Hypothermia and Other Treatment Options for Neonatal Encephalopathy: An Executive Summary of the Eunice Kennedy Shriver NICHD Workshop

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Pathophysiological Basis for Therapeutic Strategies

Our current therapeutic approach to treating neonatal encephalopathy is based on understanding the evolution of neuronal damage after hypoxic ischemic injury.9-11 The pathway of cerebral injury in term infants with HIE is not always clear. Many factors, including etiology, extent of hypoxia or ischemia, maturational stage of the brain, regional cerebral blood flow, and general health before the injury, can affect the pattern and extent of brain injury, as well as the outcome after injury.11 Nevertheless, animal models have contributed to improved understanding of the pathophysiology of HIE. The initial insult produces immediate cell loss of varying degrees and, more significantly, leads to delayed impairment in energy metabolism along with apoptotic cell death. This pathophysiological mechanism provides the basis for hypothermia therapy. However, brain injury is known to continue to evolve for weeks or even months after the initial injury, due in large part to the activation of inflammatory systems and initiation of repair processes.12,13 Understanding the later phases of injury in more detail can aid the development of new treatments to enhance brain repair and recovery after HIE.

A review of animal studies found that brain cooling to approximately 32-34°C starting within 5.5 hours after hypoxic ischemic injury and continuing for 12-72 hours reduced secondary energy failure and cell death and was associated with neuropathological and functional improvements.14 Working from these data, researchers designed human trials in which cooling was initiated as early as feasible after the brain injury but always within 6 hours of the injury. Rectal/esophageal temperature was reduced to between 32° and 34°C for effective brain cooling with whole-body hypothermia. Smaller reductions in rectal temperature (34-35°C) were considered necessary for head cooling. Cooling was continued for approximately 48-72 hours. Although optimal methods for rewarming have not been tested in newborn animals, adult animal studies have indicated that slow rewarming is preferable.15,16

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*A list of Eunice Kennedy Shriver National Institute of Child Health and Human Development Hypothermia Workshop speakers and moderators is available at www.jpeds.com (Appendix).

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Clinical Trials of Hypothermic Neural Rescue

Clinical trials of hypothermic neural rescue have shown remarkably similar results using a core temperature of 33.5-34.5°C for 72 hours, starting within 6 hours of birth. Although some trials have used preferential head cooling, whereas others have used whole-body cooling, all trials controlled the therapy using temperature monitoring. In all trials, both the degree of cooling and core temperature were monitored continuously.

The CoolCap, NICHD, TOBY, neo.nEURO.network, China Study Group, and ICE trials all showed either an overall benefit of cooling for HIE or benefits within subgroups. All of these trials were powered to detect a difference in the primary composite outcome of death and/or disability. Meta-analysis of the first 3 trials showed that therapeutic hypothermia reduced death or disability at 18 months with a risk ratio of 0.81 (95% CI, 0.71-0.93) and a number needed to treat of 9. Some smaller studies have reported data consistent with the large pragmatic trials. Preliminary data from the CoolCap Trial indicate that favorable outcome in survivors of HIE at age 18 months is highly associated with favorable functional outcome at age 7-8 years. The NICHD Whole-Body Cooling Trial found that the beneficial effects of hypothermia for neonatal HIE noted at 18 months persist into childhood. Safety data for adverse events, such as arrhythmias, bleeding, skin effects due to cooling, hypotension, persistent pulmonary hypertension, and infection, are reassuring. The American Academy of Pediatrics published a commentary in 2006 after publication of the first 2 trials. The American Heart Association recommends induced therapeutic hypothermia as postresuscitation care for infants meeting the criteria used in published clinical trials. In the United Kingdom, the National Institute for Health and Clinical Excellence developed an interventional procedure guideline specifying the use of hypothermia as a normal treatment in the National Health Service, and the British Association of Perinatal Medicine has published guidelines to help neonatal units and networks standardize hypothermia therapy. Hypothermic neural rescue is now widely practiced in high-resource settings.

Further Research into Hypothermic Neural Rescue

Despite the strong evidence of benefits from multiple large, well-controlled studies, many gaps in knowledge remain. Cooling was intended as a treatment for HIE, but neonatal encephalopathy may have diverse etiologies (besides hypoxia and ischemia) despite a consistent clinical presentation. In infants with recognized HIE, the precise timing, nature, and severity of the hypoxic-ischemic insult is seldom certain. The infant’s maturity, nutritional and hormonal status, inflammatory, and preexisting developmental abnormalities may alter the responses to acute insults. Further work is needed to determine the optimal application of hypothermia for different clinical conditions.

The high level of consistency among the large, randomized trials means that this could be addressed in part by individual patient meta-analyses using the patient populations studied in these large randomized trials. Such analyses could identify the response rates to variations in patient characteristics (eg, age, race, ethnicity, sex, Apgar scores, maternal medications) or treatment (eg, timing of initiation of hypothermia, degree and duration of cooling, adjunct therapies). Additional questions that might be addressed include factors affecting responses to hypothermia, the role of infection, the nature of the insult (eg, sentinel event, unprovoked signs of fetal distress, prelabor events, prenatal events) as predictive of outcomes. The panel noted that an individual patient meta-analysis would provide an opportunity to address these important clinical questions.

Other potential clinical issues related to therapeutic hypothermia include the influence of obstetric factors, such as maternal history (eg, previous losses, stillbirth, coagulopathy, infection), race/ethnicity, age, genetic background, folate deficiency, and vitamin D deficiency, which may affect encephalopathy, as well as the infant’s response interventions. The panel noted the need for multidisciplinary collaboration to address these questions.

Recent studies have suggested that hypothermia significantly reduces the predictive value of both clinical neurologic examination findings and electroencephalography (EEG) recordings. The addition of amplitude-integrated EEG (aEEG) at <9 hours of age resulted in a nonsignificant increase in the predictive value of stage of HIE at random assignment at <6 hours of age, from 0.72 (95% CI, 0.64-0.80) to 0.75 (95% CI, 0.66-0.83). In contrast, the prognostic value of postcooling magnetic resonance imaging (MRI) appears to be unaffected by hypothermia. Thus, prospectively generated hypotheses regarding resuscitation variables, aEEG recordings, full EEG recording, seizure identification and treatment, concurrent care practices, and management of infants before active cooling could enrich the value of future trials. Similarly, the utility of continuously monitoring EEG activity during treatment, and of obtaining EEG and MRI studies before discharge and at specific times during follow-up for prognostic evaluation, remains to be evaluated. Assessment of interventional variables, such as targeted temperature management, sedation practices, and concurrent medications, could provide insight into the optimal management of infants with HIE. Investigation of the role of sedation and pain management in infants with brain injury is also desperately needed.

The appropriate management of patients eligible for therapeutic hypothermia at referring hospitals and during transport to treatment centers, as well as management in level III and IV neonatal intensive care units before the initiation of hypothermia, is controversial and is in need of evidence-based studies. If the healthcare team at a referring hospital decides to initiate hypothermic therapy before and during transport, then care must be taken to avoid overcooling.
Safety in particular must be documented if hypothermia is to be used during transport. Furthermore, there is a need for a device that can reproducibly target temperature appropriately. Whether medical management during cooling therapy affects outcomes is unclear. Cotherapies, including fluid management, nutrition, electrolyte and glucose management, ventilator strategies, and management of pH, partial pressures of O2 and CO2, and concurrent medications, particularly anticonvulsants (whose hepatic clearance is reduced by cooling therapy), are all areas requiring further research.

Because the overall timing, depth, and duration of hypothermia strategies used in all major trials of therapeutic hypothermia reported to date have been remarkably similar, the relative benefits of variation in the administration of hypothermia cannot be estimated from the available data. Thus, temperature selection, duration of cooling, rewarming techniques, and temperature management were discussed as continued knowledge gaps in the area to optimize hypothermia therapy. The ideal temperature for cooling remains unclear. The cost/benefit of incremental studies of any selective modification of parameters for hypothermia therapies requiring many years with large clinical trials was raised as a controversy.

The spectrum of the potential window or windows for opportunities needs to be broadened beyond the 6-hour window after birth. Trials are underway to evaluate the safety and effectiveness of cooling started after 6 hours of age. Some recent studies have included a significant portion of infants (13% and 18%) cooled beyond the 6-hour window in randomized trials, and limited data support the potential benefits of such delayed cooling.

Because HIE is common in resource-limited countries, some have proposed that designing studies in such settings may be of benefit to all, including host countries. There are several reasons why the safety and efficacy data on therapeutic hypothermia from completed trials from high-income countries cannot be extrapolated to neonatal units in low- and middle-income countries.

In low-resource countries, brain injury may occur at long intervals before birth due to multiple antenatal insults (eg, maternal malnutrition and other comorbidities), delayed hospital admissions in obstructed labor, long delays in performing emergency cesarean section delivery, and lack of effective networks for neonatal transport. It is possible that the therapeutic window for hypothermia might have passed by the time of birth or before hypothermia therapy can be started.

The incidence and profile of perinatal infections differ in this population. Cooling in the presence of infection might be deleterious, because hypothermia may impair innate immune function, including neutrophil migration and function. Hypothermia during sepsis in adult patients has been associated with increased mortality, higher circulating levels of tumor necrosis factor α and interleukin-6, prolonged nuclear factor-κB activation, and altered cytokine gene expression. Hypothermia for head injury in adults increases the risk of pneumonia. These factors may explain the higher morbidity and mortality associated with hypothermia in some clinical settings, and emphasize the need for careful monitoring of infection and mortality in cooled infants. In addition, convincing experimental and epidemiologic evidence suggests that the “dual hit” of combined infection and ischemia results in more severe brain injury and increased risk of cerebral palsy. Whether or not therapeutic hypothermia would be neuroprotective in such situations is not known.

Cooling may be unsafe in the presence of meconium aspiration and pulmonary hypertension, because facilities for advanced multiorgan support might not be available in neonatal units in low-and middle-income countries. The cooling equipment used in high-income countries is expensive, requires maintenance, and has recurring costs. Costs and benefits should be weighed in low-resource settings. Many “low-tech” cooling methods, such as ice or frozen gel packs, are labor-intensive and may result in marked temperature fluctuations and shivering, with a potential loss of neuroprotective efficacy. Thus, rigorous and carefully conducted randomized controlled trials of therapeutic hypothermia are important in regions with adequate facilities and health care infrastructure to determine whether hypothermia is safe and effective for infants with encephalopathy with different risk factors in low- to moderate-resource settings.

It should be emphasized that potential prevention of HIE, as well as access to obstetric and neonatal care including resuscitation, are needed before institution of therapy for encephalopathy.

### Clinical Trials of Adjuvant Therapies

Data from animal models of asphyxia suggest that neurologic outcome after HIE can be improved by adding adjuvant therapies to hypothermia, beginning in the hours to days after the insult. Thus, a high priority is the development of sufficient experimental knowledge to warrant assessment of these promising neuroprotective agents in clinical trials. Phase 1-2 studies using biomarker outcomes and involving small numbers of infants are essential to assess safety and potential efficacy before new treatments are taken to pragmatic trials. Promising neuroprotective agents include antiepileptic drugs, erythropoietin, melatonin, and xenon. Phase 1-2 trials of xenon and erythropoietin are already planned or underway.

Further characterization of the evolution of injury and healing over a time course of days to weeks after the insult is needed to provide essential background information for developing potential therapies for later intervention for HIE. Therapies directed at minimizing ongoing injury as well as improving the healing and repair process are vital to further improve outcomes of infants with HIE. Potential candidate therapies for use in the days to weeks after injury include erythropoietin, stem cells, and cell-based therapies that may facilitate tissue repair and regeneration after an insult. Speculatively, N-acetylcysteine, vitamin D,
antiepileptic drugs, and antioxidants might be of value, although at present evidence for this is lacking.

**Biomarkers**

Biomarkers have been essential to research in HIE. The original finding of delayed brain injury in the human infant after an asphyxial event was discovered using phosphorus magnetic resonance spectroscopy (MRS). This technique was subsequently used as the prototypical bridging biomarker of HIE to evaluate the therapeutic effect of hypothermia in early animal studies. Phosphorus MRS is cumbersome and not widely available; however, MRS biomarkers, such as proton spectroscopy and diffusion tensor imaging, have been developed and are now in use in phase 2 clinical trials, allowing adjuvant treatment to be assessed quickly and efficiently, potentially allowing phase 3 pragmatic trials to be targeted to treatments with a high likelihood of success. Given the high cost of large randomized trials and longer-term follow-up of children, these biomarker-led studies will be increasingly important in the triage of therapies before large trials.

There is a continuing need to develop a range of simple biomarkers that detect disease and treatment response to investigate specific neuroprotective therapies. Additional bridging biomarkers that identify later phases of injury and repair or differentiate the severity of disease are especially needed, and a valid surrogate, such as serum biomarkers, would be particularly valuable. New proteomic and metabolomic technologies merit further investigation.

Bedside biomarkers that define the stage, progression, and improvement of encephalopathy would be valuable. Biomarkers reported in clinical trials to date include lactate, MRS, MRI, and aEEG. An elevated urinary lactate-to-creatinine ratio has been associated with adverse outcome in infants with HIE. aEEG was found to be useful for documenting seizures as well as abnormal patterns in some studies, but not in others. In 2 studies, infants with hypothermia only and infants with both normothermia and hypothermia underwent continuous aEEG recording before, during, and after hypothermia therapy. The aEEG pattern within 6 hours of age had lost its predictive power. The time it took for the background aEEG to normalize had a positive predictive value of 94% in the infants with hypothermia.

The value of MRI in predicting neurodevelopmental outcome for infants with HIE has been reported. In a nested substudy of the infants in the TOBY trial, the predictive value of scoring the MRI images was equally good in infants with normothermia and those with hypothermia, with positive predictive values for poor outcome of 84% and 85%, respectively. In a study evaluating the NICHD trial participants using neonatal MRI evidence of brain injury, a comprehensive classification of MRI findings was correlated with death and disability at 18 months. A recent study of 125 cooled infants with HIE found that Pourcelot’s resistance index, obtained from Doppler ultrasound measurements on an intracerebral artery, was a poor predictor; the positive predictive value for poor outcome with a resistance index of <0.55 was only 60% in cooled infants, compared with 84% in normothermic infants. When examining predictors in infants treated for hypothermia, it is important to assess whether old predictors are valid with new thresholds. The value of MRI has been reviewed in 2 publications.

In summary, few of the biomarkers reported to date have been qualified. Thus, MRI remains the leading qualified biomarker at present. The development of additional biomarkers is warranted.

**Implementation Issues for HIE Therapy**

The workshop participants suggested a framework for hospitals as well as practicing clinicians in which therapeutic hypothermia is available. Therapeutic hypothermia can be offered for infants who meet the criteria of published trials provided that the infrastructure and trained personnel to perform hypothermia are in place. Eligibility criteria include a pH of ≤7.0 or a base deficit of ≥16 mmol/L in a sample of umbilical cord blood or any blood obtained during the first hour after birth. If blood gas data are not available, then additional criteria are required. These include an acute perinatal event and either a 10-minute Apgar score of ≤5 or assisted ventilation initiated at birth and continued for at least 10 minutes. Neurologic examination demonstrating moderate to severe encephalopathy and, in some trials, an EEG with specific findings are required. Infants offered therapeutic hypothermia should meet previously studied inclusion criteria. Efficacy data are lacking for preterm infants; further safety concerns may increase the risk in this population, which is already at risk for temperature instability. Infants not meeting the inclusion criteria for previously published clinical trials, including infants <36 weeks gestation, those presenting outside of the previously studied 6-hour window, and those with encephalopathy not attributable to HIE, remain in the unstudied realm for cooling therapy.

Management at referral hospitals and during transport was also reviewed. Targeted temperature management with avoidance of hyperthermia was emphasized from a safety perspective. In the CoolCap and NICHD trials, hyperthermia was strongly associated with worse outcomes compared with normothermia; thus, particular attention should be paid to fever and/or heating. The literature contains some evidence, based on case series, supporting mild hypothermia before arrival at a center for cooling, but concerns remain regarding the potential for temperature overshoot, rapid fluctuations in temperature, and excessive cooling during transport. In a recently published case series, one-third of the infants had a temperature <32°C. A more recent report described the cooling of 9 infants during transport using the CritiCool, a servo-controlled cooling device. When cooling is started at a referral hospital, assessment of encephalopathy by trained staff (either local staff or transport staff), and safe and accurate therapy during transport, are crucial. This requires the ability to perform continuous
temperature monitoring, as well as to intervene to adjust the

For hospitals that perform therapeutic hypothermia, training programs and infrastructure need to be established and maintained in a highly organized and reproducible manner to ensure patient safety. Hospitals offering hypothermia should be capable of providing comprehensive intensive

temperature to maintain it within the target range during transport. Unfortunately, there currently are no Food and Drug Administration–approved devices for cooling during transport.

Table. Comparison of categories of gaps in knowledge and change from 2005 to 2010

<table>
<thead>
<tr>
<th>Category</th>
<th>2005 workshop</th>
<th>2010 workshop</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementing hypothermia for HIE</td>
<td>Identified gap</td>
<td>Per protocols, appears safe and effective through 2 years of age</td>
<td>Now offered at many level III NICUs</td>
</tr>
<tr>
<td>Lack of safety and efficacy data</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>CoolCap 6-year follow-up undertaken but incomplete; NICHD and TOBY trial 7-year follow-up underway</td>
</tr>
<tr>
<td>Longer-term follow-up</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Hypothermia safe and effective</td>
</tr>
<tr>
<td>Ongoing trials (TOBY, ICE) Registries</td>
<td>Identified gap</td>
<td>Completed showing benefit VON and TOBY registries established</td>
<td>Gives practice based data, rare adverse effects detected</td>
</tr>
<tr>
<td>Practice guidelines</td>
<td>Identified gap</td>
<td>AAP commentary (2006); NICE and BAPM guidelines (2010)</td>
<td>Practice guidelines published</td>
</tr>
<tr>
<td>Temperature management before arrival at the cooling center</td>
<td>Identified gap</td>
<td>Identified gap: emerging reports; need for birth hospital and transport safety data</td>
<td>Being addressed as a local issue for neonatal units and networks</td>
</tr>
<tr>
<td>Hypothermia in low-resource settings</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Preliminary data available</td>
</tr>
<tr>
<td>Identification of infants for offering hypothermia</td>
<td>Identified gap</td>
<td>Neurologic exam</td>
<td>With moderate encephalopathy, apparent benefit; with severe encephalopathy, less benefit hypothermia altering early prognostic value</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>Identified gap</td>
<td>Predictive but not essential for clinical practice</td>
<td></td>
</tr>
<tr>
<td>aEEG</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>Scoring system</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Mild hypothermia for clinical care</td>
</tr>
<tr>
<td>Preterm infants</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Mild hypothermia for clinical care</td>
</tr>
<tr>
<td>Severely growth-restricted infants</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Ongoing trial registry data documenting use</td>
</tr>
<tr>
<td>Infants with severe encephalopathy</td>
<td>Identified gap</td>
<td>Benefit from mild hypothermia</td>
<td>Benefit from mild hypothermia</td>
</tr>
<tr>
<td>Infants &gt;6 hours of age</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Ongoing study</td>
</tr>
<tr>
<td>Safety data and rare side effects</td>
<td>Identified gap</td>
<td>Area of emerging knowledge</td>
<td>Registry data accruing</td>
</tr>
<tr>
<td>Developmental outcomes based on level of encephalopathy</td>
<td>Identified gap</td>
<td>Area of emerging knowledge</td>
<td>Moderate encephalopathy most likely to benefit from cooling therapy Hypothermia results in increased normal survival</td>
</tr>
<tr>
<td>Effect on mortality</td>
<td>Identified gap</td>
<td>Area of emerging knowledge</td>
<td>Hypothermia reduces mortality</td>
</tr>
<tr>
<td>Specific aspects of hypothermia treatment</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Ongoing trial</td>
</tr>
<tr>
<td>Depth of cooling</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Ongoing trial</td>
</tr>
<tr>
<td>Duration of cooling</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Both are effective and unlikely to be compared in a study</td>
</tr>
<tr>
<td>Rewarming strategies</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td></td>
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<tr>
<td>Mode of cooling (head vs whole-body)</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td></td>
</tr>
<tr>
<td>Safety data</td>
<td>Identified gap</td>
<td>Accumulating evidence thus far suggests safety</td>
<td>Registry data are accumulating</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Ongoing trial</td>
</tr>
<tr>
<td>Role of MRI</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Ongoing trial</td>
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<tr>
<td>Role of EEG</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Ongoing studies</td>
</tr>
<tr>
<td>Proteomic and genomic biomarkers</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Ongoing studies</td>
</tr>
<tr>
<td>Hospitals providing cooling therapy</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Rare event requiring systematic training for recognition by obstetrics, pediatrics, family medicine, and nursing staff</td>
</tr>
<tr>
<td>Awareness and identification of eligible infants</td>
<td>Identified gap</td>
<td>Identified gap</td>
<td>Ongoing studies</td>
</tr>
<tr>
<td>Certification and/or training of personnel for institution of hypothermia</td>
<td>Identified gap</td>
<td>Need for education</td>
<td>Need for rigorous randomized clinical trials of therapeutic hypothermia in moderate-resource settings</td>
</tr>
<tr>
<td>Outreach education to referral centers</td>
<td>Identified gap</td>
<td>Need for education</td>
<td></td>
</tr>
<tr>
<td>Cooling in low-resource environments</td>
<td>Identified gap</td>
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Research and treatment of hypothermia in perinatal hypoxic-ischemic encephalopathy: a systematic review and meta-analysis of trial data.


Higgins et al
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Sarkar S, Parks JD, Donn SM. Should amplitude-integrated electroencephalography be used to identify infants suitable for hypothermia neuroprotection? J Perinatol 2008;28:117-22.


Appendix

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