PAMC NICU-Therapeutic Hypothermia Guideline for Neonatal Hypoxic Ischemic Encephalopathy (HIE)

Purpose: To provide medical and nursing guidelines for therapeutic whole-body cooling of infants with evidence of hypoxic ischemic encephalopathy (HIE).

Supportive Data: Hypoxic-ischemic injury remains an important cause of perinatally acquired brain injury in near-term and full-term infants. The best predictor of mortality and long-term outcome following perinatal injury is the presence of neonatal encephalopathy. If moderate encephalopathy is present, the risk of death is small (<10%) and as many as 1/3 of the survivors have physical disabilities. With severe encephalopathy, mortality is higher (as much as 60%) and many, if not all survivors have significant disability. Induced hypothermia with total body cooling has been used to reduce the incidence of death and disability in infants having encephalopathy that follows an acute perinatal hypoxic-ischemic event. The reduction in death or major neurodevelopmental disability by 18 months was 25% overall for moderate and severe HIE (32% for moderate, 18% for severe). Recent studies have shown a trend towards improved neurodevelopmental outcomes in patients with mild HIE – these updated criteria reflect including patients demonstrating mild to moderate HIE.

Inclusion Criteria:
Eligible infants include those ≥ 35 weeks gestation, birth weight ≥ 1800gm, and presenting for hypothermia intervention before 6 hours of life. Infants otherwise meeting criteria but greater than 6 hours from time of delivery may be eligible to receive cooling at the discretion of the attending neonatologist.

Infant must meet **both** physiologic and neurologic criteria.

A. Physiologic criteria
    1. Cord gas or any blood gas from infant within first hour of life: pH ≤7.1 or base deficit of ≥10, then proceed to neurologic criteria
    2. No blood gas with an acute perinatal event (abruption placenta, cord prolapse, severe FHR abnormality: variable or late decals, uterine rupture, maternal hemodynamic instability, etc), plus either a or b, then proceed to neurologic criteria.
        a. A 10-minute Apgar less than 5
        b. A continued need for positive pressure ventilation initiated at birth and continued for at least 10 minutes.
B. Neurologic Criteria
    1. The presence of seizures is automatic inclusion
    2. Physical exam findings consistent with moderate or severe encephalopathy in 2 of the 6 categories that persist beyond 45 minutes of life.

Neuro Criteria Box*

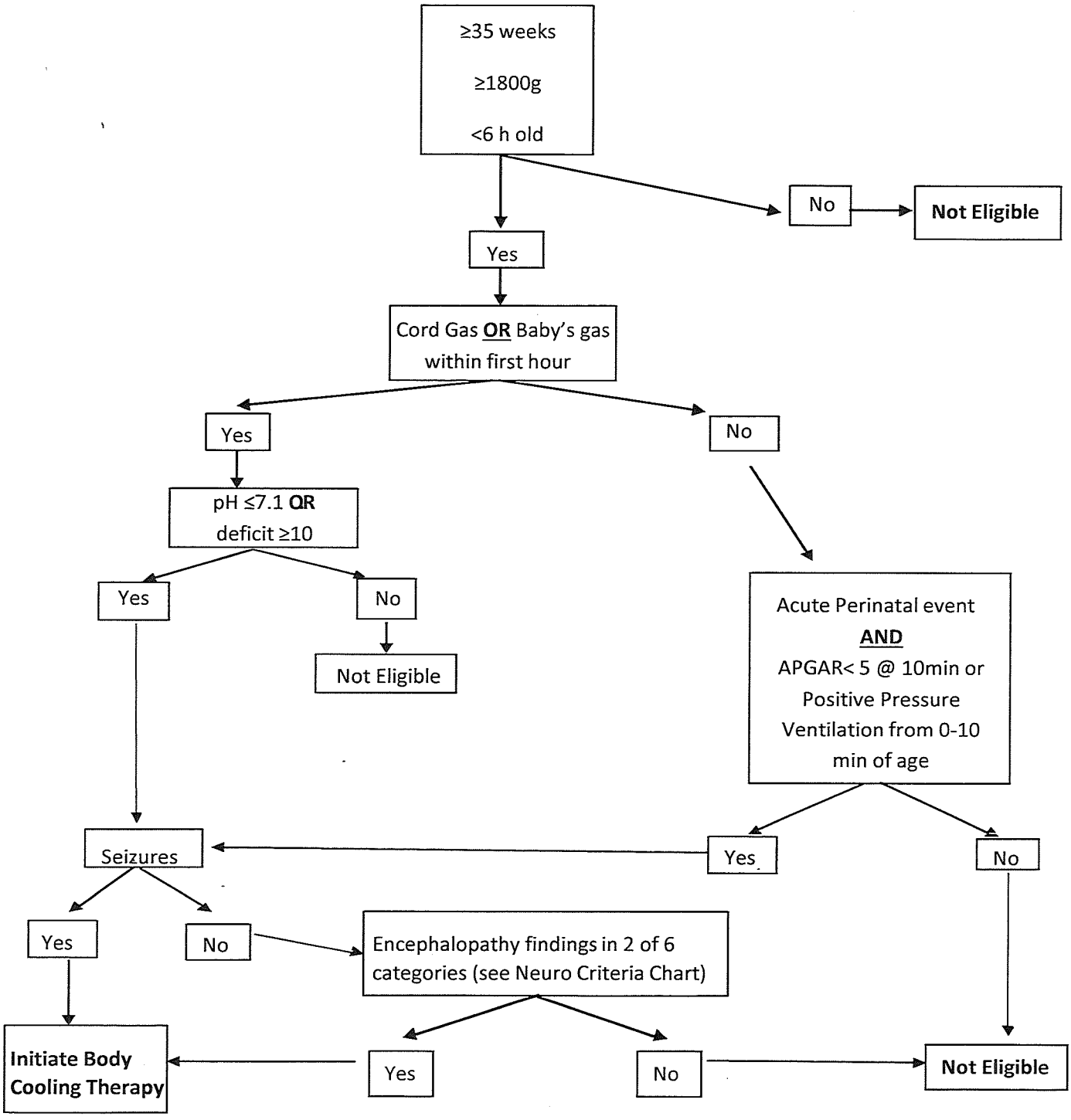
	Neuro Exam	Moderate Encephalopathy	Severe Encephalopathy
1	***Level of Consciousness***	Lethargic	Stupor or coma
2	***Spontaneous movement***	Decreased activity	No activity
3	***Posture***	Distal flexion	Decerebrate
4	***Tone***	Hypotonia (focal, general)	Flaccid
5	***Primitive Reflexes***		
	Suck	-Weak	-Absent
	Moro	-Incomplete	-Absent
6	***Autonomic System***		
	Pupils	-Constricted	-Dilated, nonreactive
	Heart Rate	-Bradycardia	-Variable
	Respiration	-Periodic breathing	-Apnea

*NICHD hypothermia trial criteria.

RESOURCE: Hypoxic Ischemic Encephalopathy Scoring Exam and Videos - Stanford

https://med.stanford.edu/wusthoff-lab/encephalopathy.html

Body Cooling Algorithm



Exclusion criteria:

1. Gestational Age < 35 weeks
2. Birth weight < 1800 grams
3. Unable to initiate active body cooling by 6-12 hours
4. Relative contraindications (at discretion of Neonatologist)
    a. Severe PPHN
        i. (Pulmonary hypertension should be managed aggressively and with maximum therapy.
        ii. Hypothermia should be discontinued if infant still has significant fetal circulation and/or cardiovascular instability on maximum therapy).
    b. Severe hemodynamic compromise
    c. Severe coagulopathy with active bleeding
    d. Presence of known major life-limiting congenital anomaly/chromosome anomaly

Documentation: Ensure H&P includes clear documentation of inclusion criteria with the specific neurologic findings factored into the decision to initiate therapeutic hypothermia. Access encephalopathy documentation feature in note program.

EPIC order set: "Neo NICU Hypothermia Therapy".

Cooling Guideline: Please see attachments for specific equipment set-up

1. Prepare bed - Use Radiant Warmer in manual mode with heat OFF.
2. Place skin temperature probe on the infant on the clavicle, may need to be repositioned to avoid direct contact with the bed. The radiant warmer must remain turned off during the cooling phase.
3. Placement of esophageal temperature probe
    a. Nasal route is preferred. Appropriate placement is in the distal 1/3 of the esophagus.
    b. Calculation for the depth of insertion: (patient length in cm divided by 5) + 4.8cm. Round up to the nearest whole number and that is the depth when taped at the nose. Alternately, measure distance from nares to the ear to sternum, minus 2 cm and mark location. This should position the temp probe in the lower 3rd of the esophagus (nasal route is preferred).
    c. Soften the probe prior to insertion by placing it between 2 heel warmers.
    d. Lubricate tube (first 5 cm) and carefully insert to desired length.
    e. Secure to face.
    f. Placement will be confirmed with CXR.
4. Place cardio-respiratory leads on the infant.
5. Place pre and post ductal pulse oximeter probes on the infant.

e. EEG - Obtain within 24 hours of rewarming.
f. Neurology Consultation - Obtain at the discretion of the attending neonatologist.
g. OT/PT/SLP
    i. Standing order for evaluation while in NICU
    ii. Follow-up outpatient per in-patient evaluation/recommendations

Re-Warming Procedure:

1. Please see attachments for specific equipment instructions
2. Objective is to gradually increase the infant's core body temperature by approximately 0.5 degrees Celsius/hour to a goal temperature of 36.5 degrees Celsius (should take 6-7 hours to achieve).
3. During re-warming
    a. Record esophageal and skin temp q 30 minutes until goal temp reached.
    b. Record HR, RR, BP q2hours until goal temp reached.
4. Once goal temp reached
    a. Infant's thermoregulation will be returned to the overhead warmer.
    b. Continue esophageal monitoring for another 6 hours, then remove esophageal probe.
    c. Do not allow infant's temperature to exceed 37 degrees Celsius for 24 hours following re-warming.
    d. Continue aEEG monitoring for another 6 hours then remove leads.
    e. Vital signs should be obtained every 3 hours x 24 hours then routine per unit policy.
5. Monitor closely for seizures, hypotension, acidosis, electrolyte disturbance, diuresis/oliguria.

References:

Shankaran S, et al. "Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy." N Engl J Med. 2005 Oct 13;353(15):1574-84

Papile LA, Baley JE, et al. "Hypothermia and neonatal encephalopathy." Committee on Fetus and Newborn. Pediatrics 2014; 133:1146

Bhagat I, Sakar S. "Multiple organ dysfunction during therapeutic cooling of asphyxiated infants." Neoreviews 2019: 20: e653

Alburaki W, et al. "Feeding during therapeutic Hypothermia is safe and may improve outcomes in newborns with perinatal asphyxia." Journal of Mat-Fet-Neonatal Medicine 2022: 35: 9440-44.

Lemyre B, Chau V. "Hypothermia for newborns with hypoxic-ischemic encephalopathy." Canadian Paediatric Society Position Statement. Paediatrics & Child Health 2018, 285-291

Montaldo et al. "Therapeutic hypothermia initiated within 6 hours of birth is associated with

reduced brain injury on MR biomarkers in mild hypoxic-ischemic encephalopathy: a non-randomized cohort study." Arch Dis Child Fetal Neonatal Ed. 2019 Sep;104(5):F515-F520.

Conway et al. "Mild hypoxic ischaemic encephalopathy and long term neurodevelopmental outcome – A systematic review. Early Hum Dev. 2018 May:120:80-87

Qiao MY, Cui HT, Zhao LZ, Miao JK, Chen QX. Efficacy and Safety of Levetiracetam vs. Phenobarbital for Neonatal Seizures: A Systematic Review and Meta-Analysis. Front Neurol. 2021 Nov 18

O'Kane A, Vezina G, Chang T, Bendush N, Ridore M, Gai J, Bost J, Glass P, Massaro AN. Early Versus Late Brain Magnetic Resonance Imaging after Neonatal Hypoxic Ischemic Encephalopathy Treated with Therapeutic Hypothermia. J Pediatr. 2021 May

References:

1. Ter Host H, Sommer C, Bergman KA, Fock JM, van Weerden TW, Bos AF. Prognostic significance of amplitude integrated EEG during the first 72 hours after birth in severely asphyxiated neonates. Pediatric Research. 2004;55:1026-1033. doi: 10.1203/01.pdr.0000127019.52562.8c
2. Azzopardi D; TOBY study group. Predictive value of the amplitude integrated EEG in infants with hypoxic ischaemic encephalopathy: data from a randomised trial of therapeutic hypothermia. Arch Dis Child Fetal Neonatal Ed. 2014;99(1):F80-2. doi: 10.1136/archdischild-2013-303710.
3. Hellstrom-Westas L, Rosen I, de Vries LS, Greisen G. Amplitude-integrated EEG classification and interpretation in preterm and term infants. Neoreviews. 2006:7(2):e76-e87. doi: 10.1542/neo.7-2-e76.
4. Thorensen M, Hellstrom-Westas L, Liu X, de Vries, LS. Effect of hypothermia on amplitude-integrated electroencephalopgram in infants with asphyxia. J Pediatr. 2010;126:2009-2938. doi: 10.1542/peds.2009-2938

Transport/pre-admission guide for infants with suspected hypoxic ischemic encephalopathy.

1. Identify infants eligible for cooling with referring Provider
2. Eligible infants should not be actively cooled prior to arrival of neonatal transport team.
3. Initiate passive cooling.
    a. Turn off all external heat sources.
    b. Monitor core temperature (rectal most common in referral centers)
        i. Continuous is preferred – insert lubricated probe 6cm and tape to thigh.
        ii. Intermittent temps with rectal thermometer inserted 2cm every 15 minutes.
        iii. Target temperature is 33.5 degrees Celsius or 92.5 degrees Fahrenheit.
4. If temp falls below 33.5 degrees Celsius, restart heat sources at lowest settings. Avoid over cooling.
5. Secure vascular access (umbilical catheters if possible, peripheral IVs at minimum) and support with D10W at 60ml/kg/day.
6. Send blood culture and start antibiotics (amp/gent) if indicated
7. Keppra for clinical seizures: load with 20mg/kg IV, repeat once prn seizures. May use phenobarbital if Keppra not available: load with 20mg/kg IV, repeat once prn seizures.
8. Monitor electrolytes an maintain within normal ranges (Ca, K, Mg, glucose)
9. Avoid over-ventilation and over-oxygenation.
    a. Target pCO2 (corrected for temperature) = 45-55 mmHg
    b. Target saturations = 92-98% with PaO2 <100 mmHg
10. Tolerate HRs <100 bmp in cooled patients as long as blood pressure and oxygenation remain normal. Some patients experience HRs as low as 70-80 when cooled.
11. Temperature Conversion Chart

Celsius	Fahrenheit
38	100.4
37	98.6
36	96.8
35	95
34	93.2
33	91.4
32	89.6
31	87.8
30	86