Newborn Critical Care Center (NCCC) Clinical Guidelines

Hypoxic Ischemic Encephalopathy* – Whole Body Cooling

BACKGROUND

Hypoxic-ischemic injury remains an important cause of perinatally acquired brain injury in full term infants.[1] Induced hypothermia reduces the incidence of death and disability in full term infants with encephalopathy following an acute perinatal hypoxic-ischemic event.[2-4] A 2013 Cochrane review of therapeutic hypothermia showed a significant reduction in the combined death/major neurodevelopmental disability (RR = 0.75, 95%CI 0.68-0.83).[5]

* *These guidelines also apply to newborns with cardiac arrest who qualify for therapeutic hypothermia. There is an additional 'post cardiac arrest' guideline for older infants (Pediatric Post Cardiac Arrest Pathway)*

QUALIFICATION

Eligible infants include those delivered at ≥ 36 weeks gestational age, with a birth weight of ≥ 1800 grams, and with hypothermia initiated < 6 hours after delivery.[3-4] Other infants including those < 36 weeks gestation, <1800g, or who present 6-24 hours after delivery may be eligible to receive cooling therapy at the discretion of the attending physician or if enrolled in a research study, although we caution that risks and benefits of cooling in this population remain unclear. Infants should meet ***both*** physiologic and neurologic criteria. *(See Whole Body Cooling Algorithm on page 2)*

Physiologic Criteria

1. Blood gas* pH < 7.0 or base deficit of > 16 mEq/L, then proceed to neurologic criteria
2. No blood gas **OR** blood gas* pH 7-7.15 or base deficit of 10-15.9 mEq/L with an acute perinatal event (abruption placenta, cord prolapse, severe FHR abnormality: variable or late decelerations), **PLUS** either a or b, then proceed to neurologic criteria
    a. A 10 minute Apgar score < 5
    b. A need for assisted ventilation initiated at birth and continued for ≥ 10 minutes

* *Blood gas is defined as: a cord gas* **OR** *any blood gas within the first hour of life*

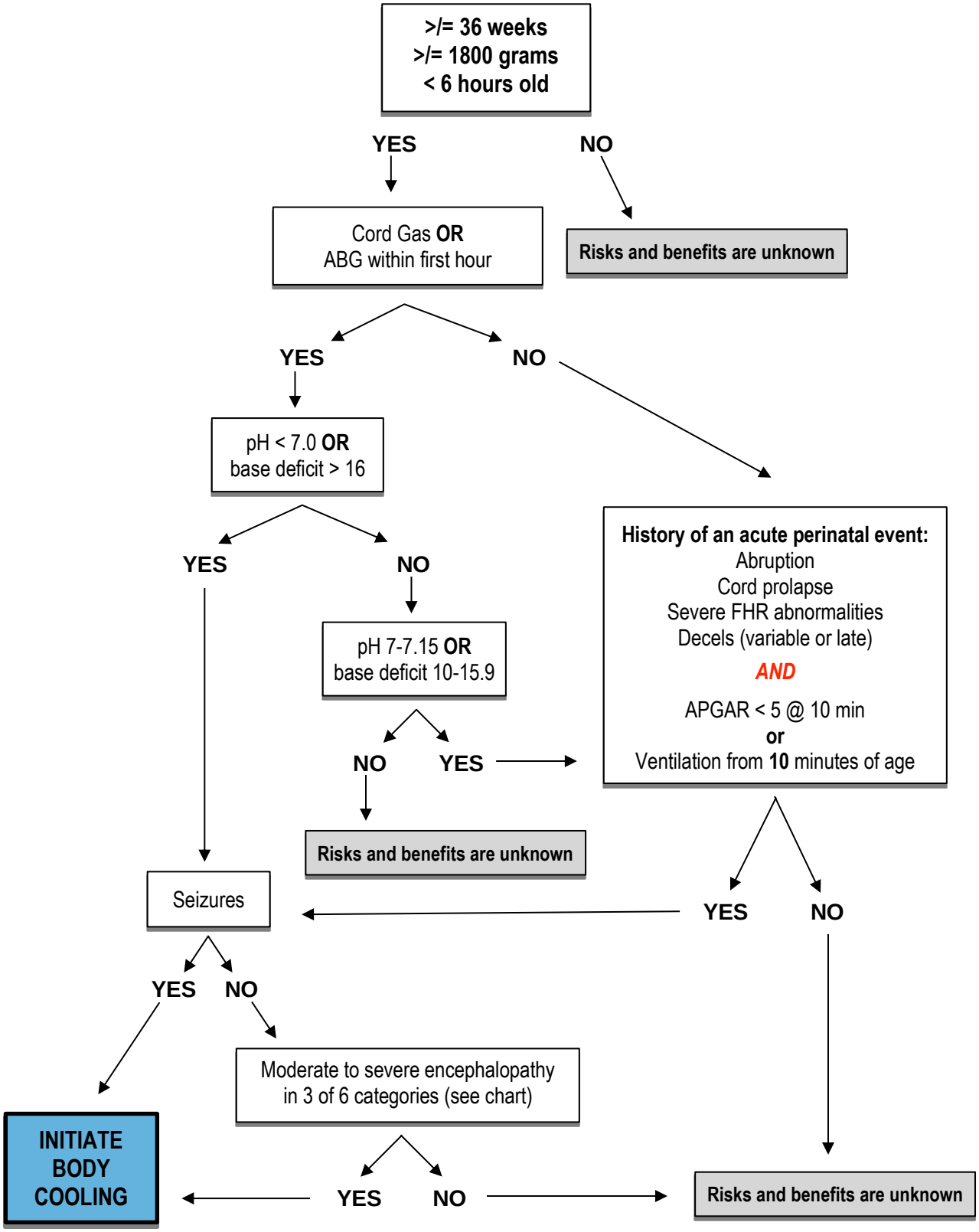
Neurologic Criteria

1. The presence of seizures is automatic inclusion
2. Physical exam consistent with *moderate* to *severe* encephalopathy in 3 of the 6 categories

	NEUROLOGIC EXAM	Mild Encephalopathy	Moderate Encephalopathy	Severe Encephalopathy
1	**Level of Consciousness**	Hyperalert	Lethargic	Stupor or Coma
2	**Spontaneous Movement**	Normal	Decreased Activity	No Activity
3	**Posture**	Mild distal flexion	Strong distal flexion	Decerebrate
4	**Tone**	Normal	Hypotonia (focal, general)	Flaccid
5	**Primitive Reflexes** • Suck • Moro	 Weak Strong	 Weak Incomplete	 Absent Absent
6	**Autonomic system** • Pupils • Heart Rate • Respiration	 Dilated, reactive Tachycardia Normal	 Constricted Bradycardia Periodic Breathing	 Dilated, nonreactive Variable Apnea

Choose the most severe level within each category. For example, if infant has some exam findings of moderate and some findings of severe encephalopathy, then choose severe encephalopathy.

Whole Body Cooling Algorithm



DOCUMENTATION:

Please ensure the H&P and a procedure note for Whole Body Cooling include clear documentation of the cord gas or initial ABG, the time and age of the infant at onset of cooling, and the specific neurologic criteria that factored into the decision to initiate therapeutic hypothermia. The H&P should include documentation of rationale if therapeutic hypothermia is deferred.

TRANSPORT

1. During the initial call to the referral facility, inform the referring provider:
    a. Maintain normothermia until active cooling can be initiated by UNC AirCare or the UNC NCCC.
    b. Consider passive cooling only if it seems that the infant will meet criteria for therapeutic hypothermia and it will not be possible to initiate active cooling within the 6 hour window.

       Note: *If passive cooling is initiated, it is very important to avoid excessive hypothermia.*[6] *An esophageal temperature probe is ideal, with a target temperature of 35.0 ºC. If this is unavailable, ask provider to place a skin temperature probe and set the servo temp at 34.0°C. If the skin temperature should fall below 34.0°C, turn on the warmer and set the servo control for 34.0°C.*
    c. Obtain a blood gas and serum lactate level.
    d. Ask the referring provider to report a full neurologic exam to you to help ensure the infant meets cooling criteria. This neurologic exam ideally should take place *after* initial stabilization in the delivery room.
2. On transport:
    a. There is a “Tecotherm” cooling blanket that can be paired with an esophageal temp probe and used for active cooling during transport. The initial Tecotherm temperature should be set to 35°C. Discuss with the transport team whether this is available. If not, do not attempt any other method of active cooling on transport. Transport team should follow UNC AirCare Pediatric Transport Team Tecotherm Guidelines.
    b. Tecotherm unavailable: Consider passive cooling only if the infant will not arrive to UNC NCCC within 6 hours of life - adjust the temperature in the transport incubator to attempt to maintain axillary body temperature of 34.0°C. Be wary of temperature overshoot and consider delaying cooling until infant arrives at NCCC based on timing of transport.
3. MCO (Medical Control Officer): Keep in mind that time to initiate proper cooling is important.
    a. Consider deferring line placement until admission to UNC if concerned about being able to initiate cooling by 6 hours of life.
    b. Be mindful of ground transportation time if weather does not permit air transport.

WHOLE BODY COOLING PROTOCOL

EPIC Order Set: Neonatal Hypoxic Ischemic Encephalopathy (HIE) Admission

PROCEDURE

1. Preparing the infant prior to cooling:
    a. Radiant warmer should remain off
    b. Nurse to place a PIV while team sets up for umbilical lines
    c. MD/NNP to place UAC and UVC
        a. While the team is preparing and placing lines, the nursing staff should start the Arctic Sun Stat Temperature Management System in the hypothermia/neonate mode and place a nasal or oral esophageal probe. Refer to the Body Cooling Worksheet - Artic Sun for checklist and specific instructions.
    d. Obtain radiograph to confirm line placement and to assess location of esophageal probe. Appropriate placement of probe is in the distal 1/3 of the esophagus.
    e. Time when cooling is initiated will be recorded by nurses. This will serve as hour 0. Cooling will continue for 72 hours.
    f. Temperatures will be monitored using continuous esophageal and skin temperature measurements. All clinical decisions will be made using the esophageal temperature. Skin temperature monitoring acts as a safety measure that provides continuous back-up monitoring in case of esophageal probe malfunction. An esophageal temperature of 33.5°C should correspond to a skin temperature of 31.5-32°C
    g. Set the lower limit of HR monitor to 90 bpm as the HR of the infant being cooled will often have HR below 100. Heart rates in the 70s will be tolerated, provided the infant has a normal sinus rhythm, stable BP, and adequate oxygen saturations.

NURSING GUIDELINES FOR WHOLE BODY COOLING

See: Body Cooling Worksheet - Arctic Sun

Epic Order Set: Neonatal Hypoxic Ischemic Encephalopathy (HIE) Labs and Rewarming

LABORATORY EVALUATION SCHEDULE ***All hours refer to hours post start of cooling, not hours of life***						
HOUR 0	**HOUR 12**	**HOUR 24**	**HOUR 36**	**HOUR 48**	**HOUR 60**	**HOUR 72**
*** Blood gas** (If not previously obtained)	**Blood gas** (POC or lab gas) iCa Glucose	**Blood gas** (POC or lab gas) iCa Glucose	**Blood gas** (POC or lab gas) iCa Glucose	**Blood gas** (POC or lab gas) iCa Glucose	**Blood gas** (POC or lab gas) iCa Glucose	**Blood gas** (POC or lab gas) iCa Glucose
Chem 10	Chem 10	Chem 10		Chem 10		Chem 10
CBC with differential		CBC with differential		CBC with differential		
Blood culture						
	Bilirubin	Bilirubin		Bilirubin		Bilirubin
Liver Function Tests AST ALT Total Protein Albumin Total bilirubin Direct bilirubin Alk Phosphatase GGT		**Liver Function Tests** AST ALT Total Protein Albumin Total bilirubin Direct bilirubin Alk Phosphatase GGT				**Liver Function Tests** AST ALT Total Protein Albumin Total bilirubin Direct bilirubin Alk Phosphatase GGT
Coagulation Studies PT PTT INR Fibrinogen		**Coagulation Studies** PT PTT INR Fibrinogen				

**** For blood gas results, always look at the temperature corrected values.***

ACCESS

The goal is to obtain central line access - umbilical arterial and umbilical venous access is preferred. If unable to obtain umbilical access, a peripheral arterial line for continuous blood pressure monitoring/lab draws and/or a peripheral IV will be inserted.

NUTRITION

It has been convention to maintain NPO during hypothermia and through completion of rewarming. However, recent studies have not shown increased risk of NEC or mortality in infants fed low volume (10-20 mL/kg/day) enteral feeding during hypothermia.[7] Decisions regarding feeding will be left to the discretion of the attending provider. Aim to achieve euglycemia. Carefully consider renal function when ordering electrolytes, especially potassium.

FLUIDS

Start fluids at 50-60 mL/kg/day and increase as needed based on clinical status. Follow UOP and renal function closely (electrolytes / serum creatinine) as these infants are at increased risk of acute kidney injury and SIADH.

SUBCUTANEOUS FAT NECROSIS

Skin should be examined daily for infants with HIE or therapeutic hypothermia due to the risk of subcutaneous fat necrosis (SCFN). Onset of skin lesions is within the first week of life for over half of infants with SCFN and within the first month for 92% of patients. Of infants with SCFN, about half will develop hypercalcemia, which is often asymptomatic. Case reports and case series demonstrate the median onset of hypercalcemia at 28 days of life, with a range of 1-210 days. Median duration of hypercalcemia is about 4 weeks, and ~90% have resolved by 3 months.[8,9] The following pragmatic algorithm has been suggested for monitoring of calcium in infants with SCFN[10]:

Normocalcemia (iCal):

1. Check total and ionized Ca weekly through 1 month of age.
2. Check total and ionized Ca monthly until 6 months of age or until skin lesions resolve, whichever is later.
3. If Ca becomes elevated, move to hypercalcemia algorithm.

Hypercalcemia (iCal):

1. Repeat total and ionized Ca at least twice weekly or more often as indicated by clinical symptoms.
2. If persistently elevated or symptomatic, consider endocrinology consult and interventions including: limitation of enteral Ca and vit D, hyperhydration, diuresis, glucocorticoids, and bisphosphonates.

ECHOCARDIOGRAPHY

Obtain at the discretion of the attending physician. Routine echocardiogram is not necessary. Birth asphyxia is a risk factor for PPHN.

EEG

1. Numerous studies have shown a high rate of subclinical seizures among infants with moderate to severe encephalopathy. Thus, all infants meeting criteria for therapeutic hypothermia should have EEG monitoring initiated during cooling and continued through rewarming.[11,12]
2. Place a formal neurology consult and order a stat video EEG. Page the on-call EEG tech to let them know that a stat EEG order has been placed. Page neurology for preliminary results after the EEG leads have been in place for approximately 1 hour, or sooner if clinical concern for seizure is high. Note that all EEG leads used at UNC are MRI compatible.

MEDICATIONS

1. **Antibiotics:** Begin antibiotic coverage with ampicillin and one dose of gentamicin after obtaining blood cultures. Obtain a gentamicin level before the giving the next dose. Follow urine output and creatinine closely. If renal dysfunction is severe, consider changing gentamicin to cefotaxime/cefepime
2. **Antiepileptics:** There is no consensus on first-line antiepileptic therapy in the setting of seizures and HIE. Decisions about antiepileptics should be made in conjunction with the neurology team.
3. **Sedation:** Consider the use of morphine for sedation on an as-needed basis. Morphine clearance is slower in asphyxiated infants.[13] If initiating a morphine drip, use a loading dose of 0.025-0.075 mg/kg and a maintenance dose of 0.0025-0.015 mg/kg/hr.

OTHER CONSIDERATIONS

These are left to the discretion of the attending physician:

1. If inborn, consider contacting risk management.
2. In cases requiring transfer to the PICU, including need for ECMO due to PPHN, please provide a copy of this protocol for the PICU team. Cooling may be continued while the infant is on ECMO.

REWARMING

After completion of 72 hours of whole body cooling

1. The Arctic Sun will gradually increase the infant's core body temperature by ~0.5°C per hour. The goal temperature set on the Arctic Sun will be 36.5°C to ensure core body temperature reaches 36.5°C. This should take 6-7 hours to achieve.
2. During rewarming:
   a. Record esophageal and skin temperatures every 30 minutes until goal temperature is achieved.
   b. Record HR, RR, and BP every 2 hours until goal temperature is achieved.
3. Once goal temperature of 36.5°C is achieved:
   c. Transition to "Normothermia" setting on Arctic Sun for 24h. Radiant warmer should remain off during the 24h of normothermia. NOTE: This step can be omitted or ended early if the Arctic Sun is needed for another patient or if this is prohibitive to obtaining an MRI. It is also acceptable to allow infants to be taken off the mattress for skin-to-skin with close monitoring of temperature to avoid large fluctuations.
   d. Vital signs should be obtained every 3 hours.
   e. Monitor esophageal temperature for another 4 hours, recording temperature every 30 minutes for the first hour then every hour for the final 3 hours.
4. Obtain the following **LABS** 6 hours after rewarming has started, even if rewarming is not completed.
   a. Chem 7 (including glucose)
   b. CBC
   c. Coagulation Studies (PT, PTT, INR, Fibrinogen)
   d. ABG with lactate
5. If the hemodynamic status becomes unstable or the infant has seizures, consider slower rewarming.

EXPECTATIONS DURING WHOLE BODY COOLING AND REWARMING

The infant will receive body cooling for the full 72 hours. Some infants' clinical status may improve, but the studies show the demonstrated benefits of cooling occur only with full 72 hours of cooling.

During cooling expect:

- Decreased heart rate (often as low as 70-80 bpm)
- Increased blood pressure initially due to increased peripheral vasoconstriction.
- Increase in urine output initially due to peripheral vasoconstriction and shunting of blood to the kidneys
- Decrease in calcium, magnesium, phosphorus and potassium
- Labile glucose levels due to relative insulin resistance, decreased metabolic rate, and shivering

During rewarming expect:

- Increase in heart rate
- Decrease in blood pressure due to decrease in peripheral vascular resistance
- Decrease in urine output due to increased third spacing and shunting of blood to the periphery
- Electrolyte shifts, as renal and liver clearance rates change
- Emergence of seizure activity may occur during rewarming

IMAGING

1. Attempt to obtain an MRI at 3-5 days of life after rewarming is complete if infant is medically stable. This is the time period when diffusion-weighted imaging (DWI) sequences are most sensitive to detect ischemic change. Consider repeat MRI at 7-10 days if initial MRI is equivocal or if MRI is unable to be obtained in the 3–5-day timeframe. T2 changes are most apparent at 7-10 days post-insult.[14]

   Note: *Be cautious when informing families about normal MRI results, as approximately 25% of infants who receive therapeutic hypothermia and have normal MRI findings have abnormal neurodevelopmental outcomes*[15]

2. Consider early imaging if infant is exhibiting seizures

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