

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. Induced hypothermia reduces the incidence of death and disability in full term infants with encephalopathy following an acute perinatal hypoxic-ischemic event. 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).

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. Other infants including those < 36 weeks gestation or who present 6-24 hours after delivery may be eligible to receive cooling therapy at the discretion of the attending physician or due to a study protocol. Infant must meet **both** physiologic and neurologic criteria. (See attached [Whole Body Cooling Algorithm](#))

Physiologic Criteria

Blood gas is defined as: (A) a cord gas or (B) any blood gas within the first hour of life.

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 continued need for ventilation initiated at birth and continued for ≥ 10 minutes

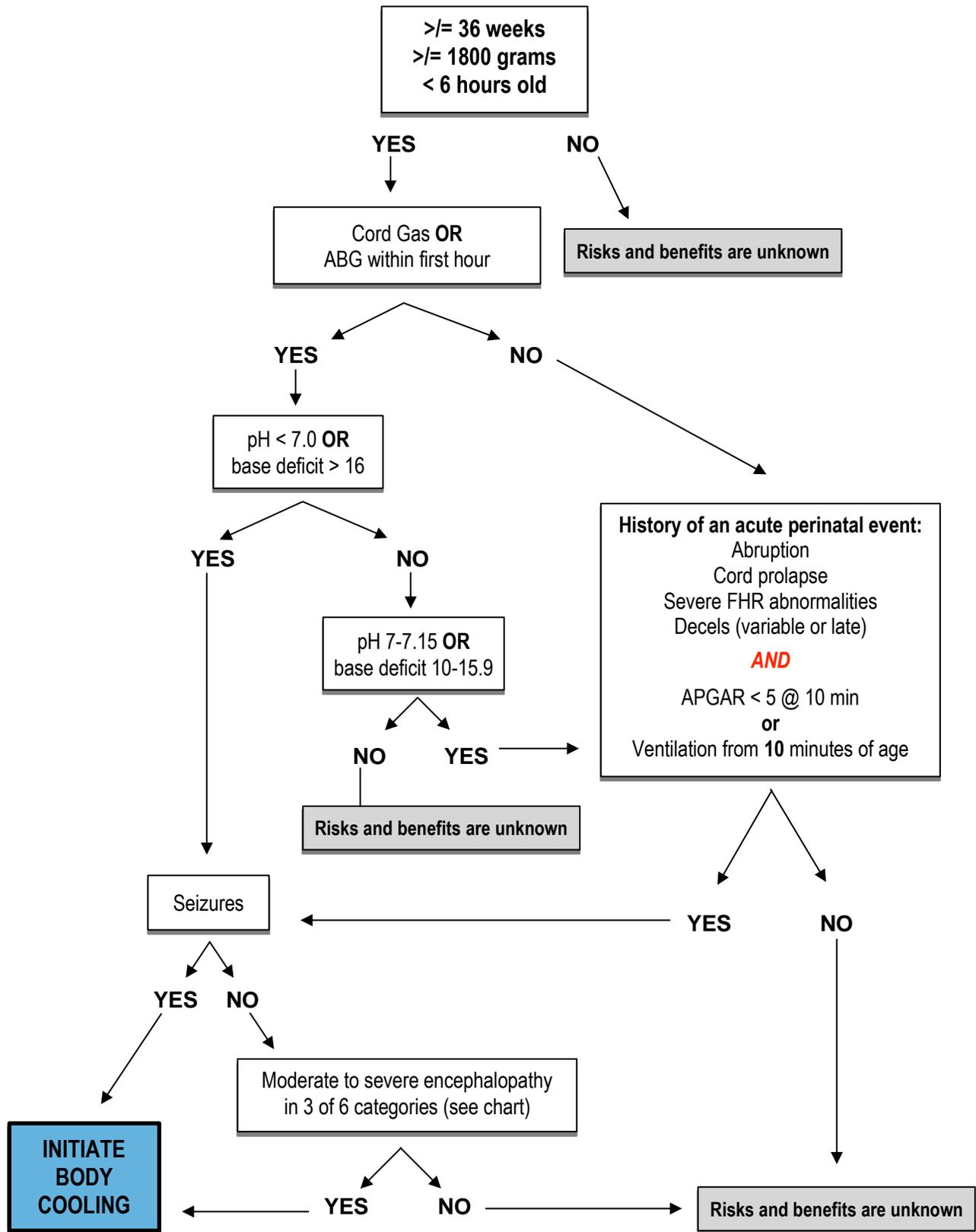
Neurologic Criteria

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	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 <ul style="list-style-type: none"> • Suck • Moro 	Weak Incomplete	Absent Absent
6	Autonomic system <ul style="list-style-type: none"> • Pupils • Heart rate • Respiration 	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 that there is clear documentation in the H&P of the cord gas or initial ABG, the age of the infant at onset of cooling, and the specific neurologic criteria that factored into the decision to initiate or defer therapeutic hypothermia

TRANSPORT

1. During the initial call to the referral facility, inform the referring provider:
 - a. Do not use any exogenous heat sources (do not turn on the radiant warmer heat).
 - b. Consider passive cooling if it seems that the infant will meet criteria for therapeutic hypothermia and infant is likely to arrive at UNC NCCC within the 6 hour window. If passive cooling is initiated, 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, then 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. Monitor axillary temperatures every 15 minutes while en route.
 - b. Consider passive cooling- adjust the temperature in the transport isolette to attempt to maintain axillary body temperature of 34.0°C. Be wary of temperature overshoot and fluctuations and consider delaying cooling until infant arrives at NCCC based on timing of transport
 - c. 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.
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.

UNC WHOLE BODY COOLING PROTOCOL

EPIC Order Set: UNCH 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 putting in lines, the nursing staff should start the Blanketrol unit and begin cooling the blanket to 35°C then place nasal esophageal probe. Refer to nursing protocol for specifics
- 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 on the [Neonatal Body Cooling Worksheet](#) (to be kept at bedside). 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 as long as the infant has a normal sinus rhythm, stable BP, and adequate oxygen saturations.

Lab Schedule:

LABORATORY EVALUATION SCHEDULE <i>All hours refer to hours post start of cooling, not hours of life</i>						
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		
	Neobili	Neobili		Neobili		Neobili
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 if at all possible - 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

Keep NPO during hypothermia treatment until completion of rewarming. Aim to achieve euglycemia.

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.

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 with an abnormal neurologic exam meeting criteria for therapeutic hypothermia should have EEG monitoring initiated during cooling and continued through rewarming.
2. Please order a stat vEEG and page the on-call EEG tech to let them know that a stat EEG order has been placed. If there are no clinical concerns for seizure, page the neurology fellow for preliminary results after the EEG leads have been in place for approximately 1 hour. Place a formal neurology consult for seizure activity or if the primary team desires a consult. Note that all EEG leads used at UNC are MRI compatible.

MEDICATIONS

1. **Antibiotics:** Begin antibiotic coverage with ampicillin and one dose of gentamicin. 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. 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. If the blanket temperature needed to keep the infant cool is $> 37^{\circ}\text{C}$ (which may happen in a situation of a late preterm infant, a sick infant, or an SGA infant) it is permissible to increase the Blanketrol temperature up to $38\text{-}39^{\circ}\text{C}$. If there is a need to increase the blanket temperature higher than 39°C , contact the attending. The attending may choose to turn on the radiant warmer to a low manual control temperature to decrease the effects of convection on the infant.

REWARMING

After completion of 72 hours of whole body cooling

1. Gradually increase the infant's core body temperature by manually increasing the Blanketrol set point by 0.5°C per hour. The final goal temperature is 36.5°C and should take ~ 7 hours to achieve.

DO NOT TURN THE RADIANT WARMER ON UNTIL TEMPERATURE OF 36.5°C IS REACHED

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. Vital signs should be obtained every 3 hours.
 - d. 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** once the goal temperature of 36.5°C is achieved:
 - 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 beats per minute)
- 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. Consider obtaining 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.

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*

2. Consider early imaging if infant is exhibiting seizures

References:

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2. Committee on Fetus and Newborn, Papile LA, et al. "Hypothermia and neonatal encephalopathy." *Pediatrics.* 2014 Jun;133(6):1146-50.
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4. Jacobs SE, et al. "Cooling for newborns with hypoxic ischaemic encephalopathy." *Cochrane Database Syst Rev.* 2013;(1):CD003311.
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6. Merhar S, et al. "Neuroimaging and other neurodiagnostic tests in neonatal encephalopathy." *Clinics in Perinatol.* 2016;43(3):511-27
7. Róka A, et al. "Elevated morphine concentrations in neonates treated with morphine and prolonged hypothermia for hypoxic ischemic encephalopathy." *Pediatrics.* 2008 Apr;121(4):e844-9.
8. Rutherford M, et al. "Mild Hypothermia and the distribution of cerebral lesions in neonates with hypoxic-ischemic encephalopathy." *Pediatrics.* 2005 Mar;28(3):171-5.
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12. Zanelli S, et al. "Implementation of a 'Hypothermia for HIE' program: 2-year experience in a single NICU." *J of Perinatology.* 2008 Mar;28(3):171-5.

NURSING GUIDELINES FOR THERAPEUTIC HYPOTHERMIA

EQUIPMENT

1. Blanketrol Cooling Device
2. Cooling blankets (Maxi-therm Lite)
3. Esophageal temperature probe or rectal temperature probe

Start the Blanketrol unit and begin cooling the blanket while the team is putting in lines. Set the initial Blanketrol unit temperature to 35°C.

OPERATION OF THE BLANKETROL 3
1. Allow the infant to cool, most likely the infant will become cooler than 35°C.
2. Press the TEMP SET button and adjust the set point to 33.5°C.
3. Press the GRADIENT 10C mode button.
4. The desired SET PT temperature is displayed on the panel.
5. Touch the hyper / hypothermia blanket to confirm the water is heating / cooling.
OPERATION OF THE BLANKETROL 2
1. Begin with the unit in manual mode with the temperature set at 35°C.
2. Allow the infant to cool. (Most infants will overshoot to a temperature less than 35°C. See example below.)
3. Once the infant has reached their coolest temperature at this setting and has warmed by 0.1°C0.2°C, then decrease the manual temperature to 34°C.
4. Allow the infant to cool. (Most infants will overshoot to a temperature less than 34°C.)
5. Once the infant has reached their coolest temperature at this setting and has warmed by 0.1°C0.2°C, then decrease the manual temperature to 33.5°C.
6. Allow the infant to stabilize at 33.5°C. This is the goal for the esophageal temperature. Example: The infant whose initial esophageal temperature is 36°C is placed on the blanket that is set at 35°C. The infant will cool and will overshoot. They may overshoot to 34.1°C. When the infant has reached this coolest temperature and has begun to increase their temperature to 34.2°C or 34.3°C, then set the manual control for 34°C. The infant's temperature may rise a little bit before it will begin to decrease again. Allow the infant to cool off and they will likely overshoot the desired 34°C and will get cooled to 33.2°C, when this occurs and the infant starts to warm up to 33.3°C or 33.4°C, then switch the manual control temp to 33.5°C. Then allow the infant to stabilize around this temperature.
7. Operate the Blanketrol 2 cooling unit in the Manual Control Mode during the initiation of cooling. Once the child has reached the desired temperature of 33.5°C and is stable, a switch to servo control on the Blanketrol can be attempted.
8. Adjust the blanket temperature to maintain the goal esophageal temperature of 33.5°C. All management will be based on esophageal temperature. Goal temperature should be obtained as quickly and safely as feasible.

PROCEDURE

2. Preparing the infant prior to cooling:
 - a. **Do NOT turn on radiant warmer**
 - b. Nurse to place a PIV while team sets up for umbilical lines if one not already in place
 - c. MD/NNP to place UAC and UVC

- a. While the team is putting in lines, the nursing staff should start the Blanketrol unit and begin cooling the blanket to 35°C.
- d. Place nasal esophageal probe

**CALCULATION FOR DEPTH OF INSERTION: (patient length in cm divided by 5) + 4.8 cm.
Round up to the nearest whole number and that is the depth when taped at the nose.**

- a. Appropriate placement is in the distal 1/3 of the esophagus.
- b. If two different esophageal probes malfunction, then place a rectal probe. *If a rectal probe is required, assume all instances of 'esophageal probe' refer to 'rectal probe' for the remainder of this protocol.*
- e. Obtain radiograph for line placement.
- f. After the radiograph is obtained, place the infant on the cooling blanket. There can be one 'chux' between infant and the cooling blanket to prevent soiling.

Note: *If lines need to be adjusted, they can be adjusted while the infant is on the cooling blanket.*

3. Place a skin temperature probe on the abdomen of the infant. This probe may need to be repositioned to avoid direct contact with the bed. The SpaceLabs (Phillips) monitor skin probe will be used instead of the radiant warmer skin probe. The radiant warmer must remain turned off during the cooling phase.
4. The distal end of the esophageal probe is placed into the designated outlet on the Blanketrol console.
5. Place cardiorespiratory leads on the infant.
6. Place pre and post ductal pulse oximeter probes on the infant.
7. Document the time when cooling was initiated on the [Neonatal Body Cooling Worksheet](#). This will serve as hour 0. **Cooling will continue for 72 hours.**
8. **Respiratory Care:** All inspired gases will be set at 36°C. DO NOT change this temperature in an attempt to help cool the infant.
9. Reposition the infant every 2-3 hours and assess skin for redness, breakdown, or necrosis.
10. The infant's body must remain in full contact with the Maxi-therm Lite blanket.

MONITORING PROCEDURE

1. **Temperature** 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.

Record measurements:

1. Every 15 minutes for hours 0 - 2
2. Every 30 minutes for hours 2 - 4
3. Every 1 hour for hours 4 - 72

NOTE: *Shivering is common in these infants. Clinical monitoring is necessary to ensure these are not seizures.*

2. Heart Rate/Blood Pressure/Respirations

Set the lower limit of HR monitor to 90 bpm as the HR of the infant being cooled will be in the low 100's or below 100. Heart rates in the 70's will be tolerated as long as the infant has a normal sinus rhythm, stable BP, and adequate oxygen saturations.

Record measurements:

1. Every 15 minutes for hours 0 - 2
2. Every 30 minutes for hours 2 - 4
3. Every 1 hour for hours 4 - 6
4. Every 3 hours for hours 6 – 72

Labs:

LABORATORY EVALUATION SCHEDULE <i>All hours refer to hours post start of cooling, not hours of life</i>						
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		
	Neobili	Neobili		Neobili		Neobili
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				

NURSING GUIDELINES FOR REWARMING

1. Gradually increase the infant's core body temperature by manually increasing the Blanketrol set point by 0.5°C per hour. The final goal temperature is 36.5°C and should take ~ 7 hours to achieve.

DO NOT TURN THE RADIANT WARMER ON UNTIL TEMPERATURE OF 36.5°C IS REACHED

2. During rewarming:
 - e. Record esophageal and skin temperatures every 30 minutes until goal temperature is achieved.
 - f. Record HR, RR, and BP every 2 hours until goal temperature is achieved.
3. Once goal temperature of 36.5°C is achieved:
 - g. Vital signs should be obtained every 3 hours.
 - h. 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** once the goal temperature of 36.5°C is achieved:
 - 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.