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

Rosemary D. Higgins, MD, Tonse Raju, MD, A. David Edwards, DSc, FMedSci, Denis V. Azzopardi, MD, Carl L. Bose, MD, Reese H. Clark, MD, Donna M. Ferriero, MD, Ronnie Guillet, MD, PhD, Alistair J. Gunn, MB, ChB, PhD, Henrik Hagberg, MD, PhD, Deborah Hirtz, MD, Terrie E. Inder, MB, ChB, MD, Susan E. Jacobs, MD, Dorothea Jenkins, MD, Sandra Juul, MD, PhD, Abbot R. Laptook, MD, Jerold F. Lucey, MD, Mervyn Maze, MB, ChB, Charles Palmer, MB, ChB, LuAnn Papile, MD, Robert H. Pfister, MD, Nicola J. Robertson, PhD, FRCPCH, Mary Rutherford, MD, Seetha Shankaran, MD, Faye S. Silverstein, MD, Roger F. Soll, MD, Marianne Thoresen, MD, PhD, and William F. Walsh, MD, and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Hypothermia Workshop Speakers and Moderators*

Perinatal hypoxic-ischemic encephalopathy (HIE), a subset of neonatal encephalopathy, is associated with high neonatal mortality and severe long-term neurologic morbidity. Until recently there were no proven treatments, but 6 large trials have confirmed an association between 72 hours of therapeutic hypothermia in infants with neonatal encephalopathy and a significant reduction in death and disability at an 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 suffer significant neurologic disability.[7] Thus, there is an urgent need to refine current hypothermia treatment protocols and to develop additional treatment strategies.

See related article, p 731

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, and suggest research priorities as a follow-up to the 2005 NICHD workshop.[8] This article summarizes the major issues discussed.

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 contining 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]

aEEG	Amplitude-integrated electroencephalography
EEG	Electroencephalography
HIE	Hypoxic-ischemic encephalopathy
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NICHD	National Institute of Child Health and Human Development

From the 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

*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).

The Workshop was supported by the National Institutes of Health Office of Rare Diseases. R.G. receives financial support from Olympic Medical/Natus for follow-up of the Cool Cap cohort of infants. The other authors declare no conflicts of interest.

 10.1016/j.jpeds.2011.08.004

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,[1] NICHD,[2] TOBY,[3] neo.nEURO.network,[4] China Study Group,[5] and ICE[6] 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[1-3] 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.[7] Some smaller studies have reported data consistent with the large pragmatic trials.[17-22] 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.[23] The NICHD Whole-Body Cooling Trial found that the beneficial effects of hypothermia for neonatal HIE noted at 18 months persist into childhood.[24] Safety data for adverse events, such as arrhythmias, bleeding, skin effects due to cooling, hypotension, persistent pulmonary hypertension, and infection, are reassuring.[25,26] The American Academy of Pediatrics published a commentary in 2006 after publication of the first 2 trials.[27] The American Heart Association recommends induced therapeutic hypothermia as postresuscitation care for infants meeting the criteria used in published clinical trials.[28] 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,[29] and the British Association of Perinatal Medicine has published guidelines to help neonatal units and networks 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 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.[31,32] 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).[33] In contrast, the prognostic value of postcooling magnetic resonance imaging (MRI) appears to be unaffected by hypothermia.[34-36] Thus, prospectively generated hypotheses regarding resuscitation variables, aEEG recordings, full EEG recording, seizure identification[37] 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,[38] 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 O_2 and CO_2,[39] 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,[1-6] 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.[40] 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.[41,42] Some recent studies have included a significant portion of infants (13% and 18%) cooled beyond the 6-hour window in randomized trials,[43,44] and limited data support the potential benefits of 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 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.[46] Hypothermia during sepsis in adult patients has been associated with increased mortality, higher circulating levels of tumor necrosis factor α and interleukin-6,[47] prolonged nuclear factor-κB activation,[48] 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 experimental[50-52] and epidemiologic evidence suggests that the "dual hit" of combined infection and ischemia results in more severe brain injury and increased increase risk of cerebral palsy.[53] 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[54,55] and may result in marked temperature fluctuations and shivering,[54,56,57] 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.[58]

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[59-61] 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 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,[64-67] stem cells,[68,69] and cell-based therapies that may faciliate 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.[70] The original finding of delayed brain injury in the human infant after an asphyxial event was discovered using phosphorus magnetic resonance spectroscopy (MRS).[71] This technique was subsequently used as the prototypical bridging biomarker of HIE to evaluate the therapeutic effect of hypothermia in early animal studies.[72] 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.[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 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 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.[74] aEEG was found to be useful for documenting seizures as well as abnormal patterns in some studies,[1,75-77] but not in others.[33,78] In 2 studies, infants with hypothermia only[79] and infants with both normothermia and hypothermia[32] 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[35,36,80] in predicting neurodevelopmental outcome for infants with HIE has been reported. In a nested substudy[35] 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.[36] A recent study of 125 cooled infants with HIE found that Pourcelot's resistance index, obtained from Doppler unltrasound 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.[81] When examining predictors in infants treated for hypothermia, it is important to assess whether old predictors are valid with new thresholds.[82] The value of MRI has been reviewed in 2 publications.[82,83]

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.[28-30] 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, aEEG 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 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[26] and NICHD[84] 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,[85] 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.[85,86] A more recent report described the cooling of 9 infants during transport using the CritiCool, a servo-controlled cooling device.[87] 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

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

Category	2005 workshop	2010 workshop	Change
Implementing hypothermia for HIE			
Lack of safety and efficacy data	Identified gap	Per protocols, appears safe and effective through 2 years of age	Now offered at many level III NICUs
Longer-term follow-up	Identified gap	Identified gap	CoolCap 6-year follow-up undertaken but incomplete; NICHD and TOBY trial 7-year follow-up underway
Ongoing trials (TOBY, ICE)	Identified gap	Completed showing benefit	Hypothermia safe and effective
Registries	Identified gap	VON and TOBY registries established	Gives practice based data, rare adverse effects detected
Practice guidelines	Identified gap	AAP commentary (2006); NICE and BAPM guidelines (2010)	Practice guidelines published
Temperature management before arrival at the cooling center	Identified gap	Identified gap: 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	Identified gap	Identified gap	Preliminary data available
Identification of infants for offering hypothermia			
Clinical examination	Identified gap	Neurologic exam	With moderate encephalopathy, apparent benefit; with severe encephalopathy, less benefit
aEEG	Identified gap	Predictive but not essential for clinical practice	aEEG changes over time with hypothermia altering early prognostic value
Scoring system	Identified gap	Identified gap	
Preterm infants	Identified gap	Identified gap	Ongoing study
Severely growth-restricted infants	Identified gap	Identified gap	
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	Identified gap	Identified gap	Ongoing trial registry data documenting use
Safety data and rare side effects	Identified gap	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
Specific aspects of hypothermia treatment			
Depth of cooling	Identified gap	Identified gap	Ongoing trial
Duration of cooling	Identified gap	Identified gap	Ongoing trial
Rewarming strategies	Identified gap	Identified gap	
Mode of cooling (head vs whole-body)	Identified gap	Identified gap	Both are effective and unlikely to be compared in a study
Safety data	Identified gap	Accumulating evidence thus far suggests safety	Registry data are accumulating
Biomarkers			
Role of MRI	Identified gap	MRI is predictive for longer term outcome	MRI for prognostic information
Role of EEG	Identified gap	Identified gap	Ongoing studies
Proteomic and genomic biomarkers		Identified gap	Ongoing studies
Hospitals providing cooling therapy			
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	Identified gap	Need for education	
Cooling in low-resource environments		Identified gap	Need for rigorous randomized clinical trials of therapeutic hypothermia in moderate-resource settings

VON, Vermont Oxford Network; *AAP*, American Academy of Pediatrics; *NICE*, National Institute for Health and Clinical Excellence; *BAPM*, British Association of Perinatal Medicine.

temperature monitoring, as well as to intervene to adjust the 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.

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

care, including mechanical ventilation, physiological (temperature) and biochemical (blood gas) monitoring, neuroimaging including MRI, seizure detection and monitoring with EEG, neurologic 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 sustained HIE. This will involve education of obstetricians, maternal and fetal medicine specialists, family practitioners, midwives, and labor, delivery, and newborn nursery staff, as well as pediatricians and neonatologists. A checklist was proposed for identification of infants at risk for HIE after resuscitation. A "train-the-trainer" program could possibly be instituted for training (and retraining) 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, the Vermont Oxford Network has an encephalopathy registry,[44] and a TOBY registry is in place.[43] Registries ideally should 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 helpful to allow comparison of data. Registries potentially can 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 with a single cause, but rather is characterized by great diversity in the timing and magnitude of brain injury. Thus, it is unreasonable to expect any single intervention to provide uniformly favorable outcomes. The known heterogeneity in neuropathological changes after perinatal HIE, combined with the potential regional heterogeneity of treatment effects, will lead to marked differences in outcomes among survivors of HIE (eg, physical disability vs cognitive deficits). This underscores the need for longer-term follow-up of all infants with HIE undergoing any treatment.

Despite the rapidly accumulating clinical and laboratory data related to hypothermia as a neuroprotective strategy for HIE, the speakers and discussants at the workshop identified many gaps in knowledge in this field. The Table compares the gaps identified at the 2005 NICHD workshop[8] with currently identified gaps. The participants noted that with only 6 completed studies[1-6] providing information on follow-up up to 18 months of age, the longer-term neurodevelopmental impact of hypothermia for HIE remains unclear.[23,24] This, they concluded, should lead to an overall measure of caution in applying therapeutic hypothermia indiscriminately in all cases of HIE.

Based on the available data and the significant knowledge gaps, the expert panel suggested that although hypothermia is unequivocally a promising therapy for HIE, a substantial proportion of infants still die or are left with 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 moderate-resource settings with different risk factors but adequate facilities and infrastructure are urgently needed, and were identified as areas of high priority for study. ■

Submitted for publication Apr 13, 2011; last revision received Jun 16, 2011; accepted Aug 2, 2011.

Reprint requests: Rosemary D. Higgins, MD, Pregnancy and Perinatology Branch, Center for Developmental Biology and Perinatal Medicine, NICHD, NIH, 6100 Executive Blvd, Room 4B03B, MSC 7510, Bethesda, MD 20892. E-mail: higginsr@mail.nih.gov

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.
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.
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.
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. Pediatrics 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.
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. Arch Pediatr Adolesc Med 2011;165:692-700.
7. Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ 2010;340:c363.
8. Higgins RD, Raju TNK, Perlman J, Azzopardi DV, Blackmon LR, Clark RH, et al. Hypothermia and perinatal asphyxia: executive summary of the National Institute of Child Health and Human Development Workshop. J Pediatr 2006;148:170-5.
9. Yager JY. Animal models of hypoxic-ischemic brain damage in the newborn. Semin 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.
11. Gunn AJ, Bennet L. Fetal hypoxia and patterns of brain injury: insights from animal models. Clin Perinatol 2009;36:579-93.
12. Colbourne F, Li H, Buchan AM. Indefatigable CA1 sector neuroprotection with mild hypothermia induced 6 hours after severe forebrain ischemia in rats. J Cereb Blood Flow Metab 1999;19:742-9.
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.
14. Gunn AJ, Gunn TR. The pharmacology of neuronal rescue with cerebral hypothermia. Early Hum Dev 1998;53:19-35.
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;12:235-42.
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.
17. Thoresen M, Whitelaw A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infant with hypoxic-ischemic encephalopathy. Pediatr 2000;106:92-9.
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. Pediatrics 2002;110:377-85.
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;32:11-7.
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.
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.
22. Li T, Xu F, Cheng X, Guo X, Ji L, Zhang Z, et al. Systemic hypothermia induced within 10 hours after birth improved neurological outcome in newborns with hypoxic-ischemic encephalopathy. Hosp Pract (Minneap) 2009;37:147-52.
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. Pediatr Acad Soc 2011. 4750.10.
24. Shankaran S, and Extended Hypothermia Follow-Up Subcommittee, Follow-Up PIs of the NICHD NRN. Do neuroprotective effects of whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy persist to childhood. Pediatr Acad Soc 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. Pediatrics 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. Pediatrics 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. Pediatrics 2006;117:942-8.
28. Kattwinkel J, Perlman JM, Aziz K, Colby C, Fairchild K, Gallagher J, et al. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 15: neonatal resuscitation. Circulation 2010;122(Suppl 3):S909-19.
29. National Institute for Health and Clinical Excellence,.Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury: interventional procedure guidance 347. Available from: http://www.nice.org.uk/nicemedia/live/11315/48809/48809.pdf. Accessed August 22, 2011.
30. Adams A, Austin T, Becher JC, Chang J, Edwards D, Jones S, et al. British Association of Perinatal Medicine position statement on therapeutic cooling for neonatal encephalopathy. Available from: http://www.bapm.org/publications/documents/guidelines/Position_Statement_Therapeutic_Cooling_Neonatal_Encephalophay_July%202010.pdf. Accessed August 22, 2011.
31. Gunn AJ, Wyatt JS, Whitelaw A, Barks J, Azzopardi D, Ballard R, et al. Therapeutic hypothermia changes the prognostic value of clinical evaluation of neonatal encephalopathy. J Pediatr 2008;152:55-8.
32. Thoresen M, Hellström-Westas L, Liu X, de Vries LS. Effect of hypothermia on aEEG in infants with asphyxia. Pediatrics 2010;126:e131-9.
33. Shankaran S, Pappas A, McDonald SA, Laptook AR, Bara R, Ehrenkranz R, et al. Neonatal hypoxic ischemic encephalopathy: predictive value of an early amplitude integrated EEG and neurological examination. Pediatr 2011;128:e112-20.
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;158:360-5.
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.
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. Pediatr Acad Soc 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.
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. Pediatr Crit Care Med 2011. April 14 [Epub ahead of print].
39. Pappas A, Shankaran S, Laptook AR, Langer JC, Bara R, Ehrenkranz RA, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Hypocarbia and adverse outcome in neonatal hypoxic-ischemic encephalopathy. J Pediatr 2011;158:752-8.
40. Perlman JM. Summary proceedings from the Neurology Group on Hypoxic-Ischemic Encephalopathy. Pediatrics 2006;117:S28-33.
41. Shankaran S. Optimizing (longer, deeper) cooling for neonatal hypoxic-ischemic encephalopathy (HIE). Available from: http://www.clinicaltrials.gov/ct2/show/study/NCT01192776?term=hypothermia+and+infant. Accessed August 22, 2011.
42. Laptook AR. Late hypothermia for hypoxic-ischemic encephalopathy. Available from: http://www.clinicaltrials.gov/ct2/show/study/NCT00614744?term=hypothermia+and+infant&rank=1. Accessed August 22, 2011.
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.
44. Pfister R, Bingham P, Carpenter JH, Horbar JD, Kenny MJ, et al. Hypothermia in practice: initial observations from the Vermont Oxford Network. Pediatr Acad Soc 2010;2632.5.
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.
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.
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.
48. Fairchild KD, Singh IS, Patel S, Drysdale BE, Viscardi RM, Hester L, et al. Hypothermia prolongs activation of NF-κB and augments generation of inflammatory cytokines. Am J Physiol Cell Physiol 2004;287:C422-31.

49. Gadkary CS, Alderson P, Signorini DF. Therapeutic hypothermia for head injury. Cochrane Database Syst Rev 2002;1:CD001048.
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.
51. Girard S, Kadhim H, Lavoie K, Brochu ME, Larouche A, Sebire G. Role of perinatal inflammation in cerebral palsy. Pediatr Neurol 2009;40: 168-74.
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.
53. Longo M, Hankins GD. Defining cerebral palsy: pathogenesis, pathophysiology and new intervention. Minerva Ginecol 2009;61:421-9.
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; 48:445-51.
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.
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. Pediatrics 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.
58. Wilkinson D, Thayyil 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.
59. Thoresen M. A feasibility study of adding xenon to cooling therapy in babies at high risk of brain injury following poor condition at birth. Available from: http://isrctn.org/ISRCTN75602528. Accessed August 22, 2011.
60. Thoresen M. The cool xenon study. Available from: http://www.controlled-trials.com/ISRCTN75602528. Accessed August 22, 2011.
61. Azzopardi D. Neuroprotective effects of hypothermia combined with inhaled xenon following perinatal asphyxia (TOBYXe). Available from: http://www.clinicaltrials.gov/ct2/show/NCT00934700?term=xenon+and+infant&rank=1. Accessed August 22, 2011.
62. Wu YW. Neonatal erythropoietin in asphyxiated term newborns (NEAT). Available from: http://www.clinicaltrials.gov/ct2/show/NCT00719407?term=Erythropoietin+and+infant&rank=14. Accessed August 22, 2011.
63. Andropoulos DB. Erythropoietin neuroprotection for neonatal cardiac surgery. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00513240?term=Erythropoietin+and+infant&rank=11. Accessed August 22, 2011.
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.
65. McPherson RJ, Juul SE. Erythropoietin for infants with hypoxic-ischemic encephalopathy. Curr Opin Pediatr 2010;22:139-45.
66. Givehchian M, Beschorner R, Ehmann C, Frauenlob L, Morgalla M, Hashemi B, et al. Neuroprotective effects of erythropoietin during deep hypothermia circulatory arrest. Eur J Cardiothorac Surg 2010;37: 662-8.
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.
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.
70. Bennet L, Booth L, Gunn AJ. Potential biomarkers for HIE. Semin Fetal Neonat 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;25:445-51.
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;37:667-70.
73. Azzopardi D, Edwards AD. Magnetic resonance biomarkers of neuroprotective effects in infants with hypoxic ischemic encephalopathy. Semin Fetal Neonat M 2010;15:261-9.
74. Oh W, Perritt 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.
75. Mathur AM, Morris LD, Teteh F, Inder TE, Zempel J. Utility of prolonged bedside amplitude-integrated encephalogram in encephalopathic infants. Am J Perinatol 2008;25:611-5.
76. Foran A, Cinnante C, Groves A, Azzopardi DV, Rutherford MA, Cowan FM. Patterns of brain injury and outcome in term neonates presenting with postnatal collapse. Arch Dis Child Fetal Neonatal Ed 2009; 94:F168-77.
77. Lawrence R, Mathur A, Nguyen T, 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.
78. Sarkar S, Barks JD, Donn SM. Should amplitude-integrated electroencephalography be used to identify infants suitable for hypothermia neuroprotection? J Perinatol 2008;28:117-22.
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.
80. Azzopardi D, Edwards AD. Magnetic resonance biomarkers of neuroprotective effects in infants with hypoxic ischemic encephalopathy. Semin Fetal Neonatal Med 2010;15:261-9.
81. Elstad M, Whitelaw A, Thoresen M. Cerebral Resistance Index is less predictive in hypothermic encephalopathic newborns. Acta Paediatr 2011; 10.1111/j.1651-2227.2011.02327.x [Epub ahead of print].
82. Thoresen M. Patient selection and prognostication with hypothermia treatment. Semin Fetal Neonat Med 2010;15:247-52.
83. 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.
84. 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. Pediatrics 2008;122:491-9.
85. 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.
86. 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.
87. 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].

Appendix

NICHD Hypothermia Workshop Speakers and Moderators include: Denis Victor Azzopardi, MD, FRCP, Imperial College of London, London, UK; Carl L. Bose, MD, University of North Carolina, Chapel Hill, NC; Reese H. Clark, MD, Pediatrix Medical Group, Inc, Sunrise, FL; A. David Edwards, FMedSci, Imperial College London, London, UK (Co-Chair); Donna M. Ferriero, MD, University of California, San Francisco, CA; Ronnie Guillet, MD, PhD, University of Rochester Medical Center, Rochester, NY; Alistair J. Gunn, MBChB, PhD, University of Auckland, Auckland, New Zealand; Henrik Hagberg, MD, PhD, Imperial College London, London, UK; Deborah Hirtz, MD, National Institute of Neurological Disorders and Stroke, Bethesda, MD; Terrie E. Inder, MBChB, MD, Washington University School of Medicine, St Louis, MO; Susan E. Jacobs, MD, Royal Women's Hospital, Victoria, Australia; Dorothea Jenkins, MD, Medical University of South Carolina, Charleston, SC; Sandra E. Juul, MD, PhD, University of Washington, Seattle, WA; Abbot R. Laptook, MD, Women and Infants Hospital, Providence, RI; Jerold F. Lucey, MD, University of Vermont School of Medicine, Burlington, VT; Mervyn Maze, MBChB, University of California, San Francisco, CA; Charles Palmer, MBChB, Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey, PA; LuAnn Papile, MD, Baylor College of Medicine, Texas Children's Hospital, Houston, TX; Robert Pfister, MD, University of Vermont School of Medicine, Burlington, VT; Tonse N. K. Raju, MD, DCH, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD; Nicola J. Robertson, PhD, FRCPCH, University College London, London, UK; Mary Rutherford, MD, FRCPCH, FRCR, Imperial College London, London, UK; Seetha Shankaran, MD, Wayne State University School of Medicine, Detroit. MI; Faye Silverstein, MD, University of Michigan, Ann Arbor, MI; Roger F. Soll, MD, University of Vermont School of Medicine, Burlington, VT; Marianne Thoresen, MD, PhD, University of Bristol, Bristol, UK and Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; William F. Walsh, MD, Monroe Carell Jr Children's Hospital at Vanderbilt, Nashville, TN.