Published in final edited form as:

Clin Perinatol. 2018 June ; 45(2): 241–255. doi:10.1016/j.clp.2018.01.010.

Therapeutic Hypothermia: How Can We Optimize This Therapy to Further Improve Outcomes?

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Synopsis

Neonatal hypoxic-ischemic encephalopathy remains associated with considerable death and disability. In multiple randomized controlled trials, therapeutic hypothermia for neonatal moderate or severe hypoxic-ischemic encephalopathy among term infants has been shown to be safe and effective in reducing death and disability in survivors. In this chapter, the current status of infant and childhood outcomes following this therapy will be reviewed. The clinical approaches that may help to optimize this innovative neuroprotective therapy will be presented.

Keywords

Hypoxic-ischemic encephalopathy; cooling; neonate

Current rates of mortality and disability following hypothermia therapy

Neonatal encephalopathy is a condition of disordered neonatal brain function and is associated with many risk factors. The incidence of neonatal encephalopathy is estimated to be 3.0 per 1,000 live births. Neonatal encephalopathy due to hypoxic-ischemic events is a subset of neonatal encephalopathy and occurs in 1.5 per 1,000 livebirths. About 15% to 20% of affected newborns die in the postnatal period and an additional 25% will sustain childhood disabilities¹. Six randomized clinical trials of induced therapeutic hypothermia

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Disclosures: The authors have no relationship with any commercial company that has a direct financial interest in subject matter or materials discussed in article or with a company making a competing product

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(TH) at 33.0 – 34.0°C for 72 hours for neonatal moderate or severe hypoxic-ischemic encephalopathy (HIE) have demonstrated a decrease in death or disability up to 24 months of age^{2–7}. This neuroprotection continues to childhood^{8–10}. TH is currently the standard of care for term neonates with encephalopathy due to hypoxia-ischemia¹¹. The rate of death or disability in the cooled group ranged from 44–55% in these clinical trials. In the most recent *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) randomized clinical trial of standard cooling at 33.0 – 34.0°C for 72 hours compared to deeper or longer cooling, the rate of death or disability in the usual care group following neonatal moderate or severe HIE was 29%¹². This lower rate may be due to fewer infants with severe HIE in the recent trial (23% compared to 38% in the cooled group of the first NICHD NRN trial³), lower acuity of neonates and earlier initiation of cooling.

How effective is Therapeutic Hypothermia?

TH is an effective therapy to reduce death or disability at 18 months of age after moderate or severe neonatal HIE (typical RR 0.75, 95% CI 0.68 to 0.83)¹¹. TH was also associated with significant reduction in mortality and in disability in survivors¹¹. The number needed to treat (NNT) to prevent one case of death or disability is 7¹¹, much lower than the NNT of adults receiving statins to prevent cardiovascular disease (n=72)¹³, or that of neonates receiving surfactant to prevent complications of respiratory distress syndrome (n=25)¹⁴; thus TH for moderate or severe HIE is a very robust therapy.

Selection of neonates for TH

It is important to select the appropriate neonates for hypothermia therapy; the safety and efficacy of this therapy has been demonstrated only for neonates with moderate or severe HIE^{11,15}. All the clinical trials have had a two-step process of selection, initially with biochemical evidence of hypoxia-ischemia followed by evolving moderate or severe encephalopathy. In the NICHD NRN trials^{3,12}, acidosis was required at birth on cord pH or the first blood gas within 1 hour of age (pH <7.0 or base deficit >16 mmol/L). If a blood gas was not available or pH was between 7.01–7.15, base deficit was between 10 and 15.9 mmol/L, additional criteria were required including a history of an acute perinatal event and either a 10-minute Apgar score ≤ 5 or assisted ventilation initiated at birth and continued for at least 10 minutes. The second parameter was evidence of moderate or severe encephalopathy on the neurological examination.

The neurological examination for moderate or severe encephalopathy

The clinical trials of hypothermia for neonatal HIE have required 3 or more out of 6 abnormalities in the moderate or severe categories of the neurological examination or clinical seizures within 6 hours of age for trial eligibility. The CoolCap and TOBY trials mandated that one of the abnormal categories of the neurological examination needed to be level of consciousness and they both also required an abnormal amplitude integrated electroencephalogram (aEEG)^{2,4}. The NICHD NRN has standardized the examination to minimize examiner variability and promote enrollment of appropriate infants. The exam is

challenging since it is subjective and the one performed within 6 hours of age (the therapeutic window for initiation of cooling) may be influenced by the delivery process and/or maternal anesthesia or analgesia. The examination findings are dynamic and may change based on the neonates' compensatory response to the hypoxic-ischemic insult and the timing and severity of the insult. The most important characteristic is that there can be a mix of findings in the normal or mild as well as moderate or severe encephalopathy stage of the modified Sarnat examination (Table 1). This examination has 6 categories; each category contributes one point. Primitive reflexes (suck and Moro) and autonomic nervous system (pupils, heart rate and respiration) have multiple signs but these contribute only one point; when multiple signs within a category are moderate or severe the higher severity of encephalopathy is noted; i.e. if suck is moderate and Moro is severe, severe encephalopathy is selected for the primitive reflexes category. The neurological examination should be conducted in two phases; the first phase is the observation phase (assessment of spontaneous activity, posture, heart rate and respiration) and the second the active manipulation phase (assessment of level of consciousness, tone, suck, Moro and pupils) where, the least noxious part should be performed first, leaving the pupils for last part of the examination. The infant should be assessed in the awake state and when stimuli are applied to assess activity, the examiner should start with a mild stimulus before proceeding to a more severe one.

The following definitions have been developed for the NICHD NRN examination: under level of consciousness, *lethargic* is delayed but a complete response to external stimuli, while *stupor or coma* is not arousable and non-responsive or a delayed incomplete response to external stimuli. For assessment of spontaneous activity, if the infant is sedated, clinical judgement needs to be used to decide whether the examination is reliable; paralysis of the infant will preclude a meaningful exam. *Posture* under moderate encephalopathy is strong distal flexion, complete extension or a "frog-legged" position; *decerebrate* is legs and arms extended, wrists flexed and hands fisted. If posture is abnormal but does not fit either the moderate or severe category, the infant should be coded as moderate. For assessment of tone, the extremities, neck and trunk should be assessed and the predominant tone should be categorized. Abnormalities may be either an increase or decrease in tone. *Hypotonia* is floppy, either focal or generalized and can be assessed in ventral suspension; *flaccid* resembles a rag doll; in the severe category of hypertonia, *rigid* is stiffness or inflexibility. The *Moro* reflex can be elicited in an intubated infant by gently raising and lowering the head. If the infant has brachial plexus injury or fracture of the clavicle, the other extremity should be assessed. Under autonomic nervous system *bradycardia* is a heart rate <100/min with only occasional increases to >120/min, a *variable* heart rate is not constant and varies widely between <100 and >120/min. It should be noted that the heart rate may be influenced by the phase of cooling and should not be part of the evaluation if cooling has been initiated. *Periodic breathing*, whether associated with desaturations, and with or without supplemental oxygen is categorized as moderate and an intubated infant is categorized as severe encephalopathy since it cannot be ascertained whether the infant could sustain spontaneous respirations without ventilator support. Asymmetric or non-reactive pupils should be coded as severe encephalopathy. The classification as moderate or severe HIE is based on the predominant number of categories that are moderate or severe; if the number of moderate and severe categories are equal, the infant should be assigned the stage of HIE based on level

of consciousness. Clinical seizures can be subtle; the infant may have ocular deviations, sucking, lip smacking, rowing, swimming or bicycling movements. In addition seizures can be tonic/clonic, localized, multifocal or generalized. An infant with clinical seizures (documented by a neonatal nurse clinician or neonatologist) is coded as moderate HIE whether the neurological exam for eligibility is moderate or normal/mild. Increased tone in the neurological examination for eligibility was infrequent but decerebrate posture was noted in the eligibility criteria of the first NICHD NRN trial³.

The additional components of the neurological examination that are added to the assessment of the stage of HIE during serial and discharge assessments are clonus, fisted hand, abnormal movements, gag reflex and asymmetric tonic neck reflex (ATNR). *Clonus* is defined as >4–5 beats, *fisted hand* is the thumb across the palm or cortical thumb, *abnormal movements* are tremulous, excessive movements, either jerky, involuntary, bicycling or myotonic. The *ATNR* is assessed with the infant supine and head rotated to either side. A normal TNR is extension of arm and leg to side to which face is turned with flexion of arm and leg of the opposite side (fencing position). Infant should spontaneously (within 30 seconds) terminate this position. For the NICHD NRN hypothermia trials^{3,12}, the site or trial principal investigator (PI) was the gold standard examiner and reviewed the training slides developed by 2 trial PIs (SS and AL) with all site physicians. Physician examiners at each clinical site performed two examinations with the gold standard examiner, within an hour of each other. Examination findings were reviewed for concordance by the trial PIs (SS and AL); agreement of at least 5 of 6 categories were needed for certification and allow investigators to independently evaluate infants for inclusion in trials. An annual refresher course using training slides was conducted. The NICHD certification process is currently utilized for ongoing BABYBAC II: A Phase II Multi-site study of Autologous Cord Blood Cells for Hypoxic-Ischemic Encephalopathy funded by Duke University and the Robertson Foundation and the Hypothermia for Encephalopathy in Low and Middle-Income Countries (HELIX) trial. The performance of serial examinations, daily during hypothermia therapy and at discharge is important for prognosis; the persistence of severe HIE at 72 hours increased the risk of death or disability at 18 months of age after controlling for treatment group, with an OR (95% CI) of 60 (15–246). An increased risk of death or disability was also associated with abnormal findings in the extended neurological examination OR 2.7 (1.1–6.7). Gavage tube or gastrostomy feedings at discharge also increased risk of death or disability, OR 8.6 (2.7–26.8)¹⁶. Therefore, careful neurological examinations prior to initiation and following TH and at discharge should be part of clinical practice.

Time to initiation of cooling and transport cooling

In both the NICHD NRN and TOBY trials neither time to initiation of cooling nor location of birth (inborn versus outborn) impacted outcome, although enrollment heavily clustered around 3–4 hours^{4,15,17}. However, in the most recent NICHD NRN trial of usual cooling compared to longer and deeper cooling, the mortality and disability rates were lower in the usual care cooled group; time to initiation of cooling was earlier in spite of more out-born infants when compared to the first NICHD NRN trial¹².

The NICHD workshop in 2011 identified targeted temperature management before arrival at a cooling center as a knowledge gap¹⁸. Passive cooling during transport or active cooling without a servo-controlled device are associated with risks of temperature overshoot and rapid fluctuations, with infants with severe HIE being at the greatest risk^{19,20}. Following these reports, studies have shown that active cooling with servo-controlled devices and continuous core temperature monitoring achieve target temperatures in less time, have less variability and greater efficacy in maintaining temperatures within a target range, compared to passive cooling during transport^{21–23}. In situations where transport distances are long, transport cooling with servo-controlled devices and careful temperature monitoring may be important to ensure its initiation within the window of 6 hours.

Delivery room management

A persistently low Apgar score at 10 min is associated with death or moderate/severe disability at 18 months and also at 6–7 years of age^{24,25}. However, not all infants with a 10 min Apgar score ≤ 3 had a uniformly poor outcome; 20% of children with score of 0 at 10 mins survived without disability at school age²⁵.

Optimum duration of cooling

Early discontinuation of cooling due to clinical improvement has been reported in registry data²⁶; this practice should be discouraged as evidence of brain injury has been noted with incomplete cooling following mild encephalopathy²⁷.

Management of elevated temperature

Elevated temperature in the control group of the NICHD NRN and CoolCap trials was associated with higher risk of death or disability compared to non-cooled infants without elevated temperatures after controlling for stage of encephalopathy, race and gender^{28,29}. In the NICHD NRN childhood follow up data, the association with elevated temperature and death or IQ <70 was still present³⁰. Brain temperature measured with magnetic resonance spectroscopy reveals a higher temperature among cooled infants with brain injury on magnetic resonance imaging (MRI) compared to cooled infants without brain injury on MRI³¹. Therefore it is important to avoid and treat elevations of temperature prior to and after TH.

Hemodynamic stability during TH

The link between cerebral ischemia and cardiac dysfunction is unclear but HIE is associated with multiorgan dysfunction including myocardial dysfunction^{15,32}. Cooling may exacerbate blood pressure and temperature instability especially in smaller sicker infants during induction and maintenance of cooling³³; hence the need to provide hemodynamic support during cooling and rewarming³⁴.

Hypocarbica during TH

The cumulative exposure to hypocarbica in the early phase of TH was linked with a higher risk of death or disability at 18 months of age in the NICHD NRN first randomized controlled trial³⁵. The CoolCap data noted that PCO₂ during the 72 hours of TH was inversely related to an unfavorable outcome after adjustment for HIE severity and other confounding variables³⁶. Low carbon dioxide levels may impact cerebral perfusion thus exacerbating risk of brain injury. Thus, it is essential to maintain PCO₂ in the normal range during TH. This may be challenging if an infant is hyperventilating from metabolic acidosis or the hyperventilation is centrally driven due to possible brainstem dysfunction.

Hyperoxemia during TH

In an evaluation of infants with birth acidosis, hyperoxemia during the first hour of life was associated with a higher incidence of encephalopathy and among infants with HIE who had a brain MRI, there was a higher incidence of brain injury³⁷. An association between an increased inspired oxygen concentration during the first 6 hours of life and an adverse outcome (death or Bayley II Mental Developmental Index or Psychomotor Index <70) was noted in another study, although no association was found between hypocarbica and adverse outcome³⁸. Neonates are susceptible to an increase in free radical production and oxidative stress immediately after birth. Therefore, hyperoxemia should be avoided in high-risk infants during TH.

Hypoglycemia and Hyperglycemia during TH

In a single center study conducted between 1994 and 2010, 15 of 94 (16%) of neonates with neonatal encephalopathy and early brain imaging studies had hypoglycemia (glucose values <46 mg/dl) in the first 24 hours after birth. TH was provided for 10 infants in the no-hypoglycemia group (n=79) and one infant in the hypoglycemia group. Among all infants, hypoglycemia was associated with an increased risk of corticospinal tract injury on brain MRI imaging and lower Bayley II psychomotor developmental and mental developmental indices, or Bayley III cognitive and language scores at one year of age, after adjusting for perinatal distress and need for resuscitation.³⁹ The CoolCap study examined the association of hypoglycemia (<40 mg/dl) and hyperglycemia (>150 mg/dl) among trial participants and outcome⁴⁰. Among 234 infants enrolled, 121 had abnormal plasma glucose values within the first 12 hours and an unfavorable outcome was noted among 160 infants. Death or neurodevelopmental disability at 18 months of age was more common among infants with hypoglycemia (81%), hyperglycemia (67%) or any glucose derangement (67%) during the first 12 hours, compared with 48% among normoglycemic infants, after controlling for stage of encephalopathy, birthweight, Apgar score, pH and intervention. The impact on death or disability separately are not presented. The authors suggested that the data confirm pathophysiological observations of deranged glucose metabolism in the preclinical models of hypoxia-ischemia. Maintaining glucose levels in the normal range should be the goal during TH for neonatal HIE.

Seizures during TH

In the NICHD NRN randomized controlled trial, 127 of 208 neonates had clinical seizures at <6 hours of age. In the univariate analysis, death or disability at 18 months of age was associated with seizures and severe HIE; on multivariate analysis, seizures no longer had an independent effect on outcome.⁴¹ It should be noted that clinical seizures may not always represent electrographic seizures and instead may be abnormal movements. In another study in 47 neonates with HIE who underwent continuous electroencephalography, 62% had electrographic seizures⁴². Seizures per se were not associated with abnormal outcome but the risk of abnormal outcome at 24–48 months of age increased over nine fold if the total seizure burden was more than 40 minutes or maximum hourly seizure burden was more than 13 minutes per hour⁴². TH decreases seizure burden, as noted on electroencephalography⁴³. The administration of phenobarbital prior to initiation of TH may cause lower temperatures during the induction phase of cooling⁴⁴. During TH, continuous video EEG monitoring and treatment of clinical seizures confirmed by EEG or amplitude integrated EEG should be considered, although definitive data justifying treatment of electrographic seizures are lacking.

Cerebral functioning monitoring at <6 hours of age

Both the CoolCap and TOBY trials had an abnormal aEEG as an eligibility criterion, in addition to birth acidosis or need for resuscitation and moderate or severe encephalopathy^{2,4}. Death or disability was lower among infants who had a less severely abnormal background aEEG pattern and an absence of seizures on the aEEG was associated with a better outcome in the CoolCap trial². The effect of cooling did not vary according to the severity of the abnormality on the aEEG²⁹. In an observational study comparing cooled infants to a prior non-cooled cohort, the positive predictive value of an abnormal aEEG at 3–6 hours of age was 84% for infants not cooled and lower (59%) in cooled infants⁴⁵. The recovery to normal of the background pattern of the aEEG was the best predictor of outcome; infants with good outcome normalized by 24 hours if they were not cooled and in 48 hours if undergoing TH. The NICHD NRN aEEG study, which included infants from the first NRN TH trial as well as those following the trial, demonstrated that severe HIE and an abnormal aEEG pattern < 9 hours of age were related to poor outcome in the univariate analysis. Severe HIE alone persisted as a predictor in the multivariate analysis and the addition of the aEEG to HIE stage did not add to the predictive value (AUC increased from 0.72 to 0.75)⁴⁶. The TOBY trial noted that the positive predictive values of a severely abnormal aEEG assessed by voltage and pattern prior to study intervention for an adverse outcome at 18 months of age were 0.63 and 0.59 respectively in the non-cooled infants and 0.55 and 0.51 in the cooled infants with the lower effect in cooled infants related to the neuroprotective effect of cooling⁴⁷. The positive predictive value of an abnormal aEEG for abnormal outcome in the NICHD NRN study was 0.56, while that of severe HIE by exam was 0.81 and moderate HIE by exam was 0.32; thus, the predictive value of the aEEG to identify infants who will subsequently manifest brain injury is limited.

Use of sedation-analgesia during TH

The administration of sedation, analgesia and neuromuscular blockade during TH for neonatal HIE is determined by center and clinician preferences and may be a surrogate of the severity of illness. Of the neonatal trials of TH, only the Neo-nEURO study treated all infants with morphine (0.1 mg/kg) or an equivalent dose of fentanyl every four hours or by continuous infusion⁵. In the TOBY trial, all infants underwent sedation with morphine infusions or with chloral hydrate if they “appeared to be distressed”⁴. In multiple studies in animals, adults and older children, mild to moderate TH has been shown to decrease the systemic clearance of cytochrome P450 metabolized drugs between approximately 7% and 22% per °C below 37°C⁴⁸. In a small study in neonates, serum morphine concentrations at 6, 12, 24, 48 and 72 hours after birth was higher and clearance lower in infants who underwent TH, compared to normothermia, at similar morphine infusion rates and cumulative doses⁴⁹. In addition, sedation, analgesia and neuromuscular blockade used during TH may affect the neurologic examinations, seizure detection and the results of electroencephalograms, duration of mechanical ventilation and hemodynamic status. The effects of sedation, analgesia and neuromuscular blockade on long-term neuro-development are unclear. There is insufficient evidence for routine use of these agents during TH and, therefore, careful use to achieve a desired level of sedation seems prudent^{50,51}.

Assessment of serum biomarkers

The assessment of the utility of serum biomarkers in HIE is an area of active research. Two markers, ubiquitin carboxyl-terminal esterase L1 (UCHL1), known to be released from neurons following cardiac arrest and glial fibrillary acidic protein (GFAP), released from astrocytes following possible hypoxia during extracorporeal oxygenation were measured in neonates with HIE undergoing cooling. The markers were elevated at differing time points; infants with brain injury on MRI had higher UCHL1 at initiation and end of cooling, while GFAP was higher at 24 and 72 hours⁵². In another observational study elevated GFAP and inflammatory cytokines were associated with an abnormal neurological outcomes at 15–18 months⁵³. Elevated cardiac troponin 1 levels have been noted to be correlated with reduced fractional shortening and severity of tricuspid regurgitation on echocardiogram and also with risk of poor neurodevelopmental outcome at 18 months in an observational study⁵⁴. Another observational study provided the cut-off values (<0.22 ng/ml for normothermic and < 0.15 ng/ml for hypothermic infants) of cardiac troponin 1 at <24 hours of age that were predictive of good outcome in infancy⁵⁵.

Heart rate variability

Monitoring of heart rate variability is a useful adjunct tool to assess severity of HIE in infants undergoing TH⁵⁶. Depressed heart rate variability (the normalized RR interval also known as the NN interval) correlates well with the EEG and neurodevelopmental outcome; a lower NN value is seen with more severe EEG grade of HIE and with abnormal neurodevelopmental outcome at 2 years^{57,58}.

Neuroimaging for neonates undergoing Therapeutic Hypothermia

The MRI findings among 131 of 325 infants who participated in the TOBY trial, performed at a mean age of 8 days, demonstrated that TH reduced injury in the basal ganglia and thalamus (BGT), OR (95% CI) 0.36 (0.15–0.84), the posterior limb of the internal capsule (PLIC), 0.38 (0.17–0.85) and white matter (WM), 0.30 (0.12–0.77) among cooled infants compared to the non-cooled group. There was no reduction of signal abnormalities in the cortex. Cooled infants were more likely to have normal scans and the brain injury on the scans were predictive of death or disability at 18 months in both cooled and non-cooled infants⁵⁹. The NICHD NRN trial evaluated 136 of 208 trial participants at a mean age of 15 days. Normal scans were noted in 38 of 73 infants (52%) in the hypothermia group and 22 of 63 (35%) in the control group ($p=0.06$). Infants in the hypothermia group had fewer areas of infarction (12%) compared to the control group (22%) ($p=0.02$). A brain injury pattern was described with each level reflecting greater involvement of injury; 0 normal, 1A minimal cerebral lesions only and no involvement of the BGT, or anterior limb of the internal capsule (ALIC) or PLIC and no area of watershed (WS) infarction, 1B, more extensive cerebral lesions without BGT, ALIC, PLIC or WS involvement, 2A, any BGT, ALIC, PLIC or WS involvement without any other cerebral lesions, 2B involvement of either BGT, ALIC, PLIC or infarction and additional cerebral lesions and 3, cerebral hemispheric devastation. This categorization of injury correlated with the outcome of death or disability and with disability among survivors at 18 months in both cooled and control groups⁶⁰. Infants with perinatal sentinel events had more BGT lesions on MRI imaging but similar neurodevelopmental outcomes at 18 months than infants without perinatal sentinel events. Outcomes correlated with neonatal MRI findings⁶¹. The neonatal MRI imaging categorization of brain injury was also a marker of childhood outcomes following the NICHD NRN trial of hypothermia for neonatal HIE. Death or IQ <70 was seen in 4 of 50 (8%) of children with pattern 0, 1 of 6 (17%) with 1A, 1 of 4 (25%) with 1B, 3 of 8 (38%) with 2A, 32 of 49 (65%) with 2B and 7 of 7 (100%) with pattern 3; ($p<0.001$). This association was seen within hypothermia and control subgroups⁶². The ICE trial evaluated MRIs from 127 of 221 trial participants obtained at mean age of 6 days. On the T1- and T2-weighted imaging, in the hypothermia group compared to the normothermia group, WM abnormalities [OR 0.28, 95% CI 0.09–.82] as well as gray matter [0.41 (0.17–1.00)] abnormalities were reduced. Abnormal MRI predicted adverse outcome, with diffusion weighted abnormalities in the BGT and PLIC having the most predictive value⁶³. The American College of Obstetrics and Gynecology and the American Academy of Pediatrics have suggested an “early” MRI between 24 and 96 hours to delineate timing of perinatal cerebral injury (to distinguish injury occurring peri-partum and remote from delivery) while one obtained at 10 days (between 7 and 21 days) would delineate the full extent of cerebral injury.⁶⁴

Withdrawal of support or decision to redirect care in the NICU following TH

The mortality rate of neonates undergoing TH for moderate severe HIE in the first NICHD NRN³ trial was 19% in the cooled arm (72 hrs at 33.5°C), while the mortality rate in the trial comparing usual depth and duration with longer and deeper cooling was 8 of 92 (9%) in the 33.5°C for 72 hours group¹². Withdrawal of support occurred among 12 of 24 infants who

died in the hypothermia group in the first NRN trial³, and in the Optimizing Cooling strategies trial, among the infants assigned to usual care of cooling for 72 hours at 33.5°C support was withdrawn for 6 of 8 infants who died¹². A single center study described characteristics of death in the NICU among neonates with moderate or severe encephalopathy receiving TH and observed that 31 of 229 infants died in a 7 year period and all deaths followed withdrawal of support or redirection of care; for 19 infants support was withdrawn during TH. Twenty eight of the infants had severe encephalopathy on examination, 87% had severely abnormal EEG and the 13 who had MRIs performed had moderate or severe brain injury⁶⁵. Available data suggest that persistence of severe encephalopathy on serial neurological examinations, lack of improvement in the abnormal background in the aEEG and EEG and MRI evidence of severe injury may be useful to identify infants at highest risk of severe neurologic sequelae^{16,66}.

Follow-up of infants who receive TH

The major RCTs of TH for neonatal moderate/severe HIE have all reported outcome at 18 or 24 months.^{2–7} The 6–7 year outcome of the CoolCap trial was assessed by parent interview with the WeeFIM, a pediatric functional independence measure, among 62 of 135 surviving children; disability rates at 18 months were strongly associated with WeeFIM ratings in childhood and there was no significant effect of treatment⁸. The NICHD NRN trial evaluated 91% of trial participants at 6–7 years of age. The primary outcome was death or IQ <70, while secondary outcomes focused on disabilities. The primary outcome occurred among 46 of 97 (47%) children in the hypothermia group and 58 of 93 (62%) children in the control group, adjusted risk ratio 0.78 (0.61–1.01); the mortality rates and death or cerebral palsy (CP) were significantly lower in the hypothermia group. The 18 month outcome correlated well with outcome in childhood⁹. The primary outcome of the TOBY trial was survival with IQ >85; data was available for 85% of children; 75 of 145 (52%) in the hypothermia group compared to 52 of 132 (39%) in the control group had this outcome, RR 1.31 (1.01–1.71). Children in the hypothermia group had significantly lower rates of CP and moderate or severe disability compared to the control group¹⁰. It is imperative that neonates who have undergone TH be evaluated for neuromotor and cognitive disabilities following NICU discharge in a standardized follow-up program.

The extent of neuromotor, cognitive, growth and functional deficits was examined in the outcomes of children in NICHD NRN trial since it has been noted in the past that the primary deficits after neonatal HIE was CP. One of the findings was the extent of growth failure among children with severe CP. Compared to those with no CP, those with CP had parameters less than the 10th percentile in weight (57 vs. 3%), height (70 vs. 2%) and head circumference (82 vs. 13%); the growth failure severity increased with increasing age. Gastrostomy feeds were associated with better growth. These findings emphasize the need for early nutritional supplements for children who develop CP following neonatal HIE⁶⁷.

The functional status of the children was evaluated by parental report in another study from the NICHD NRN hypothermia trial cohort⁶⁸. Children with disability, compared to those without disability, had higher rates of severe HIE, public insurance, and Impact on Family Scales and lower mean Functional Status-II (FS II) independence and general health scores.

The FS-II scores were associated with childhood disability. Each unit increase in the FS-II Independence score at 18 months was associated with reduction in disability at 6–7 years of age, highlighting the need to make early referrals for special education services for the child and support services for parents.

The trajectory of cognitive outcomes to childhood noted that subnormal IQ was identified in more than 25% of the children at 6–7 years of age, almost all surviving children with CP (96%) had an IQ <70, 9% of children without CP had an IQ <70, and 31% had an IQ of 70–84. Children with a mental developmental index <70 at 18 months, had, on average an adjusted IQ that was 42 points lower than those with a score >85. However, among the children with an IQ <70 who underwent formal testing, 23% had a normal gait, 16% had normal complex motor function and 10 % had intact fine motor and coordination skills. Twenty percent of children with normal IQ and 28% of those with IQ of 70–84 received special education support services and were held back 1 grade level in school. These findings emphasize cognitive impairment remains a concern for all children with neonatal HIE⁶⁹.

Summary

Based on the evidence presented, to optimize TH for neonatal HIE, cooling should be limited to infants with moderate or severe encephalopathy by following the eligibility criteria of the clinical trials. A careful neurological examination for eligibility should be performed after the infant has been resuscitated and stabilized after birth. Serial neurological examinations should be performed during TH and at discharge to assess prognosis. During TH, avoid hypocarbia and hypoxemia and hyperoxemia and maintain blood sugar in the normal range. Sedation and analgesia should be used with caution. Avoid elevated temperatures prior to initiation of cooling and following rewarming. Imaging studies (MRI) should be performed at 7–10 days of age. Neonates should have neurophysiological monitoring with aEEG and continuous EEG, if available. Standardized follow up should be performed on all cooled infants with a focus on optimizing nutritional status of children with CP and referrals to early intervention programs for infants at risk for later disabilities or those with limited access to health care.

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Key Points

- Therapeutic hypothermia to 33°–34°C for moderate to severe hypoxic-ischemic encephalopathy has been demonstrated to be safe and efficacious in reducing death and disability.
- In addition to biochemical criteria, evidence of moderate or severe encephalopathy on neurological examination is a prerequisite to cooling; serial examinations have prognostic utility.
- Avoidance of hypocarbia, hyperoxia and glucose derangements and detection and control of seizures during cooling are important to optimize outcomes in neonatal encephalopathy.

Table 1

Components of Neurological examination for categorization as moderate or severe HIE

CATEGORY	MODERATE HIE	SEVERE HIE
Level of consciousness	Lethargic	Stupor/coma
Spontaneous activity	Decreased activity	No activity
Posture	Distal flexion, complete extension	Decerebrate
Tone	a. Hypotonia, focal or general b. Hypertonia	a. Flaccid, b. Rigid
Primitive Reflexes		
Suck	Weak or has bite	Absent
Moro	Incomplete	Absent
Autonomic Nervous System		
Pupils	Constricted	Deviation/dilated/non-reactive to light
Heart rate	Bradycardia	Variable HR
Respirations	Periodic Breathing	On ventilator a) with or b) without spontaneous breaths