Published in final edited form as:

J Pediatr. 2011 November ; 159(5): 851–858.e1. doi:10.1016/j.jpeds.2011.08.004.

Hypothermia and Other Treatment Options for Neonatal Encephalopathy: An Executive Summary of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Workshop

Rosemary D. Higgins, M.D., Tonse Raju, M.D., A. David Edwards, DSc, F. Med. Sci, Denis V. Azzopardi, M.D., Carl L. Bose, M.D., Reese H. Clark, M.D., Donna M. Ferriero, M.D., Ronnie Guillet, M.D., Ph.D, Alistair J. Gunn, M.B., Ch.B., Ph.D., Henrik Hagberg, M.D., Ph.D, Deborah Hirtz, M.D., Terrie E. Inder, M.B., Ch.B., M.D., Susan E. Jacobs, M.D., Dorothea Jenkins, M.D., Sandra Juul, M.D., Ph.D, Abbot R. Lupton, M.D., Jerold F. Lucey, M.D., Mervyn Maze, M.B., Ch.B, Charles Palmer, M.B., Ch.B, LuAnn Papile, M.D., Robert H. Pfister, M.D., Nicola J. Robertson, Ph.D, FRCPCH, Mary Rutherford, M.D., Seetha Shankaran, M.D., Faye S. Silverstein, M.D., Roger F. Soll, M.D., Marianne Thoresen, M.D., Ph.D., William F. Walsh, M.D., and NICHD Hypothermia Workshop Speakers and Moderators*

Pregnancy and Perinatology Branch, Center for Developmental Biology and Perinatal Medicine, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

Rosemary D. Higgins: higginsr@mail.nih.gov

Index Terms

Perinatal brain injury; cerebral palsy; resuscitation; hypothermia; hypoxic-ischemic encephalopathy; biomarker

Perinatal hypoxic-ischemic encephalopathy (HIE), a subset of neonatal encephalopathy, is associated with high neonatal mortality and severe long-term neurological morbidity. Until recently there were no therapies, but six large trials have confirmed that 72 hours of hypothermia in infants with neonatal encephalopathy is associated with significant reduction in death and disability at 18-month follow-up.¹⁻⁶ However, although the collective evidence from completed trials confirms that therapeutic hypothermia (to 33.5°C) improves outcome, 40-50% of infants treated with hypothermia still die or have significant neurological disability.⁷ Thus, there is an urgent need to refine current hypothermia treatment protocols and to develop additional treatment strategies. To address these issues, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) invited a panel of experts in August 2010 to review the available evidence, identify knowledge gaps,

© 2011 Mosby, Inc. All rights reserved.

Address Correspondence to: Rosemary D. Higgins, M.D. Pregnancy and Perinatology Branch, Center for Developmental Biology and Perinatal Medicine, NICHD, NIH 6100 Executive Blvd, Room 4B03B MSC 7510 Bethesda, MD 20892, USA.

*List of NICHD Hypothermia Workshop Speakers and Moderators is available at <http://www.jpeds.com> (Appendix).

The other authors declare no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and to suggest research priorities as a follow-up to the NICHD workshop in 2005.⁸ This paper provides a summary of the major issues discussed.

Pathophysiologic Basis for Therapeutic Strategies

Our current therapeutic approach for treating neonatal encephalopathy is based on understanding the evolution of neuronal damage following hypoxic ischemic injury.⁹⁻¹¹ The pathway of cerebral injury in the term infant with HIE is not always clear. Many factors including the etiology, extent of hypoxia or ischemia, maturational stage of the brain, regional cerebral blood flow, and general health of the infant prior to the injury can all impact on the pattern and extent of brain injury as well as the outcome following injury.¹¹ Nevertheless, animal models contributed to an understanding of the pathophysiology of HIE. The initial insult produces immediate cell loss of varying degrees but more significantly leads to a delayed impairment in energy metabolism along with apoptotic cell death. This pathophysiology provides the basis for hypothermia therapy. However, it is known that brain injury continues to evolve for weeks or even months after the initial injury - particularly due to the activation of inflammatory systems and the initiation of repair processes.^{12,13} There is a need to understand the later phases of injury in more detail in order to develop new treatments to enhance brain repair and recovery after HIE.

A review of animal studies¹⁴ showed that brain cooling to about 32° to 34° C beginning before 5.5 hours following HI injury and continued for 12-72 hours reduced secondary energy failure and cell death and was associated with neuropathological and functional improvements. Working from these data, researchers designed human trials in which cooling was initiated as early as feasible after the brain injury but before 6 hours. Rectal/esophageal temperature was reduced to between 32° to 34° C for effective brain cooling with whole body hypothermia. Smaller reductions in rectal temperature (34-35° C) were thought to be needed for head cooling. Cooling would be continued for about 48-to-72 hours. Although optimal methods for re-warming were not tested in newborn animals, adult animal studies indicated that slow re-warming was preferred.^{15,16}

Clinical Trials of Hypothermic Neural Rescue

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

The Cool Cap,¹ NICHD,² TOBY,³ neo.nEURO.network Trial,⁴ the China Study Group,⁵ and ICE⁶ trials all showed either overall benefit of cooling for HIE or benefit 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 three trials¹⁻³ showed that therapeutic hypothermia reduced death or disability at 18 months with a risk ratio of 0.81[95% confidence interval 0.71-0.93] with a number need to treat (NNT) of nine.⁷ A number of smaller studies reported data consistent with the large pragmatic trials.¹⁷⁻²² Preliminary information from the Cool Cap trial shows favorable outcome in survivors of HIE at 18 months is highly associated with favorable functional outcome at 7-8 years.²³ The NICHD Whole Body Cooling trial shows that the beneficial effects of hypothermia for neonatal HIE noted at 18 months persist to childhood.²⁴ Safety data for adverse events (AEs) such as arrhythmias, bleeding, skin effects due to cooling, hypotension, persistent pulmonary hypertension (PPHN), and infection are reassuring.^{25, 26} The American Academy of Pediatrics published a commentary in 2006 following publication of the first two trials.²⁷ The American Heart Association recommends induced therapeutic hypothermia as post

resuscitation care for infants meeting criteria used in published clinical trials.²⁸ In the United Kingdom, the National Institute for Health and Clinical Excellence developed an interventional procedure guideline which declared that hypothermia should be used as a normal treatment in the National Health Service,²⁹ and the British Association of Perinatal Medicine published guidelines for neonatal units and networks to standardize hypothermia therapy.³⁰ Hypothermic neural rescue is now widely practiced in high resource settings.

Further research into hypothermic neural rescue

Despite the strong evidence of benefit 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 (not just hypoxia and ischemia), despite similar clinical presentation. Among infants with recognized HIE, the precise timing, nature, and severity of the hypoxic-ischemic insult is seldom certain. The infants' 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 in part be addressed by individual patient meta-analysis using the patient populations studied in these large randomized trials. Such analyses could identify the response rates to variations in patient characteristics (age, race, ethnicity, sex, Apgar scores, medications used in mothers, and so forth) or treatment (timing of initiation of hypothermia, degree and duration of cooling, adjunct therapies etc). Additional questions that might be addressed include factors affecting responses to hypothermia, the role of infection, and the nature of insult (sentinel event, unprovoked signs of fetal distress, pre-labor events, and prenatal events) as predictive of outcomes. The panel recommended that an individual patient meta-analysis would be an opportunity to address these important clinical questions.

Other potential clinical issues related to hypothermia therapy include the impact of obstetric factors such as maternal history (prior losses, stillbirth, coagulopathy, infection, etc.), race/ethnicity, age, genetic background, folate deficiency, and vitamin D deficiency, which may affect encephalopathy as well as the response of the infant to interventions. The panel saw a need for multidisciplinary collaborations to address these questions.

Recent studies have suggested that hypothermia significantly reduces the predictive value of both clinical neurological examination and EEG recordings.^{31,32} The addition of amplitude integrated EEG at < 9 hours of age resulted in a non-significant increase in the predictive value of stage of HIE at random assignment at < 6 hours of age, 0.72 (95% CI, 0.64-0.80) to 0.75 (0.66-0.83).³³ In contrast, the prognostic value of post-cooling MRI appears to be unaffected by hypothermia.^{34,35,36} Thus, prospectively generated hypotheses regarding resuscitation variables, aEEG recordings, full EEG recording, seizure identification³⁷ and treatment, concurrent care practices, and management of infants prior to active cooling could enrich the value of future trials. Similarly, utility of continuous monitoring of EEG activity during treatment, and of obtaining EEG and MRI studies prior to discharge and at specific times during follow-up for prognostic evaluation need to be evaluated. Interventional variables such as targeted temperature management,³⁸ sedation practices and concurrent medications could be assessed to increase our knowledge of 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 NICU's prior to 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 prior to and during transport, care must be taken to avoid overcooling. Safety, in particular, must be documented if hypothermia is to be used on transport. Further, there is a need for developing devices that reproducibly target temperature appropriately. It is unclear whether medical management during cooling therapy affects outcomes. Co-therapies including fluid management, nutrition, electrolyte and glucose management, ventilator strategies, management of pH, PO₂, and PCO₂,³⁹ and concurrent medications, particularly anticonvulsant therapy whose hepatic clearance is reduced by cooling therapy, are all areas in need of further research.

Because overall timing, depth, and duration of hypothermia strategies used in all major trials of therapeutic hypothermia to date have been remarkably similar,¹⁻⁶ the relative benefits of variation in the administration of hypothermia cannot be estimated from the current data. Thus temperature selection, duration of time of cooling, rewarming techniques and temperature management were discussed as continued knowledge gaps in the area to optimize hypothermic therapy. Ideal temperature for cooling remains an unanswered question.⁴⁰ The cost/benefit of incremental studies of any selective modification of parameters for hypothermic therapy requiring many years with large clinical trials was raised by the group as a controversy.

The spectrum of the potential window or windows for opportunities needs to be broadened beyond the 6-hour window following birth. Trials are underway to evaluate the safety and effectiveness of cooling commenced after 6 hours of age.^{41,42} There are recent reports indicating a significant portion of infants (13 and 18%) cooled beyond the 6 hours of age tested in the randomized trials^{43,44} and limited data supporting the potential benefit from such delayed cooling.²²

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.⁴⁵ There are several reasons why the safety and efficacy data on therapeutic hypothermia from complete 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 prior to birth due to multiple antenatal insults (such as maternal malnutrition and other co-morbidities), delayed hospital admissions often in obstructed labor, long delays in carrying out emergency caesarean sections and lack of effective networks for neonatal transport. It is possible that, at the time of birth or before hypothermic therapy can commence, the therapeutic window for hypothermia may have passed.

The incidence and profile of perinatal infections in this population is different. Cooling in the presence of infection might be deleterious as hypothermia may impair innate immune function, including neutrophil migration and function.⁴⁶ Hypothermia during sepsis in adult patients has been associated with increased mortality, higher circulating levels of TNF- α and IL-6,⁴⁷ prolongation of NF- κ B activation⁴⁸ and altered cytokine gene expression. Hypothermia for head injury in adults increases the risk of pneumonia.⁴⁹ 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 experimental⁵⁰⁻⁵² and epidemiological evidence suggests that the 'dual hit' of combined infection and ischemia results in more severe brain injury and increase in the risk of cerebral palsy.⁵³ It is not known if therapeutic hypothermia would be neuroprotective in such situations. Cooling may be unsafe in the presence of meconium

aspiration and pulmonary hypertension as facilities for advanced multi-organ support may not be available in low and mid income neonatal units.

Cooling equipment used in high-income countries is expensive, requires maintenance and has recurring costs. Cost and benefit should be considered for low resource settings. Many “low tech” cooling methods like ice or frozen gel packs are labor intensive,^{54,55} may result in marked temperature fluctuations and shivering^{54, 56,57} with a potential loss of neuroprotective efficacy. It is therefore important that rigorous and carefully conducted randomized controlled trials of therapeutic hypothermia are performed where there are 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 mid resource settings.⁵⁸ It should be emphasized that potential prevention of HIE as well as access to obstetric and neonatal care including resuscitation is needed prior to institution of therapy for encephalopathy.

Clinical trials of adjuvant therapies

Data from animal models of asphyxia suggest that neurological outcome after HIE can be improved by the addition of 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. It is essential that phase 1-2 studies using biomarker outcomes and involving small numbers of infants be carried out 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 Xenon⁵⁹⁻⁶¹ and erythropoietin are already planned or underway.^{62,63}

Further characterization of the evolution of injury and healing over a time course of days to weeks after the insult is needed in order to provide essential background information to develop 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 days to weeks following injury include erythropoietin,⁶⁴⁻⁶⁷ stem cells^{68,69} or cell-based therapies which may be helpful in tissue repair and regeneration following an insult. Speculatively, N-acetylcysteine (NAC), vitamin D, anti-epileptic drugs (AED) and antioxidants might be of value although at present evidence is lacking.

Biomarkers

Biomarkers have been essential to research in HIE.⁷⁰ The original discovery that brain injury in the human infant is delayed after an asphyxial event was made using phosphorus magnetic resonance (MR) spectroscopy.⁷¹ The technique was subsequently used as the prototypical bridging biomarker of HIE to evaluate the therapeutic effect of hypothermia in early animal studies.⁷² Phosphorus MR spectroscopy is cumbersome and is not widely available. However MR 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 so potentially allowing phase 3 pragmatic trials to be targeted to treatments with a high chance of success.⁷³ 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 in order to investigate specific neuroprotective therapies.⁷⁰ 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 a serum biomarker(s) would be particularly valuable. New proteomic and metabolomic technologies deserve further investigation.

Bedside biomarkers that define stage, progression, and improvement of encephalopathy would be valuable. Biomarkers reported in clinical trials include lactate, magnetic resonance spectroscopy (MRS), MRI, and aEEG. An elevated urinary lactate to creatinine ratio has been associated with adverse outcome in infants with HIE.⁷⁴ Amplitude integrated EEG has been useful in some studies to document seizures as well as abnormal patterns,^{1,75-77} but not in other studies.^{33, 78} In two studies, either infants with hypothermia only⁷⁹ or both normothermia and hypothermia⁸⁰ had aEEG recorded continuously before during and after hypothermia therapy. The aEEG pattern within 6 h of age had merely lost its predictive power. The time it took for the background aEEG to normalize had a positive predictive value of 94% in infants with HT.

The value of MRI^{35,36,81} in predicting neurodevelopmental outcome for infants with HIE has been reported. In a nested substudy³⁵ of the infants in the TOBY trial the predictive value of scoring the MRI picture were equally good for infants with normothermia and hypothermia, PPV for poor outcome were 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 correlated with death and disability at 18 months.³⁶ A recent study of 125 cooled infants with HIE showed that Pourcelots resistance index, RI, obtained from Doppler measurements on an intracerebral artery, was no longer a good predictor; the PPV for poor outcome if RI was <0.55 was only 60% in cooled as compared with 84% in infants with normothermia.⁸² On examining predictors in infants treated for hypothermia, it is important to assess whether old predictors are valid with new thresholds.⁸³ MRI value has been reviewed in two publications.^{83,84} In summary, few of the reported biomarkers have been qualified. Thus MR imaging remains the leading qualified biomarker at present. 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 should be available. Therapeutic hypothermia can be offered for infants who meet criteria of the published trials provided infrastructure and trained personnel to undertake hypothermia are in place.²⁸⁻³⁰ Eligibility criteria include a pH of 7.0 or less or a base deficit of 16 mmol per liter or more in a sample of umbilical cord blood or any blood during the first hour after birth. If a blood gas is not available, additional criteria are required. These include an acute perinatal event and either a 10 minute Apgar score of 5 or less or assisted ventilation initiated at birth and continued for at least 10 minutes. A neurological exam showing moderate to severe encephalopathy, and in some trials amplitude integrated EEG with specific findings, are required.^{1,3-6} Infants offered therapeutic hypothermia should meet previously studied inclusion criteria. Efficacy data are lacking for preterm infants; further safety concerns may pose increased risk in this population as they are already at risk for temperature instability. Infants outside of inclusion criteria for previously published clinical trials including infants < 36 weeks gestation, infants who present outside of the previously studied 6 hour window, and infants 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. Hyperthermia has been shown in the CoolCap²⁶ and NICHD⁸⁵ trials to be strongly associated with worse outcomes compared with infants who did not have elevated

body temperatures, thus particular attention should be paid to fever and/or heating. There is some evidence in the literature based on case series⁸⁶ for mild hypothermia prior to arrival at a center for cooling, but concern remains over the potential for temperature overshoot, rapid fluctuations in temperature, and excessive cooling of infants during transport. In a recent published case series, one third of infants in the report had temperatures $< 32^{\circ}\text{C}$.^{86,87} A new report details cooling of nine infants using the CritiCool, a servo-controlled cooling device during transport.⁸⁸ The question remains if cooling is begun at a referral hospital, infant assessment of encephalopathy by trained staff (either local staff or transport staff), and how one safely and accurately continues the therapy on transport. There is need for continuous temperature monitoring as well as the ability to intervene to adjust the temperature to maintain it within the target range on transport. Unfortunately, there are currently no FDA-approved devices for cooling on transport.

For hospitals that perform therapeutic hypothermia, training 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 care including mechanical ventilation, physiologic (temperature) and biochemical (blood gas) monitoring, neuroimaging including MRI, seizure detection and monitoring with EEG, neurological consultation, and long term follow up. Given the relatively low incidence of HIE, training needs include awareness and identification of infants at risk for HIE as well as assessment of infants who have suffered HIE. This will involve education of obstetricians, maternal fetal medicine specialists, family practitioners, midwives, labor, delivery, and newborn nursery staff, as well as pediatricians and neonatologists. A “checklist” was proposed for identification of infants at risk for HIE following resuscitation. A train-the-trainer program could potentially be instituted for training (and re-training) physicians and nurses involved in the care and delivery of hypothermia therapy. This would include identification of eligible infants, procedures for transfer of infants, and initiation and maintenance of mild hypothermia.

Registries

The establishment of several registries allows monitoring of implementation, detection of rare adverse events and the opportunity to learn from variation in practice. Currently, Vermont Oxford Network has an encephalopathy registry⁴⁴ and there is a TOBY registry.⁴³ Registries ideally could include all infants treated with hypothermia regardless of gestational age and collect information on variations and confounders including duration of cooling, timing of initiation of cooling, depth of hypothermia, seizure therapy, medications including sedative drugs, pharmacology of drugs administered to infants undergoing hypothermia, antibiotics, and others. Common data points and common definitions would be most helpful in order to compare data. Registries can potentially be used for quality improvement. Nevertheless, there are challenges in the effective use of registries including lack of control patients, lack of sensitive short-term outcomes, the need to link to long term outcomes and limited funding.

Summary

HIE is not a single disease from a single cause, and is characterized by great diversity in the timing and magnitude of brain injury. It is therefore unreasonable to expect *any* single intervention to provide uniformly favorable outcome. The known heterogeneity in neuropathological changes after perinatal HIE combined with potential regional heterogeneity of treatment effects will lead to marked differential effects on outcomes among survivors of HIE (e.g. physical disability versus cognitive deficits). This underscores the need for longer term follow up of all infants with HIE undergoing any treatment.

In spite of rapidly accumulating clinical and laboratory data related to hypothermia as a neuroprotective strategy for HIE, the speakers and discussants at the workshop underscored numerous gaps in knowledge in this field summarized in the Table, which compares the gaps identified at the 2005 NICHD workshop⁸ with current gaps. The participants noted that with only six completed studies¹⁻⁶ providing information on follow-up for up to 18 months of age, the longer-term neurodevelopmental impact of hypothermia for HIE are pending.^{23,24} This, they concluded, should lead to an overall measure of caution in applying the new therapy of hypothermia indiscriminately for all cases of HIE.

Based on the available data and large knowledge gaps, the expert panel suggested that although hypothermia is unequivocally a promising therapy for HIE, a substantial proportion of infants still suffer from death or disability despite treatment. Further analysis of existing trial data, development of adjuvant therapies to hypothermia, development of biomarkers and further refinements of hypothermia therapy for use in infants suffering from HIE and clinical trials of therapeutic hypothermia in mid resource settings with different risk factors but adequate facilities and infrastructure are all urgently needed and were identified as areas of high priority for study.

Acknowledgments

The Workshop was supported by NIH Office of Rare Diseases. R.G. receives financial support from Olympic Medical/Natus for follow up of the Cool Cap cohort of infants.

Appendix

NICHD Hypothermia Workshop Speakers and Moderators include:

Denis Victor Azzopardi, M.D. FRCP, Imperial College of London, London, England, UK; **Carl L. Bose, M.D.**, University of North Carolina, Chapel Hill, North Carolina; **Reese H. Clark, M.D.**, Pediatrix Medical Group, Inc. Sunrise, Florida; **A. David Edwards, F. Med. Sci.**, Imperial College London, London, England, UK (Co-Chair); **Donna M. Ferriero, M.D.** University of California, San Francisco, California; **Ronnie Guillet, M.D., Ph.D.**, University of Rochester Medical Center, Rochester, New York; **Alistair J. Gunn, M.B.Ch.B., Ph.D.**, University of Auckland, Auckland, New Zealand; **Henrik Hagberg, M.D., Ph.D.**, Imperial College London, London, England, UK; **Deborah Hirtz, M.D.**, NINDS, Bethesda, Maryland; **Terrie E. Inder, M.B.Ch.B., M.D.**, Washington University in St. Louis School of Medicine, St. Louis, Missouri; **Susan E. Jacobs, M.D.**, Royal Women's Hospital, Victoria, Australia; **Dorothea Jenkins, M.D.**, Medical University of South Carolina, Charleston, South Carolina; **Sandra E. Juul, M.D., Ph.D.**, University of Washington, Seattle, Washington; **Abbot R. Laptook, M.D.**, Women & Infants Hospital, Providence Rhode Island; **Jerold F. Lucey, M.D.**, University of Vermont School of Medicine, Burlington, Vermont; **Mervyn Maze, M.B., Ch.B.**, University of California at San Francisco, San Francisco, California; **Charles Palmer, M.B. Ch.B.**, Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey, Pennsylvania; **LuAnn Papile, M.D.**, Baylor College of Medicine, Texas Children's Hospital Houston, Texas; **Robert Pfister, M.D.**, University of Vermont School of Medicine, Burlington, Vermont; **Tonse N. K. Raju, M.D., D.C.H.**, NICHD, Bethesda, Maryland; **Nicola J. Robertson, Ph.D., FRCPC**, University College London, London, UK; **Mary Rutherford, M.D.FRCPC**, FRCR, Imperial College London, London, England, UK; **Seetha Shankaran, M.D.**, Wayne State University School of Medicine, Detroit Michigan; **Faye Silverstein, M.D.**, University of Michigan, Ann Arbor, Michigan; **Roger F. Soll, M.D.**, University of Vermont School of Medicine, Burlington Vermont; **Marianne Thoresen, M.D.**, University of Bristol, St. Michael's Hospital, Bristol, England, UK.,

William F. Walsh, M.D., Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee.

References

1. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicenter randomized trial. *Lancet*. 2005; 365:663–70. [PubMed: 15721471]
2. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med*. 2005; 353:1574–84. [PubMed: 16221780]
3. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med*. 2009; 361:1349–58. [PubMed: 19797281]
4. Simbruner G, Mittal RA, Rohlmann F, Muche R. neo.nEURO.network Trial Participants. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT. *Pediatr*. 2010; 126:e771–8.
5. Zhou WH, Cheng GQ, Shao XM, Liu XZ, Shan RB, Zhuang DY, et al. Selective head cooling with mild systemic hypothermia after neonatal hypoxic-ischemic encephalopathy: A multicenter randomized controlled trial in China. *J Pediatr*. 2010; 157:367–72. [PubMed: 20488453]
6. Jacobs SE, Morley CJ, Inder TE, Stewart MJ, Smith KR, McNamara PJ, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy. A randomized controlled trial. *Archives of Ped Adol Med*. 2011 Apr 4. epub ahead of print.
7. Edwards, AD.; Brocklehurst, P.; Gunn, AJ.; Halliday, H.; Juszczak, E.; Levene, M., et al. *BMJ*. Vol. 340. 2010. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data; p. c363
8. Higgins RD, Raju TNK, Perlman J, Azzopardi DV, Blackmon LR, Clark RH, et al. al Hypothermia and perinatal asphyxia: executive summary of the National Institute of Child Health and Human Development workshop. *J Pediatr*. 2006; 148:170–175. [PubMed: 16492424]
9. Yager JY. Animal models of hypoxic-ischemic brain damage in the newborn. *Seminars in Pediatr Neurol*. 2004; 11:31–46.
10. McLean C, Ferriero DM. Mechanisms of hypoxic-ischemic injury in the term infant. *Semin Perinatol*. 2004; 28:425–32. [PubMed: 15693399]
11. Gunn AJ, Bennet L. Fetal hypoxia and patterns of brain injury: insights from animal models. *Clin Perinatol*. 2009; 36:579–593. [PubMed: 19732615]
12. Colbourne F, Li H, Buchan AM. Indefatigable CA1 sector neuroprotection with mild hypothermia induced 6 hours after severe forebrain ischemia in rats. *J Cerebral Blood Flow Metab*. 1999; 19:742–749.
13. Gonzalez FF, Abel R, Almli CR, Mu D, Wendland M, Ferriero DM. Erythropoietin sustains cognitive function and brain volume after neonatal stroke. *Dev Neurosci*. 2009; 31:403–11. [PubMed: 19672069]
14. Gunn AJ, Gunn TR. The pharmacology of neuronal rescue with cerebral hypothermia. *Early Hum Devel*. 1998; 53:19–35. [PubMed: 10193924]
15. Eschel G, Reisler G, Berkovitch N, Shapira S, Grauer E, Barr J. Comparison of fast versus slow rewarming following acute moderate hypothermia in rats. *Paediatr Anaesth*. 2002; 12:235–242. [PubMed: 11903937]
16. Nakamura T, Miyamoto O, Sumitani K, Negi T, Itano T, Nagao S. Do rapid systemic changes of brain temperature have an influence on the brain? *Acta Neurochir (Wien)*. 2003; 145:301–7. [PubMed: 12748891]
17. Thoresen M, Whitelaw A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infant with hypoxic-ischemic encephalopathy. *Pediatr*. 2000; 106(1 Pt 1):92–99. 2000.

18. Shankaran S, Laptook A, Wright LL, Ehrenkranz RA, Donovan EF, Fanaroff AA, et al. Whole-body hypothermia for neonatal encephalopathy: animal observations as a basis for a randomized, controlled pilot study in term infants. *Pediatr.* 2002; 110(2 Pt 1):377–85.
19. Eicher DJ, Wagner CL, Katikaneni LP, Hulsey TC, Bass WT, Kaufman DA, et al. Moderate hypothermia in neonatal encephalopathy: Efficacy outcomes. *Pediatr Neurol.* 2005; 32:11–17. [PubMed: 15607598]
20. Eicher DJ, Wagner CL, Katikaneni LP, Hulsey TC, Bass WT, Kaufman DA, et al. Moderate hypothermia in neonatal encephalopathy: Safety outcomes. *Pediatr Neurol.* 2005; 32:18–24. [PubMed: 15607599]
21. Lin ZL, Yu HM, Lin J, Chen SQ, Liang ZQ, Zhang ZY. Mild hypothermia via selective head cooling as neuroprotective therapy in term neonates with perinatal asphyxia: an experience from a single neonatal intensive care unit. *J Perinatol.* 2006; 26:180–4. [PubMed: 16407967]
22. Li T, Xu F, Cheng X, Guo X, Ji L, Zhang Z, Blomgren K, Simbruner G, Cnaglian Z. Systemic hypothermia induced within 10 hours after birth improved neurological outcome in newborns with hypoxic-ischemic encephalopathy. *Hosp Pract (Minneap).* 2009; 37:147–152. [PubMed: 20877184]
23. Guillet R, Edwards AD, Thoresen M, Gunn AJ. Functional Outcome at 7-8 y of Survivors of CoolCap Trial Is Highly Associated with 18 m Neurodevelopmental Assessment. *Pediatric Academic Societies.* 2011; 4750:10.
24. Shankaran S. MD and Extended Hypothermia Follow-up Sub Committee, Follow-up PI's of the NICHD NRN. Do neuroprotective effects of whole body hypothermia for neonatal hypoxic-ischemic encephalopathy persist to childhood? *Pediatric Academic Societies.* 2011; 1660:8.
25. Shankaran S, Pappas A, Laptook AR, McDonald SA, Ehrenkranz RA, Tyson JE, et al. Outcomes of Safety and Effectiveness in a Multicenter Randomized, Controlled Trial of Whole-Body Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy. *Pediatr.* 2008; 122:e791–8.
26. Wyatt JS, Gluckman PD, Liu PY, Azzopardi D, Ballard R, Edwards AD, et al. Determinants of outcomes after head cooling for neonatal encephalopathy. *Pediatr.* 2007; 119:912–21.
27. Blackmon LR, Stark AR, American Academy of Pediatrics Committee on Fetus and Newborn. Hypothermia: a neuroprotective therapy for neonatal hypoxic-ischemic encephalopathy. *Pediatr.* 2006; 117(3):942–948.
28. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, et al. Part 15: Neonatal Resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010; 122(18 suppl 3):S909–S919. [PubMed: 20956231]
29. Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury. National Institute for Health and Clinical Excellence, interventional procedure guidance. May. 2010 <http://www.nice.org.uk/nicemedia/live/11315/48809/48809.pdf>
30. Adams, A.; Austin, T.; Becher, JC.; Chang, J.; Edwards, D.; Jones, S.; Thomson, M.; Tooley, J. British Association of Perinatal Medicine Position Statement on Therapeutic Cooling for neonatal Encephalopathy. 2010. <http://www.bapm.org/media/documents/publications/Position%20Statement%20on%20Therapeutic%20Cooling%20for%20Neonatal%20Encephalopathy%20July%202010.pdf>
31. Gunn AJ, Wyatt JS, Whitelaw A, Barks J, Azzopardi D, Ballard R. Therapeutic hypothermia changes the prognostic value of clinical evaluation of neonatal encephalopathy. *J Pediatr.* 2008; 152:55–58.e1. [PubMed: 18154900]
32. Thoresen M, Hellström-Westas L, Liu X, de Vries LS. Effect of hypothermia on aEEG in infants with asphyxia. *Pediatr.* 2010; 126:e131–139.
33. Shankaran S, Pappas A, McDonald SA, Laptook AR, Bara R, Ehrenkranz R. Neonatal Hypoxic Ischemic Encephalopathy: Predictive value of an Early Amplitude Integrated EEG and Neurological Examination. *J Pediatr.* in press.
34. Bonafacio SL, Glass HC, Vanderpluym J, Agrawal AT, Xu D, Barkovich AJ, et al. Perinatal events and early magnetic resonance imaging in therapeutic hypothermia. *J Pediatr.* 2011; 158:360–365. [PubMed: 20965514]

35. Rutherford M, Ramenghi LA, Edwards AD, Brocklehurst P, Halliday H, Levene M, et al. Assessment of brain tissue injury following moderate hypothermia in neonates with hypoxic ischaemic encephalopathy: a nested substudy of a randomised controlled trial. *Lancet Neurol*. 2010; 9:39–45. [PubMed: 19896902]
36. Shankaran S, Barnes P, Hintz S, Laptook AR, Higgins RD, McDonald SA, et al. Magnetic Resonance Imaging in Term Infants with Hypoxic Ischemic Encephalopathy in NICHD Trial of Therapeutic Hypothermia. *Pediatric Academic Societies*. 2011; 4750:1.
37. Kwon JM, Guillet R, Shankaran S, Laptook AR, McDonald SA, Ehrenkranz RA, et al. Clinical Seizures in Neonatal Hypoxic-Ischemic Encephalopathy Have No Independent Impact on Neurodevelopmental Outcome: Secondary Analyses of Data From the Neonatal Research Network Hypothermia Trial. *J Child Neurol*. 2011; 26:322–8. [PubMed: 20921569]
38. Shankaran S, Laptook AR, McDonald SA, Higgins RD, Tyson JE, Ehrenkranz RA, et al. Temperature Profile and Outcomes of Neonates Undergoing Whole Body Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy. *Pediatric Critical Care Medicine*. 2011 Apr 14. Epub ahead of print.
39. Pappas, A.; Shankaran, S.; Laptook, AR.; Langer, JC.; Bara, R.; Ehrenkranz, RA.; Goldberg, RN.; Das, A.; Higgins, RD.; Tyson, JE.; Walsh, MC. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. *J Pediatr*. Vol. 158. 2011. Hypocarbica and Adverse Outcome in Neonatal Hypoxic-Ischemic Encephalopathy; p. 752-758.e1.
40. Perlman JM. Summary proceedings from the Neurology group on hypoxic-ischemic encephalopathy. *Pediatr*. 2006; 117(3 Pt 2):S28–33.
41. <http://www.clinicaltrials.gov/ct2/show/study/NCT01192776?term=hypothermia+and+infant>
42. <http://www.clinicaltrials.gov/ct2/show/study/NCT00614744?term=hypothermia+and+infant;&rank=1>
43. Azzopardi D, Strohm B, Edwards AD, Halliday H, Juszczak E, Levene M, et al. Treatment of asphyxiated newborns with moderate hypothermia in routine clinical practice: how cooling is managed in the UK outside a clinical trial. *Arch Dis Child Fetal Neonatal Ed*. 2009; 94:F260–4. [PubMed: 19060009]
44. Pfister R, et al. Hypothermia in Practice, Initial Observations from the Vermont Oxford Network. *Pediatric Academic Societies*. 2010
45. Robertson N, Nakakeeto M, Hagmann C, Cowan FM, Acolet D, Iwata O, et al. Therapeutic hypothermia for birth asphyxia in low resource settings: a pilot randomised controlled trial. *Lancet*. 2008; 372:801–3. [PubMed: 18774411]
46. Biggar WD, Barker C, Bohn D, Kent G. Partial recovery of neutrophil functions during prolonged hypothermia in pigs. *J Appl Physiol*. 1986; 60:1186–9. [PubMed: 3700301]
47. Arons MM, Wheeler AP, Bernard GR, Christman BW, Russell JA, Schein R, et al. Effects of ibuprofen on the physiology and survival of hypothermia sepsis. *Ibuprofen in sepsis study group. Crit Care Med*. 1999; 27:669–70. [PubMed: 10321641]
48. Fairchild KD, Singh IS, Patel S, Drysdale BE, Viscardi RM, Hester L, et al. Hypothermia prolongs activation of NF-kappaB and augments generation of inflammatory cytokines. *Am J Physiol Cell Physiol*. 2004; 287:C422–31. [PubMed: 15070815]
49. Gadkary CS, Alderson P, Signorini DF. Therapeutic hypothermia for head injury. *Cochrane Database Syst Rev*. 2002; (1):CD001048. [PubMed: 11869586]
50. Eklind S, Mallard C, Leverin AL, Gilland E, Biomgren K, Mattsby-Baltzer I, et al. Bacterial endotoxin sensitizes the immature brain to hypoxic-ischemic injury. *Eur J Neurosci*. 2001; 13:1101–6. [PubMed: 11285007]
51. Girard S, Kadhim H, Lavoie K, Brochu ME, Larouche A, Sebire G. Role of perinatal inflammation in cerebral palsy. *Pediatr Neurol*. 2009; 40:168–174.
52. Girard S, Kadhim H, Beaudet N, Sarret P, Sebire G. Developmental motor deficits induced by combined fetal exposure to lipopolysaccharide and early neonatal hypoxia/ischemia: a novel animal model for cerebral palsy in very premature infants. *Neuroscience*. 2009; 158:673–82. [PubMed: 19010395]

53. Longo M, Hankins GD. Defining cerebral palsy: pathogenesis, pathophysiology and new intervention. *Minerva Ginecol.* 2009; 61:421–9. [PubMed: 19749673]
54. Thomas N, George KC, Sridhar S, Kumar M, Kuruvilla KA, Jana AK. Whole body cooling in newborn infants with perinatal asphyxia encephalopathy in a low resource setting: a feasibility trial. *Indian Pediatr.* 2010 Pii:S097475590900874-1 [Epub ahead of print].
55. Iwata S, Iwata O, Kapetanakis A, Kato T, Evans S, Araki Y, et al. Therapeutic hypothermia can be induced and maintained using either commercial water bottles or a “phase changing material” mattress in a newborn piglet model. *Arch Dis Child.* 2009; 94:387–91. [PubMed: 19155230]
56. Horn A, Thompson C, Woods D, Nel A, Bekker A, Rhoda N, et al. Induced hypothermia for infants with hypoxic-ischemic encephalopathy using a servo-controlled fan: an exploratory pilot study. *Pediatr.* 2009; 123:e1090–8.
57. Horn AR, Woods DL, Thompson C, Eis I, Kroon M. Selective cerebral hypothermia for post-hypoxic neuroprotection in neonates using a solid ice cap. *S Afr Med J.* 2006; 96:976–81. [PubMed: 17077928]
58. Wilkinson D, Thayil S, Robertson NJ. Ethical and practical issues relating to the global use of therapeutic hypothermia for perinatal asphyxia encephalopathy. *Arch Dis Child Fetal Neonatal Ed.* 2011; 96:F75–8. [PubMed: 21068075]
59. <http://isrctn.org/ISRCTN75602528>
60. <http://www.controlled-trials.com/ISRCTN75602528>
61. <http://www.clinicaltrials.gov/ct2/show/NCT00934700?term=xenon+and+infant&rank=1>
62. <http://www.clinicaltrials.gov/ct2/show/NCT00719407?term=Erythropoietin+and+infant&rank=14>
63. <http://www.clinicaltrials.gov/ct2/show/NCT00513240?term=Erythropoietin+and+infant&rank=11>
64. Cariou A, Claessens YE, Pene F, Marx JS, Spaulding C, Hababou C, et al. Early high-dose erythropoietin therapy and hypothermia after out-of-hospital cardiac arrest: a matched control study. *Resuscitation.* 2008; 76:397–404. [PubMed: 18037223]
65. McPherson RJ, Juul SE. Erythropoietin for infants with hypoxic-ischemic encephalopathy. *Curr Opin Pediatr.* 2010; 22:139–45. [PubMed: 20090525]
66. Givethchian M, Beschorner R, Ehmann C, Frauenlob L, Morgalla M, Hashemi B, Ziemer G, Scheule AM. Neuroprotective effects of erythropoietin during deep hypothermia circulatory arrest. *Eur J Cardiothorac Surg.* 2010; 37:662–8. [PubMed: 19766506]
67. Xiong T, Qu Y, Mu D, Ferriero D. Erythropoietin for neonatal brain injury: opportunity and challenge. *Int J Dev Neurosci.* 2011 Jan 28. Epub ahead of print.
68. Pimental-Coelho PM, Mendez-Otero R. Cell therapy for neonatal hypoxic-ischemic encephalopathy. *Stem Cells Dev.* 2010; 19:299–310. [PubMed: 19916801]
69. Pimental-Coelho PM, Magalhaes ES, Lopes LM, deAzevedo LC, Santiago MF, Mendez-Otero R. Human cord blood transplantation in a neonatal rat model of hypoxic-ischemic brain damage: functional outcome related to neuroprotection in the striatum. *Stem Cells Dev.* 2010; 19:351–8. [PubMed: 19296724]
70. Bennet L, Booth L, Gunn AJ. Potential biomarkers for HIE. *Seminars Fetal neonatal Med.* 2010; 15:253–60.
71. Azzopardi D, Wyatt JS, Cady EB, Delpy DT, Baudin J, Stewart AL, et al. Prognosis of newborn infants with hypoxic-ischemic brain injury assessed by phosphorus magnetic resonance spectroscopy. *Pediatr Res.* 1989; 25:445–451. [PubMed: 2717259]
72. Thoresen M, Penrice J, Lorek A, Cady EB, Wylezinska M, Kirkbride V, et al. Mild hypothermia after severe transient hypoxia-ischemia ameliorates delayed cerebral energy failure in the newborn piglet. *Pediatr Res.* 1995; 37:667–670. [PubMed: 7603788]
73. Azzopardi D, Edwards AD. Magnetic resonance biomarkers of neuroprotective effects in infants with hypoxic ischemic encephalopathy. *Semin Fetal Neonatal Med.* 2010; 15:261–9. [PubMed: 20359970]
74. Oh W, Perriett R, Shankaran S, Merritts M, Donovan EF, Ehrenkranz RA, et al. Association between urinary lactate to creatinine ratio and neurodevelopmental outcome in term infants with hypoxic-ischemic encephalopathy. *J Pediatr.* 2008; 53:375–8. [PubMed: 18534246]

75. Mathur AM, Morris LD, Tete F, Inder TE, Zempel J. Utility of prolonged bedside amplitude-integrated encephalogram in encephalopathic infants. *Am J Perinatol.* 2008; 25:611–615. [PubMed: 18841534]
76. Foran A, Cinnante C, Groves A, Azzopardi DV, Rutherford MA, Cowan FM. Patterns of brain injury and outcome in term neonates presenting with post natal collapse. *Arch Dis Child Fetal Neonatal Ed.* 2009; 94:F168–77. [PubMed: 18981034]
77. Lawrence R, Mathur A, Nguyen The Tich S, Zempel J, Inder T. A pilot study of continuous limited-channel aEEG in terms infants with encephalopathy. *J Pediatr.* 2009; 154:835–41.e1. [PubMed: 19230897]
78. Sarkar S, Barks JD, Donn SM. Should amplitude-integrated electroencephalography be used to identify infants suitable for hypothermia neuroprotection? *J Perinatol.* 2008; 28:117–122. [PubMed: 18004390]
79. Hallberg B, Grossmann K, Bartocci M, Blennow M. The prognostic value of early aEEG in asphyxiated infants undergoing systemic hypothermia treatment. *Acta Paediatr.* 2010; 99:531–6. [PubMed: 20050830]
80. Thoresen M, Hellstrom-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. *Pediatrics.* 2010; 126:e131–9. [PubMed: 20566612]
81. Azzopardi D, Edwards AD. Magnetic resonance biomarkers of neuroprotective effects in infants with hypoxic ischemic encephalopathy. *Seminars in Fetal and neonatal medicine.* 2010; 15:261–269. [PubMed: 20359970]
82. Elstad M, Whitelaw A, Thoresen M. Cerebral Resistance Index is less predictive in hypothermic encephalopathic newborns. *Acta Paediatr.* 2011 Epub ahead of print. 10.1111/j.1651-2227.2011.02327.x
83. Thoresen M. Patient selection and prognostication with hypothermia treatment In: *Hypothermia: an emerging therapy. Seminars Fetal Neonatal Med.* 2010:247–252.
84. Rutherford MA, Azzopardi D, Whitelaw A, Cowan F, Renowden S, Edwards AD, et al. Mild hypothermia and the distribution of cerebral lesions in neonates with hypoxic-ischemic encephalopathy *Pediatrics.* 2005; 116:1001–6.
85. Laptook A, Tyson J, Shankaran S, McDonald S, Ehrenkranz R, Fanaroff A, et al. Elevated temperature after hypoxic-ischemic encephalopathy: risk factor for adverse outcomes. *Pediatr.* 2008; 122:491–9.
86. Fairchild K, Sokora D, Scott J, Zanelli S. Therapeutic hypothermia on neonatal transport: 4-year experience in a single NICU. *J Perinatol.* 2010; 30:324–9. [PubMed: 19847186]
87. Hallberg B, Olson L, Bartocci M, Edqvist I, Blennow M. Passive induction of hypothermia during transport of asphyxiated infants: a risk of excessive cooling. *Acta Paediatr.* 2009; 98:942–6. [PubMed: 19484830]
88. Johnston ED, Becher JC, Mitchell AP, Stenson BJ. Provision of servo-controlled cooling during transport. *Arch Dis Child Fetal Neonatal Ed.* 2011 Mar 6. epub ahead of print.

Table 1
Comparison of Categories of Gaps in Knowledge and Change from 2005 to 2010

Category	2005 Workshop	2010 Workshop	Change
<i>Implementing Hypothermia for HIE</i>			
Lack of Safety and Efficacy Data	<i>Identified Gap</i>	Per protocols, appears safe and effective through 2 years of age	Now offered at many level III NICUs
Longer term follow up	<i>Identified Gap</i>	<i>Identified Gap</i>	Cool-Cap 6 year follow-up undertaken but incomplete. NICHD and TOBY trial 7 year follow up underway
Ongoing Trials (TOBY, ICE)	<i>Identified Gap</i>	Completed showing benefit	Hypothermia safe and effective
Registries	<i>Identified Gap</i>	VON and TOBY registries established	Gives practice based data, rare adverse effects detected.
Practice guidelines	<i>Identified Gap</i>	AAP Commentary (2006) NICE and BAPM Guidelines (2010)	Practice guidelines published
Temperature management prior to arrival at cooling center	<i>Identified Gap</i>	<i>Identified Gap</i> – emerging reports; need for birth hospital and transport safety data	Being addressed as a local issue for neonatal units and networks
Hypothermia in low resource settings	<i>Identified Gap</i>	<i>Identified Gap</i>	Preliminary data available
<i>Identification of Infants for Offering</i>			
<i>Hypothermia</i>			
Clinical exam	<i>Identified Gap</i>	Neurologic exam	With moderate encephalopathy – apparent benefit; with severe encephalopathy – less benefit
aEEG	<i>Identified Gap</i>	Predictive but not essential for clinical practice	aEEG changes over time with hypothermia altering early prognostic value
Scoring system	<i>Identified Gap</i>	<i>Identified Gap</i>	
Preterm infants	<i>Identified Gap</i>	<i>Identified Gap</i>	Ongoing study
Severely growth restricted infants	<i>Identified Gap</i>	<i>Identified Gap</i>	
Infants with moderate encephalopathy	Area of emerging knowledge	Benefit from mild hypothermia	Mild hypothermia for clinical care
Infants with severe encephalopathy	Area of emerging knowledge	Benefit from mild hypothermia	Mild hypothermia for clinical care
Infants > 6 hours of age	<i>Identified Gap</i>	<i>Identified Gap</i>	Ongoing trial Registry data documenting use
Safety data and rare side effects	<i>Identified Gap</i>	Area of emerging knowledge	Registry data accruing
Developmental outcomes based on level of encephalopathy	Area of emerging knowledge	Area of emerging knowledge	Moderate encephalopathy most likely to benefit from cooling therapy
Effect on Mortality	Area of emerging knowledge	Hypothermia reduces mortality	Hypothermia results in increased normal survival
<i>Specific aspects of hypothermia treatment</i>			
Depth of cooling	<i>Identified Gap</i>	<i>Identified Gap</i>	Ongoing trial
Duration of cooling	<i>Identified Gap</i>	<i>Identified Gap</i>	Ongoing trial

Category	2005 Workshop	2010 Workshop	Change
Rewarming strategies	<i>Identified Gap</i>	<i>Identified Gap</i>	
Mode of cooling (head versus whole body)	<i>Identified Gap</i>	<i>Identified Gap</i>	Both are effective and unlikely to be compared in a study
Safety data	<i>Identified Gap</i>	Accumulating evidence thus far suggests safety	Registry data are accumulating
<i>Biomarkers</i>			
Role of MRI	<i>Identified Gap</i>	MRI is predictive for longer term outcome	MRI for prognostic information
Role of EEG	<i>Identified Gap</i>	<i>Identified Gap</i>	Ongoing studies
Proteomic and Genomic Biomarkers		<i>Identified Gap</i>	Ongoing studies
<i>Hospitals providing cooling therapy</i>			
Awareness and identification of eligible infants		Need for education of medical and nursing staff	Rare event requiring systematic training for recognition by obstetrics, pediatrics, family medicine and nursing staff
Certification and /or training of personnel for institution of hypothermia	Need for education	Need for education	
Outreach education to referral centers	<i>Identified Gap</i>	Need for education	
Cooling in low resource environments		<i>Identified gap</i>	Need for rigorous randomized clinical trials of therapeutic hypothermia in mid resource settings