and the main lab. To get temperature corrected readings, do the following: • On workstation order, clearly write patient's temperature at time of draw • If processed in the NICU, notify respiratory therapy of the patient's current temperature and desire for temperature corrected blood gases The temperature corrected values that will appear in Health Link include: • PH, TEMP CORRECTED • PCO2, TEMP CORRECTED • PO2, TEMP CORRECTED
Glucose[24]	Every hour during initiation of cooling until temp 33.5-34.5°C is reached; thereafter, check every 6 hours during cooling. During rewarming, check glucose at the start of rewarming, every 2 hours x 2, then PRN and with lab draws
Chemistries (Ca 8.7-10.1 mg/dL) (Mg 1.8-2.3 mg/dL) (K 4.0-6.0 mEq/L)	Check Electrolytes, Ca, Mg, Phos every 12-24 hours during cooling Consider monitoring during rewarming
CBC	Check every 12-24 hours
Cultures	Obtain blood culture; consider sputum and cerebral spinal fluid culture
PT/PTT/INR	Check every 24 hours initially; reduce frequency when stable
BUN/CR	Check every 12-24 hours
AST/ALT	Check every 24 hours

Neurologic

Analgesia and Sedation
It is important that infants undergoing therapeutic hypothermia receive adequate analgesia and sedation to avoid cold stress and because lack of analgesia/sedation may adversely impact the neuroprotective effect.[25-27] Sedation level should target a Neonatal Pain, Agitation and Sedation Scale (NPASS) score of -2 to +3 and shivering should be avoided.[28]

Choice of agent
Dexmedetomidine is the preferred initial agent unless any exclusion criteria are present.[25-27,29-35] (*UW Health Low quality of evidence, Conditional recommendation*)
Remarks:

- Dexmedetomidine, an alpha-2 agonist has analgesic, sedative and anti-shivering properties and has recently been studied in multiple retrospective cohort studies of this population, generally demonstrating effectiveness comparable to IV opioids (e.g., morphine or fentanyl).[25-27,29-35]
- Dexmedetomidine **exclusion criteria**:
  - Persistent bradycardia with HR ≤60, especially if associated with:
    - Poor perfusion
    - Hypotension unresponsive to support
    - Prolonged capillary refill or decreased urine output
  - Uncontrolled or refractory seizures despite management with antiseizure medications and pediatric neurology consultation
- Common adverse effects include bradycardia and hypotension, so continuous monitoring of HR and BP is important

Dexmedetomidine initial dosing and dose adjustments
Initial dose: 0.3 mcg/kg/hr IV (no loading dose)

Adjustments to achieve goal N-PASS of -2 to +3

- If N-PASS >3 or Shivering: May increase by 0.1 mcg/kg/hr every 30-60 min (Max dose 1.3 mcg/kg/hr)
  - If agitation persists despite max dose, add PRN morphine 0.05 mg/kg IV Q3hr
- If N-PASS <-2: Decrease by 0.1 mcg/kg/hr every 30-60 min

Adjustments for bradycardia

- If HR 60-69 bpm for >30 min, decrease by 0.1 mcg/kg/hr and continue to monitor
- If HR <60 bpm
  - Hold dexmedetomidine for 30-60 min and re-evaluate
  - Use PRN morphine 0.05 mg/kg IV Q3hr to manage pain, agitation while holding
  - IF HR stabilizes, consider re-starting dexmedetomidine at lower rate with use of PRN morphine

Pediatric Neurology consultation
It is recommended to obtain a Pediatric Neurology consultation for any HIE patient and that the complete neurology exam and neonatal encephalopathy exam be documented (using .HIEEXAM SmartPhrase). *(UW Health Good Practice Statement)*

Electroencephalography (EEG)
Amplitude-integrated EEG/continuous EEG monitoring is recommended upon admission to the NICU, through the re-warming process and for 6 hours of normothermia, or until patient has been seizure free for 24-48 hours (per Pediatric Neurology recommendation.)[36-38] *(UW Health Low quality of evidence, strong recommendation)*

Seizure management
Hypoxic-ischemic cerebral injury is the most common cause of early-onset neonatal seizures however there is not consensus regarding seizure prophylaxis or what is the best medication to treat seizures in these patients.[4,18,39,40] If patient demonstrates clinical or electrographic seizures, consider load with one time dose of IV levetiracetam 60 mg/kg or IV phenobarbital 20 mg/kg and refer to Neonatal Seizures – Neonatal –Emergency Department/Inpatient Consensus Care Guideline for ongoing seizure management.[41] *(UW Health Low quality of evidence, conditional recommendation)* [18,41]

Fluids, Electrolytes and Nutrition

Central access should be established early on (e.g., UAC and double lumen UVC.) *(UW Health Good Practice Statement)*

The recommended initial total fluid goal (TFG) is 50-60 mL/kg/day using D10W.[9,18,42] *(UW Health Low quality evidence, strong recommendation)*
Remarks:
- To avoid fluid overload and prevent cerebral edema, it is important to carefully manage fluid therapy.

Consider initiating minimal trophic feeds (up to 20ml/kg/day) after 24hrs in infants undergoing therapeutic hypothermia if they are hemodynamically stable and do not show signs of feeding intolerance.[43,44] *(UW Health Low quality of evidence, Conditional recommendation)*

Cardiovascular

It is recommended to continuously monitor blood pressure with an arterial line and cardiac activity via 3-lead electrocardiograph (EKG).[45] *(UW Health Low quality evidence, strong recommendation)*

An echocardiogram is recommended if the patient is hemodynamically unstable or if there is concern for pulmonary hypertension. *(UW Health Good Practice Statement)*

If there is evidence of poor end organ perfusion and/or hypotension, treatment considerations include the following[18,46,47] (*UW Health Very Low quality evidence, Conditional recommendation*):

a. For hypovolemia, use isotonic crystalloids judiciously (10-20 mL/kg).
b. For hypotension, consider use of the following medications based on an assessment of the infant's hemodynamics:
    - Dopamine may worsen pulmonary hypertension due to pulmonary vasoconstrictive effects and should be considered with caution in this context (suggested dosing range 5-25 mcg/kg/min).
    - Epinephrine (suggested dosing range 0.01-0.1 mcg/kg/min)
    - Norepinephrine (suggested dosing range 0.05-1.0 mcg/kg/min)
    - Vasopressin (suggested starting dose 0.17-10 milliUnits/kg/min)
c. For ventricular dysfunction, dobutamine (suggested dosing range 2-20 mcg/kg/min) is an additional therapeutic option.

For cooled infants, bradycardia is to be expected (heart rate 80-100 bpm)[28,48] If blood pressure is stable, deep bradycardia (heart rate < 80 bpm) may be tolerated. If not tolerated, raising core temperature to 34°C may be sufficient. *(UW Health Low quality evidence, conditional recommendation)* If symptomatic bradycardia exists, consider administering dopamine. *(UW Health Very low-quality evidence, conditional recommendation)*

Respiratory

It is recommended that hyperoxia be avoided in HIE patients and the goal PaO_2 is 80-100 mmHg with SpO_2 94-98%. *(UW Health Low quality evidence, strong recommendation)*
Remarks:

- Hyperoxia increases oxidative stress and free radical production, leading to detrimental effects on patients. It has also been associated with death and poor long-term outcomes in HIE patients.[18,49]

Infectious Disease

It is recommended that sepsis be ruled out in all patients with HIE.[50] *(UW Health Good Practice Statement)* A lumbar puncture may also be considered to rule out meningitis infection.[51] (*UW Health Low quality of evidence, conditional recommendation)*

During sepsis workup, empiric treatment with ampicillin and gentamicin is recommended for all infants being treated with therapeutic hypothermia, with the following dosing[52,53]: *(UW Health Low quality evidence, conditional recommendation)*

- Ampicillin 50 mg/kg/dose intravenously every 8 hours
    - If concern for meningitis, increase dose to ampicillin 100 mg/kg IV Q8 hours
- Gentamicin 4 mg/kg/dose every 24 hours, with each dose administered intravenously over 30 minutes.
- In the event of acute kidney injury, ceftazidime at 50mg/kg/dose intravenously every 12 hours is recommended in lieu of gentamicin.[54] *(UW Health Low quality evidence, conditional recommendation)*

Skin

To prevent pressure ulcers, it is recommended to maintain pressure relieving device in HIE patients and to reposition every 2 hours.[55-57] *(UW Health Moderate quality evidence, strong recommendation)*

Patients should also be monitored and assessed for development of pressures ulcers and fat necrosis.[55-58] *(UW Health Moderate quality evidence, strong recommendation)*

Development

All patients will have a physical therapy, occupational therapy and speech consults ordered on admission to the NICU. Evaluation with the Prechtl General Movement Assessment (GMA) and Test of Infant Motor Performance (TIMP) is strongly recommended prior to discharge.[59-61]

Neurodevelopmental Outpatient Follow-up

Moderate to Severe HIE

All infants with moderate to severe HIE (confirmed with imaging) should be followed up at 3 months of age after discharge from the hospital at the Waisman Center Newborn Follow-Up Clinic or an equivalent neurodevelopment clinic accessible to patient. (*UW Health Good Practice Statement*)

Remarks:

- The Waisman Newborn Follow-Up Clinic offers follow-up by a multidisciplinary team, including a developmental pediatrician and pediatric neurologist
- Consultation with Waisman clinic may occur prior to discharge to assist with transition of care.

For infants with moderate to severe HIE that require antiseizure medication management following discharge, additional follow-up within 4-8 weeks with Pediatric Neurology is recommended. (*UW Health Good Practice Statement*)

Mild HIE

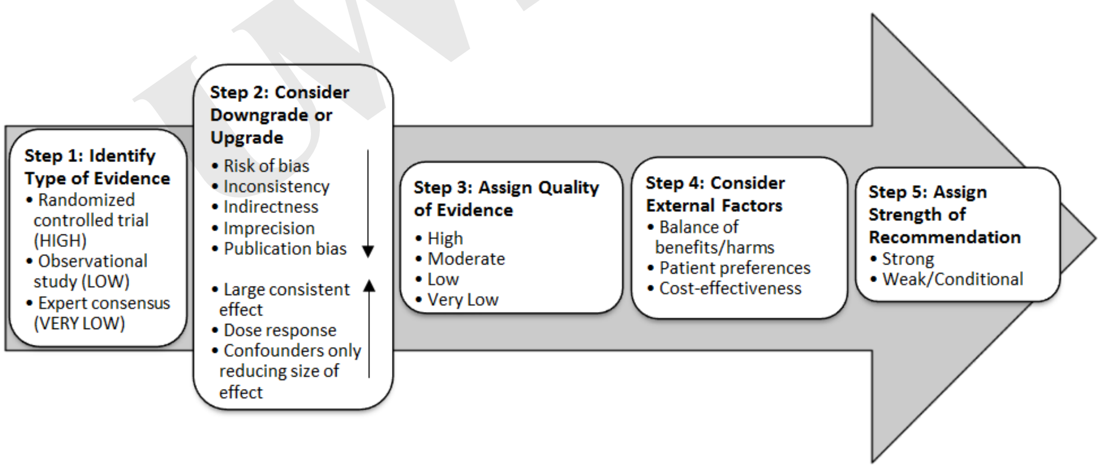
For NICU patients with mild HIE, consider follow-up at Meriter high-risk follow-up clinic (*UW Health Good Practice Statement*).

Disclaimer
Consensus care guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Conflicts of Interest
All guideline workgroup members are expected to follow institutional policies and procedures around conflicts of interest. Actions in which a guideline member discloses a conflict of interest relevant to the guideline topic may include, but is not limited to, abstaining from voting, dismissal during comment and voting period, or recusal from requesting and/or participation in the decision-making process.

Methodology
Development Process
Each guideline is reviewed and updated approximately every 3-5 years, but will vary in consideration of the primary literature and relevant practice changes. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

Table 1. GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.
Very Low - Internal Expert Opinion	The true effect is likely to be substantially different from the estimated effect. This category of recommendation for or against a specific intervention is derived strictly from the expert opinions of UW Health healthcare professionals with experience in the relevant specialty(ies). This is used in the absence of published evidence or external opinion addressing the specific intervention.

Table 2. GRADE Ratings for Recommendations for or Against Practice

Strong (S)	Generally, should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)
Conditional (C)	May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)
Good Practice Statement	Generally, should be performed (i.e., the expected benefit of the treatment is substantial, expected costs or risk are minimal, and patient values and circumstances are unlikely to affect the decision.) This classification is used for recommendations that guideline members feel are important and for which there is uniform support, but for which evidence directly assessing the specific intervention (or practice) is not available and is highly unlikely to ever be studied (because it may not be warranted or feasible). Such recommendations may have strong indirect evidence of support

Collateral Tools & Resources

The following collateral tools and resources support staff execution and performance of the evidence-based model recommendations in everyday clinical practice.

Metrics

- Number of infants who received therapeutic hypothermia within first 6 hours of life
- Number of HIE suspected infants who received therapeutic hypothermia that were NOT cooled for 72 hours
- Number of infants < 36 weeks with suspected HIE who received therapeutic hypothermia

Guidelines

Neonatal Seizures – Neonatal –Emergency Department/Inpatient Consensus Care Guideline

Order Sets & Smart Sets

IP - Hypoxic-Ischemic Encephalopathy (HIE) - Neonatal - Admission [4746]
IP – aEEG/CEEC/Video EEG – Neonatal – Supplemental [5305]
IP – Seizure – Neonatal – Supplemental (5057]

Patient Resources

HFFY #7650 - Hypothermia Treatment (Whole Body Cooling) for Hypoxic Ischemic Encephalopathy

Procedures

UW Health Neonatal Whole Body Cooling Procedure

Appendix A. Neonatal Encephalopathy Exam* (.HIEEXAM)[40,62-64]

	Level of Encephalopathy			
	Normal/None	**Mild**	**Moderate**	**Severe**
1. Level of Consciousness	0 – Normal/Alert	1 – Hyperalert or irritable (responsive to minimal stimuli)	2 – Lethargic	3 – Stupor or coma
2. Spontaneous Activity	0 – Normal	-----	2 – Decreased activity	3 – No activity
3. Posture	0 – Predominantly flexed	1 – Mild flexion of distal joints (fingers, wrist)	2 – Flexion of distal joints or complete extension	3 – Decerebrate
4. Tone	0 – Strong flexor tone in all extremities	1 – Slightly increased tone in extremities	2a – Hypotonia (focal or general) 2b – Hypertonia (focal or general)	3a – Flaccid 3b – Rigid
5. Primitive Reflexes┼:				
Suck	0 – Strong, coordinated, easy to elicit	1 – Weak, coordinated	2 – Weak and uncoordinated, and/or bite	3 – Absent
Moro	0 – Complete	1 – Exaggerated	2 – Incomplete	3 – Absent
6. Autonomic System┼:				
Pupils	0 – Normal	1 – Mydriasis (dilated), reactive	2 – Myosis (constricted), reactive	3 – Deviated/unequal, dilated, or fixed/ nonreactive to light
Heart Rate	0 – Normal: 100 – 160 bpm	1 – Tachycardia: >160 bpm	2 – Bradycardia: <100 bpm	3 – Variable
Respiration	0 – Normal: regular respirations	1 – Tachypnea, Hyperventilation	2 – Periodic breathing	3a – Apnea, requires on-going PPV or intubation, and has spontaneous breaths 3b – Apnea, requires on-going PPV or intubation, and does not have spontaneous breaths

*This encephalopathy exam is based primarily on the version found in Chalak et al.[63]. Slight modifications have been made based on consideration of numerous published variations of encephalopathy exam scoring systems[64].
┼For Primitive Reflexes (Suck, Moro) and Autonomic System (Pupils, Heart Rate, Respirations), the item with the highest score determines the level of encephalopathy.

- **No encephalopathy**: score of 0 in all six categories.
- **Mild encephalopathy**: < three categories with a score of 2 or 3, but has a score of 1, 2, or 3 in at least one category.
- **Moderate encephalopathy**: score of 2 in three or more categories.
- **Severe encephalopathy:** score of 3 in three or more categories.

Neonatal Encephalopathy Exam Definitions[65]

1. Level of Consciousness

Hyperalert - Full wakefulness with eyes open/staring but decreased frequency of blinking/tracking. Spontaneous motor activity normal or decreased with lowered threshold to all stimulus types.

Irritability - Lowered threshold with excessive response to all stimulus types. Can be seen with varied states including hyperalert, lethargy, and obtundation.

Lethargy - Slightly delayed but complete response to stimuli with slightly increased threshold for eliciting responses and decreased spontaneous movement

Obtundation - Delayed and incomplete responses with markedly increased threshold to all sensory stimuli and little or no motor activity

Stupor - No spontaneous eye opening and tactile stimulation elicits poorly sustained eye opening. Responds only to strong, noxious stimuli. Absent gag, corneal reflex.

Coma - No eye opening with vigorous tactile stimulation.

2. Spontaneous Activity

Decreased spontaneous activity - Decreased frequency or amplitude of spontaneous facial and extremity movements.

Absent spontaneous activity - Movements absent.

3. Tone

Hypotonia - Focal or generalized decreased resistance to passive movement. Associated with greater extension of the extremities than normal. *Must remove positioning barriers for accurate tone examination.

Hypertonia - Focal or generalized increased resistance to passive movement. Associated with greater flexion of the extremities than normal. *Must remove positioning barriers for accurate tone examination.

Flaccid - "Flat on the mat" appearance. May be associated with frog-leg posturing with arms and hips/legs lying in abduction. *Must remove positioning barriers for accurate tone examination.

Rigidity - "Lead pipe" feel of extremities, severe hypertonia with extreme resistance to passive movement. Does not depend on imposed speed or threshold of movement. Unilateral contraction of antagonist or agonist muscle groups can occur with rigidity, but the limb does not tend to return to a fixed posture or extreme joint angle. May be associated with exaggerated deep tendon and tactile reflexes.

4. Posture

Distal flexion - Fingers, toes in strong flexion; incomplete extension of fingers when stroked on dorsal surfaces. Thumbs flexed, adducted, opposed across palms (i.e. "cortical thumbs").

Decerebrate posturing - Head, neck, and back are arched in extension (opisthotonos), elbows are extended, wrists are pronated, and hips are adducted.

5. Primitive Reflexes: Suck

Weak suck - Some sucking noted, but it is not as vigorous or sustained as it should be. A pacifier or gloved finger can be easily pulled from the mouth.

Absent suck - No sucking or root reflex elicited.

Bite - Insertion of pacifier or gloved finger into mouth elicits neonate to "clamp down" or bite object. No sucking motion elicited.

5. Primitive Reflexes: Moro

Incomplete Moro – The Moro reflex is elicited by holding the baby's head and shoulders off the mat with arms held in flexion on chest. While supporting the head and neck, the examiner suddenly lets the head and shoulder drop while releasing the arms. The arms should fully abduct and extend, then return towards midline with the hand open and the thumb and index finger forming a "C" shape. An incomplete Moro is marked by absence of any component or any asymmetry in movements. Incomplete Moro reflex often extends irregularly but typically does not return to midline.

Absent Moro – Absence of any reflexive activity (see above for method of eliciting Moro reflex).

6. Autonomic System: Pupils

Dilated pupils (mydriasis) - Normal pupil size for term newborns is 3.9 mm +/- 0.8 mm. Dilated pupils are larger than this even in bright light.

Constricted pupils (miosis) - Normal pupil size for term newborns is 3.9 mm +/- 0.8 mm. Constricted or pinpoint pupils are smaller than this even in dim light.

Unequal; Fixed; Dilated; Poor light reflex pupils - Pupils that are not normally symmetrically aligned or symmetrically dilated, are fixed in position, or that do not accommodate (constrict) in the presence of light.

6. Autonomic System: Heart Rate

Tachycardia – Resting heart rate > 160 beats per minute, typically 170-190 beats per minute.

Bradycardia - Resting heart rate of < 100 beats per minute, typically 80-90 beats per minute. Only occasional increases to 120+ beats per minute are noted.

Variable heart rate - Resting heart rate varies considerably without a consistent baseline.

6. Autonomic System: Respiration

Periodic breathing - Three or more respiratory pauses of three seconds or longer separated by normal breathing for less than 20 seconds. Often associated with shallow breathing pattern.

Apnea - Absence of airflow and respiratory effort lasting 20 seconds or longer. Apnea may also be present if a respiratory pause is shorter than 20 seconds but is associated with heart rate change or oxygen desaturation.

References

1. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic-ischaemic encephalopathy. *Early Hum Dev*. Jun 2010;86(6):329-38. doi:10.1016/j.earlhumdev.2010.05.010
2. Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE. A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. *Am J Obstet Gynecol*. Dec 2008;199(6):587-95. doi:10.1016/j.ajog.2008.06.094
3. Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet*. Jun 5 2010;375(9730):1969-87. doi:10.1016/s0140-6736(10)60549-1
4. Jeffrey P. *Neurology : neonatology questions and controversies*. Second edition Amsterdam : Elsevier/Saunders, c2012.; 2012.
5. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev*. Jan 31 2013;(1):Cd003311. doi:10.1002/14651858.CD003311.pub3
6. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med*. Oct 13 2005;353(15):1574-84. doi:10.1056/NEJMcps050929
7. Simbruner G, Mittal RA, Rohlmann F, Muche R. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. *Pediatrics*. Oct 2010;126(4):e771-8. doi:10.1542/peds.2009-2441
8. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med*. Oct 1 2009;361(14):1349-58. doi:10.1056/NEJMoa0900854
9. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet*. Feb 19-25 2005;365(9460):663-70. doi:10.1016/s0140-6736(05)17946-x
10. Wu YW, Mathur AM, Chang T, et al. High-Dose Erythropoietin and Hypothermia for Hypoxic-Ischemic Encephalopathy: A Phase II Trial. *Pediatrics*. Jun 2016;137(6)doi:10.1542/peds.2016-0191
11. Executive summary: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. *Obstet Gynecol*. Apr 2014;123(4):896-901. doi:10.1097/01.AOG.0000445580.65983.d2
12. Faix RG, Laptook AR, Shankaran S, et al. Whole-Body Hypothermia for Neonatal Encephalopathy in Preterm Infants 33 to 35 Weeks' Gestation: A Randomized Clinical Trial. *JAMA Pediatr*. Apr 1 2025;179(4):396-406. doi:10.1001/jamapediatrics.2024.6613
13. Laptook AR, Shankaran S, Tyson JE, et al. Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: A randomized clinical trial. *JAMA*. 2017;318(16):1550-1560. doi:10.1001/jama.2017.14972
14. Higgins RD, Raju T, Edwards AD, et al. Hypothermia and other treatment options for neonatal encephalopathy: an executive summary of the Eunice Kennedy Shriver NICHD workshop. *J Pediatr*. Nov 2011;159(5):851-858.e1. doi:10.1016/j.jpeds.2011.08.004
15. Martinello K, Hart AR, Yap S, Mitra S, Robertson NJ. Management and investigation of neonatal encephalopathy: 2017 update. *Arch Dis Child Fetal Neonatal Ed*. Jul 2017;102(4):F346-f358. doi:10.1136/archdischild-2015-309639
16. Bano S, Chaudhary V, Garga UC. Neonatal Hypoxic-ischemic Encephalopathy: A Radiological Review. *J Pediatr Neurosci*. Jan-Mar 2017;12(1):1-6. doi:10.4103/1817-1745.205646

17. Chao CP, Zaleski CG, Patton AC. Neonatal hypoxic-ischemic encephalopathy: multimodality imaging findings. *Radiographics*. Oct 2006;26 Suppl 1:S159-72. doi:10.1148/rg.26si065504
18. Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: a review for the clinician. *JAMA Pediatr*. Apr 2015;169(4):397-403. doi:10.1001/jamapediatrics.2014.3269
19. Tocchio S, Kline-Fath B, Kanal E, Schmithorst VJ, Panigrahy A. MRI evaluation and safety in the developing brain. *Semin Perinatol*. Mar 2015;39(2):73-104. doi:10.1053/j.semperi.2015.01.002
20. Ment LR, Bada HS, Barnes P, et al. Practice parameter: neuroimaging of the neonate: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. Jun 25 2002;58(12):1726-38.
21. Barkovich AJ, Miller SP, Bartha A, et al. MR imaging, MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy. *AJNR Am J Neuroradiol*. Mar 2006;27(3):533-47.
22. Hyttel-Sorensen S, Greisen G, Als-Nielsen B, Gluud C. Cerebral near-infrared spectroscopy monitoring for prevention of brain injury in very preterm infants. *Cochrane Database Syst Rev*. Sep 4 2017;9:Cd011506. doi:10.1002/14651858.CD011506.pub2
23. Jacobs SE, Morley CJ, Inder TE, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. *Arch Pediatr Adolesc Med*. Aug 2011;165(8):692-700. doi:10.1001/archpediatrics.2011.43
24. Nadeem M, Murray DM, Boylan GB, Dempsey EM, Ryan CA. Early blood glucose profile and neurodevelopmental outcome at two years in neonatal hypoxic-ischaemic encephalopathy. *BMC Pediatr*. Feb 4 2011;11:10. doi:10.1186/1471-2431-11-10
25. Joshi M, Muneer J, Mbuagbaw L, Goswami I. Analgesia and sedation strategies in neonates undergoing whole-body therapeutic hypothermia: A scoping review. *PLoS One*. 2023;18(12):e0291170. doi:10.1371/journal.pone.0291170
26. Kokhanov A, Chen P. Sedation and Pain Management in Neonates Undergoing Therapeutic Hypothermia for Hypoxic-Ischemic Encephalopathy. *Children (Basel)*. Feb 19 2025;12(2)doi:10.3390/children12020253
27. McPherson C, Frymoyer A, Ortinau CM, et al. Management of comfort and sedation in neonates with neonatal encephalopathy treated with therapeutic hypothermia. *Semin Fetal Neonatal Med*. Aug 2021;26(4):101264. doi:10.1016/j.siny.2021.101264
28. MacDonald MG. *Atlas of Procedures in Neonatology*. LWW; 2012.
29. Acun C, Ali M, Liu W, Karnati S, Fink K, Aly H. Effectiveness and Safety of Dexmedetomidine in Neonates With Hypoxic Ischemic Encephalopathy Undergoing Therapeutic Hypothermia. *The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG*. Jun 2024;29(3):232-240. doi:10.5863/1551-6776-29.3.232
30. Baserga M, DuPont TL, Ostrander B, et al. Dexmedetomidine Use in Infants Undergoing Cooling Due to Neonatal Encephalopathy (DICE Trial): A Randomized Controlled Trial: Background, Aims and Study Protocol. *Front Pain Res (Lausanne)*. 2021;2:770511. doi:10.3389/fpain.2021.770511
31. Cosnahan AS, Angert RM, Jano E, Wachtel EV. Dexmedetomidine versus intermittent morphine for sedation of neonates with encephalopathy undergoing therapeutic hypothermia. *J Perinatol*. Sep 2021;41(9):2284-2291. doi:10.1038/s41372-021-00998-8
32. Elliott M, Burnsed J, Heinan K, et al. Effect of dexmedetomidine on heart rate in neonates with hypoxic ischemic encephalopathy undergoing therapeutic hypothermia. *J Neonatal Perinatal Med*. 2022;15(1):47-54. doi:10.3233/NPM-210737

33. Elliott M, Fairchild K, Zanelli S, McPherson C, Vesoulis Z. Dexmedetomidine During Therapeutic Hypothermia: A Multicenter Quality Initiative. *Hosp Pediatr*. Jan 1 2024;14(1):30-36. doi:10.1542/hpeds.2023-007403
34. Naveed M, Bondi DS, Shah PA. Dexmedetomidine Versus Fentanyl for Neonates With Hypoxic Ischemic Encephalopathy Undergoing Therapeutic Hypothermia. *The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG*. 2022;27(4):352-357. doi:10.5863/1551-6776-27.4.352
35. Cocchi E, Shabani J, Aceti A, Ancora G, Corvaglia L, Marchetti F. Dexmedetomidine as a Promising Neuroprotective Sedoanalgesic in Neonatal Therapeutic Hypothermia: A Systematic Review and Meta-Analysis. *Neonatology*. May 2 2025:1-10. doi:10.1159/000546017
36. Spitzmiller RE, Phillips T, Meinzen-Derr J, Hoath SB. Amplitude-integrated EEG is useful in predicting neurodevelopmental outcome in full-term infants with hypoxic-ischemic encephalopathy: a meta-analysis. *J Child Neurol*. Sep 2007;22(9):1069-78. doi:10.1177/0883073807306258
37. Tao JD, Mathur AM. Using amplitude-integrated EEG in neonatal intensive care. *J Perinatol*. Oct 2010;30 Suppl:S73-81. doi:10.1038/jp.2010.93
38. van Rooij LG, Toet MC, van Huffelen AC, et al. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial. *Pediatrics*. Feb 2010;125(2):e358-66. doi:10.1542/peds.2009-0136
39. Sarkar S, Barks JD, Bapuraj JR, et al. Does phenobarbital improve the effectiveness of therapeutic hypothermia in infants with hypoxic-ischemic encephalopathy? *J Perinatol*. Jan 2012;32(1):15-20. doi:10.1038/jp.2011.41
40. Allen KA, Brandon DH. Hypoxic Ischemic Encephalopathy: Pathophysiology and Experimental Treatments. *Newborn Infant Nurs Rev*. Sep 1 2011;11(3):125-133. doi:10.1053/j.nainr.2011.07.004
41. Mruk AL, Garlitz KL, Leung NR. Levetiracetam in Neonatal Seizures: A Review. *The Journal of Pediatric Pharmacology and Therapeutics : JPPT*. Mar-Apr 2015;20(2):76-89. doi:10.5863/1551-6776-20.2.76
42. Kecskes Z, Healy G, Jensen A. Fluid restriction for term infants with hypoxic-ischaemic encephalopathy following perinatal asphyxia. *Cochrane Database Syst Rev*. Jul 20 2005;(3):Cd004337. doi:10.1002/14651858.CD004337.pub2
43. Markus M, Giannakis S, Ruhfus M, et al. Fluid Supply and Feeding Practices in Cooled Asphyxiated Newborns. *Children (Basel)*. Oct 9 2021;8(10)doi:10.3390/children8100899
44. Ojha S, Dorling J, Battersby C, Longford N, Gale C. Optimising nutrition during therapeutic hypothermia. *Arch Dis Child Fetal Neonatal Ed*. May 2019;104(3):F230-F231. doi:10.1136/archdischild-2018-315393
45. Azzopardi D. Clinical management of the baby with hypoxic ischaemic encephalopathy. *Early Hum Dev*. Jun 2010;86(6):345-50. doi:10.1016/j.earlhumdev.2010.05.008
46. Pang R, Mintoft A, Crowley R, Sellwood M, Mitra S, Robertson NJ. Optimizing hemodynamic care in neonatal encephalopathy. *Semin Fetal Neonatal Med*. Oct 2020;25(5):101139. doi:10.1016/j.siny.2020.101139
47. Joynt C, Cheung PY. Cardiovascular Supportive Therapies for Neonates With Asphyxia - A Literature Review of Pre-clinical and Clinical Studies. *Front Pediatr*. 2018;6:363. doi:10.3389/fped.2018.00363
48. Gebauer CM, Knuepfer M, Robel-Tillig E, Pulzer F, Vogtmann C. Hemodynamics among neonates with hypoxic-ischemic encephalopathy during whole-body hypothermia and passive rewarming. *Pediatrics*. Mar 2006;117(3):843-50. doi:10.1542/peds.2004-1587
49. Klinger G, Beyene J, Shah P, Perlman M. Do hyperoxaemia and hypocapnia add to the risk of brain injury after intrapartum asphyxia? *Arch Dis Child Fetal Neonatal Ed*. Jan 2005;90(1):F49-52. doi:10.1136/adc.2003.048785

50. Jenster M, Bonifacio SL, Ruel T, et al. Maternal or neonatal infection: association with neonatal encephalopathy outcomes. *Pediatr Res*. Jul 2014;76(1):93-9. doi:10.1038/pr.2014.47
51. McIntyre P, Isaacs D. Lumbar puncture in suspected neonatal sepsis. *J Paediatr Child Health*. Feb 1995;31(1):1-2.
52. Frymoyer A, Meng L, Bonifacio SL, Verotta D, Guglielmo BJ. Gentamicin pharmacokinetics and dosing in neonates with hypoxic ischemic encephalopathy receiving hypothermia. *Pharmacotherapy*. Jul 2013;33(7):718-26. doi:10.1002/phar.1263
53. Cies JJ, Fugarolas KN, Moore WS, 2nd, Mason RW, Menkiti OR. Population Pharmacokinetics and Pharmacodynamic Target Attainment of Ampicillin in Neonates with Hypoxemic-Ischemic Encephalopathy in the Setting of Controlled Hypothermia. *Pharmacotherapy*. Apr 2017;37(4):456-463. doi:10.1002/phar.1916
54. Cataldi L, Leone R, Moretti U, et al. Potential risk factors for the development of acute renal failure in preterm newborn infants: a case-control study. *Archives of Disease in Childhood Fetal and Neonatal Edition*. 2005;90(6):F514-F519. doi:10.1136/adc.2004.060434
55. Baharestani MM, Ratliff CR. Pressure ulcers in neonates and children: an NPUAP white paper. *Adv Skin Wound Care*. Apr 2007;20(4):208, 210, 212, 214, 216, 218-20. doi:10.1097/01.asw.0000266646.43159.99
56. Butler CT. Pediatric skin care: guidelines for assessment, prevention, and treatment. *Pediatr Nurs*. Sep-Oct 2006;32(5):443-50.
57. Bernabe KQ. Pressure ulcers in the pediatric patient. *Curr Opin Pediatr*. Jun 2012;24(3):352-6. doi:10.1097/MOP.0b013e32835334a0
58. Woods AG, Cederholm CK. Subcutaneous fat necrosis and whole-body cooling therapy for neonatal encephalopathy. *Adv Neonatal Care*. Dec 2012;12(6):345-8. doi:10.1097/ANC.0b013e3182613bff
59. Seesahai J, Luther M, Church PT, et al. The assessment of general movements in term and late-preterm infants diagnosed with neonatal encephalopathy, as a predictive tool of cerebral palsy by 2 years of age-a scoping review. *Syst Rev*. Aug 12 2021;10(1):226. doi:10.1186/s13643-021-01765-8
60. Pouppirt NR, Martin V, Pagnotto-Hammitt L, Spittle AJ, Flibotte J, DeMauro SB. The General Movements Assessment in Neonates With Hypoxic Ischemic Encephalopathy. *J Child Neurol*. Jul 2021;36(8):601-609. doi:10.1177/0883073820981515
61. Campbell SK. Functional movement assessment with the Test of Infant Motor Performance. *J Perinatol*. Oct 2021;41(10):2385-2394. doi:10.1038/s41372-021-01060-3
62. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. *Arch Neurol*. Oct 1976;33(10):696-705.
63. Chalak LF, Nguyen KA, Prempunpong C, et al. Prospective research in infants with mild encephalopathy identified in the first six hours of life: neurodevelopmental outcomes at 18-22 months. *Pediatr Res*. Dec 2018;84(6):861-868. doi:10.1038/s41390-018-0174-x
64. Terrie E. Inder BTD, Linda S. de Vries, André J. du Plessis, Jeffrey J. Neil, Jeffrey M. Perlman. Hypoxic Ischemic Injury in the Term Infant – Clinical - Neurological Features, Diagnosis, Imaging, Prognosis, Therapy. In: Volpe JJ, ed. *Volpe's Neurology of the Newborn*. Sixth ed. Elsevier; 2018:chap 20.
65. Terrie E. Inder BTD, Linda S. de Vries, André J. du Plessis, Jeffrey J. Neil, Jeffrey M. Perlman. Neurological Examination: Normal and Abnormal Features. In: Volpe JJ, ed. *Volpe's Neurology of the Newborn*. Sixth ed. Elsevier; 2018:191-221:chap 9.