UCDAVIS HEALTH | CHILDREN'S HOSPITAL

Treatment of Neonatal Encephalopathy using Therapeutic Whole Body Hypothermia (TH).

BACKGROUND:
Neonatal encephalopathy is a rare (~3 in 1000 live births), clinically defined syndrome of disturbed neurologic function immediately after birth of a term infant. The etiology of neonatal encephalopathy is often unclear, but can be secondary to many causes, including hypoxic-ischemia, infection (meningitis or encephalitis), arterial or venous stroke, or metabolic disorders. Many infants have good neurodevelopmental outcomes with mild neonatal encephalopathy. However moderate and severe encephalopathy are associated with long-term neurodevelopmental problems, including cerebral palsy, developmental delays, epilepsy, and hearing/vision impairment. Large randomized controlled trials have shown that therapeutic hypothermia is an effective treatment for neonatal encephalopathy, particularly those with moderate encephalopathy, and supported by guidelines from the American Academy of Pediatrics (*Pediatrics* 2014; 133:1146).

INDICATIONS:
Eligibility for therapeutic whole-body hypothermia – Must fulfill **ALL THREE criteria** (1+ 2 + 3) anytime within 6 hours of life:

Criteria 1: Gestational Age

- Is infant **≥36** weeks at birth?[1] Yes/No

Criteria 2: Objective Data Criteria (must meet either scenario A or B)

- Did the infant have:
  - A. Yes/No: Acute Perinatal Event: (i.e. Shoulder Dystocia, Uterine Rupture, Cord Prolapse, Abruption, Maternal Cardiac Arrest or profound Hypotension/Hypoxia) with: (needs 1 or more of the following)
    - APGAR ≤ 5 at 10 minutes of life
    - Prolonged resuscitation at birth (e.g. chest compressions and/or positive pressure ventilation for apnea/hypopnea by 10 minutes)
    - Severe acidosis: **pH ≤ 7.1** from cord or patient blood gas within 60 minutes of birth
    - Elevated base **deficit ≥ 12** mmol/L from cord or patient blood gas within 60 minutes of birth
  - B. Yes/ No: NO obvious history of Acute Perinatal Event: (i.e. Shoulder Dystocia, Uterine Rupture, Cord Prolapse, Abruption, Maternal Cardiac Arrest or profound Hypotension/Hypoxia) with: (needs 1 or more of the following)
    - APGAR ≤ 5 at 10 minutes of life
    - Prolonged resuscitation at birth (e.g. chest compressions and/or positive pressure ventilation for apnea/hypopnea by 10 minutes)

- Severe acidosis: **pH ≤ 7.0** from cord or patient blood gas within 60 minutes of birth
- Elevated **base deficit ≥ 16** mmol/L from cord or patient blood gas within 60 minutes of birth

Criteria 3: SARNAT Exam.

- Needs to have 3 or more in Moderate or Severe Category, or with Seizure (or any event concerning for seizure)
- Exam should be performed within the first 1 hour of life, ideally confirmed by attending neonatologist

Table 1.

Clinical Criteria:	Stage:	Normal	Mild	Moderate	Severe
1. Level of consciousness		Normal	Hyperalert/ Irritable	Lethargic/ Obtunded	Stupor/Coma
2. Spontaneous activity		Normal	Normal	Decreased	Absent
3. Muscle tone		Normal	Normal	Hypotonic	Flaccid
4. Posture		Normal	Mild distal flexion	Strong distal flexion	Decerebrate
5. Primitive reflexes	Suck	Normal	Weak	Weak/ uncoordinated	Absent
	Moro	Normal	Exaggerated	Weak/ incomplete	Absent
6. Autonomic function	Pupils	Normal	Dilated	Constricted	Unequal/ Fixed/Dilated
	Heart rate	Normal	Tachycardia	Bradycardia	Variable
	Respirations	Normal	Normal	Periodic breathing	Apnea

Clinical guide:

- For clinical criteria #5 and #6 which have 2-3 items, the highest severity of the items in each category, is the score for that clinical criterion category. For example, if suck is absent (“severe” stage) and Moro is incomplete (“moderate” stage), the “Primitive Reflexes” category is scored as “severe.”

Definitions:

- Mild distal flexion – thumb adduction
- Strong distal flexion – thumb adduction, wrist flexion
- Incomplete Moro – arms abduct, but not followed by adduction
- Decerebrate – extremities in tonic extension
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RELATIVE EXCLUSION CRITERIA:

- IUGR (birth weight less than 1800 grams)
- Severe pulmonary hypertension, hemodynamic compromise, or coagulopathy
- ECMO
- Severe congenital anomalies/syndromes or known metabolic disorders
- Confirmed cerebral venous sinus thrombosis
- Large intracerebral or intraventricular hemorrhage

CLINICAL PATHWAY:

Overview

Inborn infants: If criteria "1" and "2" are met, the baby should be transferred urgently to the NICU (ideally to the Zebra room, which has EEG connectivity). If, in addition, criteria "3" clinical conditions are met, whole body hypothermia (to 33-34ºC for 72h) should be offered/initiated.
Outborn infants: If outborn infants meet criteria "1" and "2", we recommend transfer to UCDMC for further evaluation with initiation of *passive cooling* at the referring hospital and active cooling during transport. If criteria "3" conditions are met by physical examination or seizures before 6 hours of life, active cooling (to 33-34ºC for 72h) at UCDMC should be continued.

Identification of possible patient for cooling

Inborn patients who may meet criteria for therapeutic hypothermia should be identified in L&D or at the time of admission to the NICU. Criteria 1 and 2 and B are useful to confirm *potential* eligibility for cooling. If potential eligibility criteria are met, a full physical examination (including neurological assessment and SARNAT staging) should be carried out and documented. If sufficient category "3" criteria are met (either by examination or clinical spell concerning for a seizure) the baby is eligible for active cooling and the infant's parents should be informed of the diagnosis, its implications, and the potentially beneficial effects of cooling. If the "3" criteria are not fulfilled during the first examination, but the exam is concerning (e.g. 1 or 2 moderate or severe criteria or 3 or more mild criteria) passive cooling can be initiated and serial examinations performed every hour until either the "3" criteria are met or the baby is 6 hours of age. Active cooling should be initiated as soon a serial examination within the first 6 hours of life meet category "3" criteria (or if has a seizure within 6 hours of life).

For outborn infants, the physician accepting transfer should try to complete the checklist (Criteria 1 and 2) with the referring physician. Transport should be initiated for further assessment. The transport team should inform the parents that transport is being initiated for "*further assessment*" not for "*cooling*" as additional investigation (physical examination) will be required on arrival to confirm eligibility for continuing therapeutic cooling.

Passive Cooling

Objective: Passive cooling is initiated to minimize the delay in active cooling for outborn infants. It should only be initiated for infants that are likely to qualify for therapeutic hypothermia based on examination and/or seizures. Passive cooling should be initiated as soon as possible with input from the local physician and the accepting neonatologist.
Eligibility: Outborn infants who meet criteria "1" and "2" in Table 1 above.
Protocol: Passive cooling is achieved by caring for the infant naked (except for diaper) without an external heat source (*i.e.* a radiant warmer that is switched off, or an open crib). Target core temperature is 33-34°C. Rectal temperature should be checked at least every 15 min. If core temperature falls below 33°C an external heat source should be started (i.e. radiant warmer at its lowest setting) and temperature checked at least every 5 minutes. The external heat source

should be adjusted to maintain core temperature 33-34°C. Once the core temperature stabilizes, temperature checks can be reduced to every 15 minutes. Active cooling should be started on arrival of the transport team if possible. Upon arrival at UCDMC, if "3" criteria are met, active cooling should continue. If "3" criteria are not met, cooling can be discontinued.

Active Cooling
Objective: To maintain a stable core temperature between 33-34°C for 72 h.
Eligibility: Infants (outborn and inborn) who meet criteria "1", "2," and "3" in Table 1.
Protocol: The infant should be cared for naked (except for diaper) on a disposable cooling blanket that is covered with a protective fleece. A servo-controlled cooling blanket (*e.g.* Blanketrol III) should be used to maintain core temperature at 33-34°C for 72 h.

Positional changes should be carried out every 2 h. Skin integrity should be checked and documented, every 2 h. If the core temperature changes above or below the target range, this can be managed by modifications in the set temperature of the cooling blanket.

The cooling blanket allows a maximum gradient to be set (the difference between the water temperature and the baby's core temperature). This feature should be switched off during the start of cooling to allow rapid reduction in core temperature to the target core temperature. The maximum gradient can be set to 10°C once the target core temperature is achieved.

Rectal temperature should be monitored continuously during cooling and documented every hour.

DOCUMENTATION:
Use ".HIECOOLINGDECION" smart phrase in EPIC to document findings for Criteria 1, 2, and 3, and subsequent decision to perform TH or not to perform TH.

CONSULT PEDIATRIC NEUROLOGY

- Order a Pediatric Neurology consult in Epic and call pager 5252 on weekdays (07:00 to 19:00) and 5250 on weeknights/ weekends/ holidays.
- Order a routine EEG and continuous EEG monitoring in Epic.
- Of note, Continuous EEG monitoring can only be obtained currently in the ZEBRA patient room

CONTINUOUS EEG MONITORING:

- Hook up to **conventional continuous EEG with video monitoring** for at least 24-48 hours of seizure-freedom, per Pediatric Neurologist's discretion.
- If there are seizures and/or concerning background like burst suppression during the initial recording, plan to continue the EEG through rewarming.
- If continuous EEG hookup is not available, hook up to amplitude-integrated EEG in the meantime.

IMAGING:

- **Head Ultrasound**
  - As soon after admission as reasonable, based on clinical suspicion (to rule out etiologies of neonatal encephalopathy that would necessitate cessation of cooling, *e.g.* cerebral venous sinus thrombosis or severe intracranial hemorrhage)
  - If there are barriers, discuss with Pediatric Neurology to help determine urgency

- **Brain MRI without contrast**
    - As soon as possible **if** focal findings on examination, focal findings on head ultrasound (*e.g.* stroke), or focal seizures
    - After rewarming, between **day of life 5-7 (with DWI, ADC, and spectroscopy)**, to evaluate the severity of possible hypoxemic ischemic encephalopathy and aid in neurodevelopmental prognosis

CLINICAL CONSIDERATIONS DURING COOLING:

Laboratory Investigations

Pre-cooling labs:

- All infants:
    - Blood gas with lytes (for iCa and Hgb)
    - Lactate whole blood (send with gas/lytes)
    - CBC with differential
    - Coagulation panel
    - CMP
    - Blood culture (if not already performed)
- Based on clinical picture:
    - NH_4^+ **if** clinical suspicion of metabolic encephalopathy

Follow-up labs:

- All infants:
    - Blood gas with lytes at least q24 hours (frequency adjusted based on patient acuity)
    - Lactate whole blood at least q24 hours (frequency adjusted based on patient acuity)
    - BMP + bilirubin or CMP q24h
- Based on clinical picture:
    - CBC (+/- diff) **if** presence of anemia or thrombocytopenia or needed transfusion with blood product since last labs
    - Coagulation panel **if** clinical concern of coagulopathy or needed transfusion with FFP, cryoprecipitate, Factor VII since last labs
    - NH_4^+ **if** clinical suspicion of metabolic encephalopathy

Re-warming

- All infants:
    - Blood gas with electrolytes and glucose at 1 hr and 3 hrs after initiating re-warming

Empiric Antibiotics:

- If concerned for meningitis or sepsis, start empiric antibiotics, and consider a lumbar puncture, when medically able.

Feeding:

- In infants that are otherwise clinically stable, trophic feedings of colostrum or maternal breastmilk can be considered at the treatment team's discretion. Buccal swabs with colostrum if not providing trophic feeds.

Holding:

- If an infant is otherwise stable, parental holding with the cooling blanket can be considered by the treatment and nursing team after the first 24 hrs of cooling. If so, the EEG camera should be adjusted to keep the infant on video, while the EEG is

recording. If the infant has had recent seizures, the treatment team should consider deferring until a period of seizure freedom.

ANALGESIA:
Whole body hypothermia is uncomfortable. Morphine should be used as an analgesic during active cooling–load 0.1 mg/kg, followed by 20 mcg/kg/hr.

TREATMENT OF SHIVERING:
Shivering is characterized by high-frequency and low-amplitude movements, which are suppressible by touch. If the movements are not suppressible, the EEG should be evaluated to ensure that these movements are not seizures. Shivering thermogenesis can be minimized by adequate morphine, so the morphine infusion should be uptitrated gradually to decrease shivering.

TREATMENT OF SEIZURES:
Prophylactic antiseizure medications are NOT part of the therapeutic hypothermia protocol. However, clinical or electrographic seizures should be treated with phenobarbital 20 mg/kg urgently. Further seizure management should be discussed with the Pediatric Neurologist, and may include further phenobarbital boluses, levetiracetam bolus, and/or fosphenytoin bolus. In the case of medically-refractory status epilepticus, patients may require a midazolam or pentobarbital infusion. If during the rewarming period seizures emerge, rewarming should be held/delayed. At that time, seizures should be controlled before proceeding with rewarming (likely at a slower rate) per discussion with Pediatric Neurology.

REWARMING PROTOCOL:
After 72h of active cooling, slow gradual rewarming should be carried out using the servo-controlled cooling blanket. To minimize the risk of rapid increases, or wide variations, in core temperature, during rewarming the maximum temperature gradient should be set to 5°C. The target core temperature should be **increased 0.2°C every 30 minutes during rewarming**. Rewarming is expected to take between 7h and 15h.

- If infant core temp is ≥≥2˚ than the Blanketrol set point, NO further increases should be made until the infant is within 0.5˚C.
- If the infant temperature continues to remain below target temperature of 36.5, consult team and discuss the following options
  - Confirm infant has sufficient boundaries, is in flexed fetal position which decreases exposed surface area, and is in maximal contact with blanket
  - Increasing variable gradient from 5 to 8
  - If infant is ≥35.5 ˚C, consider turning on radiant warmer overhead heat to lowest setting, continuing to monitor patient temperature every 30 minutes
  - Consider decreasing sedatives

Once the infant is re-warmed and has a stable temperature for 2 hrs, the infant may be removed from the cooling blanket.

FOLLOW UP:

If the infant was started on maintenance anti-seizure medication, they should be discharged on the same dose, without dose adjustments for weight, to allow for a slow wean over time. If there are questions, contact the Pediatric Neurologist on-call for clarification.
All infants determined to have neonatal encephalopathy are at risk for developmental delays. They should be evaluated for therapies and the Regional Center (for early intervention) to maximize their developmental potential. They should be referred to the High-Risk Infant Clinic, as well as Pediatric Neurology clinic (usually 3 months after discharge, ideally with the Neurologist that saw the infant during their admission).

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