Published in final edited form as:

Semin Perinatol. 2016 October ; 40(6): 385–390. doi:10.1053/j.semperi.2016.05.009.

HYPOTHERMIA for NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY: NICHD NEONATAL RESEARCH NETWORK CONTRIBUTION to the FIELD

Seetha Shankaran, MD¹, Girija Natarajan, MD¹, Lina Chalak, MD², Athina Pappas, MD¹, Scott A. McDonald, BS³, and Abbot R. Laptook, MD⁴

¹Department of Pediatrics, Wayne State University School of Medicine

²Department of Pediatrics, University of Texas Southwestern at Dallas

³Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC

⁴Department of Pediatrics, Brown University

Abstract

In this chapter we summarize the NICHD Neonatal Research Network (NRN) trial of whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy in relation to other randomized controlled trials (RCTs) of hypothermia neuroprotection. We describe the NRN secondary studies that have been published in the last 10 years evaluating clinical, genetic, biochemical and imaging biomarkers of outcome.

WHOLE-BODY HYPOTHERMIA for NEONATES with HYPOXIC-ISCHEMIC ENCEPHALOPATHY

The NICHD NRN embarked on the RCT of whole-body hypothermia in term infants with encephalopathy after pre-clinical studies had noted that hypothermia was protective against brain injury after hypoxia-ischemia in animal models^{1–4}. The study was planned to evaluate safety and efficacy of hypothermia. After a pilot study demonstrated feasibility⁵, an RCT was conducted with infants > 36 weeks gestation who had severe acidosis or need for resuscitation at birth and manifested moderate or severe encephalopathy. Infants were assigned to intensive care with either usual temperature control or whole-body hypothermia to an esophageal temperature of 33.5°C for 72 hours, followed by slow rewarming. Neuro-developmental outcome was assessed at 18–22 months of age. The primary outcome was the combined end-point of death or moderate or severe disability. Of 239 eligible infants, 102 were assigned to the hypothermia group and 106 to the control group. There was no difference in adverse events in the two groups. The primary outcome was available for 205

Corresponding author: Seetha Shankaran MD, Children's Hospital of Michigan, 3901 Beaubien Blvd, Detroit MI 48201, Phone 313-745-1436, fax 313-745-5867, sshankar@med.wayne.edu.

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.

infants; in the hypothermia group the primary outcome occurred in 45 of 102 (44%) and in the control group 64 of 103 (62%); risk ratio 0.72 (95%CI 0.54–0.95). The mortality rate was 24% in the hypothermia and 37% in the control group RR 0.68(0.44–1.05). The rate of cerebral palsy was 19% in the hypothermia group and 30% in the control group RR 0.68(0.38–1.22)⁶. The NICHD NRN RCT was the first trial of whole-body hypothermia for neonatal HIE. The Cool Cap trial was the first RCT published of head cooling with mild systemic cooling⁷. Subsequent trials published included the TOBY trial⁸, the Neo.nEURO trial⁹, the RCT performed in China¹⁰ and the ICE trial¹¹. There was relative homogeneity of the RCTs with relative consistency of the results of the primary outcome and CP. The following tables demonstrate the rate of death or survival with disability (Table 1) and the rate of disabling cerebral palsy (Table 2) at 18–24 months among RCTs published to date.

SAFETY and EFFICACY of WHOLE-BODY HYPOTHERMIA

The safety and effectiveness of hypothermia for neonatal HIE was evaluated up to 18 months of age from the RCT data. Inotropic support, need for volume expanders, blood or platelet transfusions, rate of persistent pulmonary hypertension of the newborn, inhaled nitric oxide use and need for ECMO was similar between groups. Growth parameters were similar between survivors while rehospitalizations rates were 27% hypothermia and 42% control. A consistent trend for decreasing frequency of the components of disability was noted among cooled infants compared to control infants¹².

CHILDHOOD OUTCOMES after HYPOTHERMIA for NEONATAL HIE

We followed participants of the first RCT and evaluated cognitive, attention, executive and visuospatial function along with neurological outcomes at 6–7 years of age. The primary outcome of death or an IQ score <70 was available for 190 of 208 children. Of the 97 children in the hypothermia and 93 in the control group, death or an IQ score <70 occurred in 47% and 62% respectively ($p=0.06$), death occurred in 28% and 44% ($p=0.04$) and death or severe disability occurred in 41% and 60% ($P=0.03$). Moderate or severe disability occurred in 24 of 69 children (35%) in the hypothermia and 19 of 50 children (38%) in the control group, respectively ($p=0.87$). Attention-executive dysfunction occurred in 5% and 13%, respectively, of children receiving hypothermia and those receiving usual care ($p=0.19$), and visuospatial dysfunction occurred in 4 and 3% ($p=0.80$). Thus, the neuroprotection noted at 18 to 22 months of age persisted to childhood¹³ and was driven by group differences in death. Importantly better survival with hypothermia did not result in salvage of more brain injured children. The CoolCap study reported on WeeFIM ratings at 7–8 years of age on 62 of 135 surviving children; disability status at 18 months was strongly associated with WeeFIM ratings ($p<0.001$); there was no significant effect of treatment¹⁴. The TOBY trial evaluated neurocognitive function of trial participants at 6–7 years of age with a primary outcome of IQ of 85 or higher; 75 of 145 children (52%) in the hypothermia group vs. 52 of 132 (39%) in the control group survived with an IQ >85 (relative risk, 1.31; $p=0.04$).¹⁵

BIOMARKERS OF OUTCOME

A. CLINICAL BIOMARKERS

1. The stage of HIE at <6 hours of age and evolution of HIE—The predictive ability of stage of HIE for death or moderate severe disability was examined among trial participants; moderate and severe HIE occurred at <6 hours of age among 68% and 32% of 101 hypothermic and 60% and 40% of 103 control group infants, respectively. At 24 and 48 hours of study intervention, infants in the hypothermia group had less severe HIE than infants in the control group. Persistence of severe HIE at 72 hours increased the risk of death or disability after controlling for treatment group, OR 60 (95% CI 15–246). The discharge exam improved the predictive value of stage of HIE at <6 hours of age for death/disability. The presence of abnormal tone, clonus, fisted hand, abnormal movements, absent gag and presence of an asymmetric tonic neck reflex increased risk for death/disability, OR of 2.7 (1.1–6.7) and need for gavage or gastrostomy feedings at discharge was associated with a higher risk for death/disability; OR 8.6 (2.7–26.8)¹⁶. The CoolCap¹⁷, TOBY⁸ and Neo.nNEURO trial⁹ also demonstrated an association of severe HIE at <6 hours of and poor outcome at 18 months.

2. Variables at <6 hours of age—A classification and regression tree analysis of variables at <6 hours of age in the NICHD trial noted that cord pH, evaluation of spontaneous activity on the initial neurological examination, base deficit and PCO₂ in the cord blood gas were useful in predicting outcome at 18 months. Infants with a cord pH <6.7 had a greater risk of death or disability than those with a pH between 6.7 and 7.0. Among those with a cord pH >6.7, no spontaneous activity on the neurological examination was associated with a greater risk of death or disability than those with normal/decreased activity. Among those with normal or decreased activity, base deficit >18.5mEq/L was associated with a greater risk of death/disability than those with a lower base deficit. Among infants with a base deficit <18.5mEq/L, a PCO₂ <87 was associated with a higher risk of death/disability than a higher PCO₂¹⁸.

3. 10 min Apgar score—The relationship of the Apgar score at 10 minutes of age and outcome at 18 months was assessed; a persistently low Apgar score at 10 minutes was associated with death or moderate/severe disability at 18 months of age¹⁹. This association persisted when this relationship was re-examined with 6–7 year outcome after adjusting for birth weight, gestational age, gender, outborn status, hypothermia treatment and center. Among 174 infants, 64/85 (74%) of those with a 10 min Apgar score of 0–3 had death or disability compared to 40/89 (45%) of those with scores >3. Each point increase in the 10 min Apgar score was associated with a significantly lower adjusted risk of death or disability, death, death/IQ <70, death/CP and among survivors with CP, disability and IQ <70 (all p<0.05). The risk-adjusted probabilities were significantly lower in cooled infants; there was no interaction between cooling and Apgar scores. Not all infants with a 10 min Apgar score of <3 had a poor outcome; at 6–7 years of age, of the 24 children with a 10 min Apgar score of 0, five (20.8%) survived without disability²⁰. This finding has implications for clinical practice (duration of resuscitative efforts) and counselling.

4. Elevated Temperatures in the control group—An important observation from some of the trials was that elevated temperatures were recorded in non-cooled comparison groups. In the NRN Hypothermia trial, the mean esophageal temperature was $37.2 \pm 0.7^{\circ}\text{C}$ in the non-cooled group during the 72 hour intervention period, and 63%, 22% and 8% of all temperatures were $> 37^{\circ}\text{C}$, $> 37.5^{\circ}\text{C}$ and $> 38^{\circ}\text{C}$, respectively. These data were analyzed to examine the hypothesis that elevated body temperature is associated with worse outcomes among infants ≥ 36 weeks gestation with HIE. For each infant in the non-cooled group ($n=99$) esophageal temperatures were rank ordered. A high temperature was defined as the average of the highest quartile of esophageal temperatures; the median temperature of each infant was also analyzed. Logistic regression analysis was used to determine if temperature was associated with death or disability at 18 months of age following adjustment for level of encephalopathy at randomization, gender, gestational age and race. The odds of death or disability were increased 4 fold and death 6 fold for each 1°C increase in the highest quartile of esophageal temperature²¹. There are multiple potential explanations for the observed associations; brain injury raises body temperature, elevated body temperature results in brain injury, or elevated temperature is a marker of HIE and brain injury. A similar association was reported among infants in the non-cooled group in the CoolCap trial¹⁷. Among the NICHD NRN trial participants the odds of a worse outcome (death or an $\text{IQ} < 70$) associated with an elevated core temperature were also evident at 6–7 years²².

5. Neonatal Seizures—It remains controversial as to whether neonatal seizures have additional direct effects on the developing brain separate from severity of the underlying encephalopathy; hence the association of clinical seizures and outcome at 18 months was assessed. Of the 208 infants enrolled in the RCT, 127 infants had clinical seizures; they were generally noted in the first four days. In the multivariate analysis, adjusting for study treatment and severity of HIE, there were no differences in outcome²³.

6. Location of birth—A pilot study had noted that infants transported to the cooling center were found to be significantly more likely to die than those born in the participating centers, after controlling for treatment group²⁴. The NICHD NRN data from the hypothermia RCT was used to evaluate the effect of birth location on hypothermia-related outcomes. Outborn infants, $n=93$ experienced a later initiation of therapy (mean, SD) 5.5 (1.1) vs. 4.4 (1.2) hours, lower baseline temperatures 36.6 (1.2) $^{\circ}\text{C}$ vs. 37.1 (0.9) $^{\circ}\text{C}$, and more severe HIE (43 vs. 29%) than inborn infants ($n=115$). Maternal education < 12 years (50 vs. 14%) and African-American ethnicity (43 vs. 25%) were more common in the inborn group. When adjusted for NRN center and HIE severity, there were no significant differences in 18 month outcomes or in-hospital organ dysfunction between inborn and outborn infants²⁵.

7. Temperature profile of cooled infants—Decreases below target esophageal temperatures were noted among neonates undergoing cooling in the RCT of hypothermia for neonatal HIE; hence the impact on outcome of the temperature profile among cooled infants was examined. Infants who had temperature decreases $< 32.0^{\circ}\text{C}$ during induction ($n=33$) or maintenance phase ($n=10$) had lower birth weights and a greater need for blood pressure support compared to all other cooled infants ($n=58$). No increase in acute adverse events was

noted among infants with temperatures $<32.0^{\circ}\text{C}$, and hours spent at $<32.0^{\circ}\text{C}$ were not associated with the primary outcome of death or disability or the Bayley II Mental Developmental Index (MDI) scores at 18 months²⁶. In a separate analysis evaluating the effects of phenobarbital administration at less than 6 hours of age on the temperature profile, it was noted that the administration of phenobarbital among 54 infants was associated with lower temperatures during induction and a shorter time to target temperature compared to infants cooled who did not receive phenobarbital ($n=44$)²⁷.

The NRN Hypothermia trial used the Cincinnati Sub-Zero Blanketrol II (CSZ, Cincinnati, OH) in the automatic control mode (servo control). The Blanketrol III device now available has additional cooling modes that may result in better temperature control. A retrospective comparison was conducted of infants undergoing hypothermia with either the Blanketrol II ($n=100$) from the NRN trial or the Blanketrol III ($n=90$) in a gradient mode from two new NRN centers. The primary outcome, time spent between 33.0°C and 34.0°C during the maintenance phase was similar between the cohorts; thus the ability to maintain esophageal temperature within the target range of 33°C to 34°C was similar for the automatic and gradient modes of the Blanketrol devices²⁸.

8. Early Hypocarbica—As PCO_2 can impact cerebral perfusion and since the initial ventilator minute volume required to maintain normocarbica may be significantly lower for infants undergoing hypothermia, the extent and impact of early hypocarbica after HIE (both minimum PCO_2 and cumulative exposure to $\text{PCO}_2 <35$ mm Hg) on death or disability at 18 months was evaluated in the NRN RCT dataset. After adjusting for severity of acidosis, level of HIE, treatment group, time to spontaneous respiration and ventilator days, both minimum PCO_2 and cumulative PCO_2 within 12 hours of study intervention were associated with increased risk for death and disability²⁹. These data suggest that it would be important to maintain PCO_2 in the normal range when supporting ventilation for HIE infants; however, for some infants hypocarbica appears to reflect intrinsic CNS driven hyperventilation and may not be modifiable.

9. Amplitude Integrated EEG (aEEG)—Multiple studies of aEEG performed at <6 hours of age have reported accurate prediction of outcome in term infants with HIE prior to the era of neuroprotection with hypothermia^{30–34}. The Cool Cap¹⁷ and TOBY⁸ trials noted that death or disability was lower among infants with a less severe aEEG background pattern at <6 hours of age. The NRN examined the predictive validity of the aEEG at <9 hours of age and the stage of HIE among infants eligible for cooling among 108 infants (71 moderate and 31 severe HIE); 46 of the infants were part of the RCT and 62 were enrolled following the RCT. Severe HIE and an abnormal aEEG were related to poor outcome at 18 months of age in univariate analysis, whereas severe HIE alone was predictive of outcome in multivariate analysis. Addition of aEEG pattern to HIE stage did not add to the predictive value of the model; the area under the curve changed from 0.72 to 0.75 ($p=.19$)³⁵. The TOBY trial investigators similarly reported that the positive predictive value (PPV) of a severely abnormal aEEG at <6 hours of age by voltage and pattern methods was 0.63 and 0.59 in non-cooled and 0.55 and 0.51 in cooled infants³⁶. Thus under conditions of an RCT, the predictive value of aEEG is lower than that reported in observational studies.

10. Clinical assessment of disability at 18 months—The relationship of 18 month disability and disability at 6–7 years was assessed in the NRN Hypothermia RCT participants¹³. Among children treated with hypothermia, moderate or severe disability at 18 months had sensitivity (SENS) of 63%, specificity (SPEC) of 96%, PPV of 88% and a negative predictive value (NPV) of 83%, while for the control group children these were 95%, 97%, 95% and 97% respectively. Among hypothermia group children moderate/severe CP at 18 months had a SENS, SPEC, PPV and a NPV of 100%; for the control group these values were 93%, 100%, 100% and 97%. Thus the 18 month outcome serves as a surrogate of 6–7 year outcome regarding disability.

11. Neonatal, Family and 18 month Functional status and 6–7 year outcome—Among children with neonatal HIE, the association between 18-month functional status by parental report and disability at 6–7 years was examined. Parents of participants of the NICHD NRN RCT responded to three questionnaires; the Functional Status-II (FS-II), the Impact on Family (IOF) and the Family Resource Scale (FRS) at the 18 month follow-up visit. These data were correlated with 6- to 7-year neurodevelopmental assessments among 37 children with moderate/severe disability and 74 with mild/no disability. Rates of severe HIE at birth (32 vs. 15%) and public insurance at 18 months (73% vs. 47%) as well as IOF scales were higher among children who had moderate/severe disability compared to mild/no disability. The 18 month FS-II Independence and General Health scores were significantly lower in children with moderate severe disability, compared to mild/no disability. The FRS revealed that both total resources and money subscales were significantly lower among the disabled children compared to those with mild/no disability. The IOF revealed that families with children with moderate/severe disability had higher scores on financial Impact, duration of planning and caretaker and family burden compared to families with no disabilities. On path analysis, severe HIE, greater IOF and public insurance were associated with poorer 18-month FS-II Independence scores, which, in turn, were associated with disability at 6 to 7 years. Each unit increase in FS-II Independence score at 18 months was associated with a reduction in childhood disability, OR (95% CI) 0.92(0.87–0.97)³⁷.

12. CP and outcome in childhood—The association between severity of CP and growth until 6–7 years of age was also studied in the same NRN Hypothermia RCT cohort. Children with moderate or severe CP (n=23) at 6–7 years of age had higher rates of slow growth (weight <10th centile 57% vs. 3%, length < 10th centile 70% vs. 2% and head circumference <10th centile 82% vs. 13%, all p<0.0001), compared to those with no CP (n=92). Increasing severity of slow growth was associated with increasing age (p< .04 for weight, p< .001 for length, and p< .0001 for head circumference). Lack of head growth at 18 months was a strong predictor of moderate/severe disability at 6–7 years. Gastrostomy feeds were associated with better growth of weight and length. Rates of cognitive and motor impairment and rehospitalizations at 18 to 22 months (59 vs 25%, p<0.001) and 6 to 7 years (78 vs. 25%, p<0.0001) were significantly higher in children with moderate or severe CP³⁸. These findings highlighted growth failure in children with CP and the need for close nutritional surveillance and management.

13. Cognitive outcomes at 18 months—The spectrum of cognitive outcomes among school-aged survivors of the NICHD NRN RCT of whole-body hypothermia for neonatal HIE has been described. IQ <70 was noted in 28% of the children overall; and among 96% of survivors with CP and 9% of children without CP. Children with an MDI <70 at 18 months had, on average, an adjusted IQ at 6 to 7 years that was 42 points lower than that of those with an MDI >84 (95% CI, -49.3 to -35.0; $p<.001$). When 18 month and 6–7 year outcomes were compared, 72% of children remained in the same developmental range. Overall, an MDI <70 at 18 months of age had a SENS of 0.87, SPEC of 0.96, PPV and NPV of 0.90 and 0.95 respectively for IQ score <70 at school age. All children with IQ < 70, 20% of children with normal IQ and 28% of those with IQ 70 to 84 received special educational support services or were held back 1 grade level. These data suggested that assessment and intervention for cognitive impairment should be undertaken in all children with neonatal encephalopathy, regardless of motor impairment³⁹.

B. GENETIC BIOMARKERS OF OUTCOME

Presence of the Apolipoprotein E (APOE) e4 allele has been associated with CP and the e2 allele with worse neurological outcomes in children with congenital heart disease. The presence of the APOE genotype and outcome was assessed among the NRN hypothermia RCT participants. 129 infants had genotype and outcome data; disability prevalence was 30 and 19% among those with and without the e3 genotype, 25 and 26% among those with and without the e2 allele and 18 and 29% among those with and without the e4 allele respectively. None of the differences were statistically significant. CP prevalence was also similar between groups. Thus, disability was not associated with APOE genotype among survivors of neonatal HIE⁴⁰.

C. BIOCHEMICAL MARKERS OF OUTCOME FOLLOWING HIE

The NRN Hypothermia study protocol included a secondary study evaluating the association between urinary lactate to creatinine ratio (ULCR) and neurodevelopmental outcome with spot urine samples collected on 58 term infants (28 hypothermia and 30 controls). The ULCR was significantly higher in infants who died or had moderate or severe disability at 18 months; this association OR 5.52 (95%CI 1.36–22.42) was seen after controlling for hypothermia and severity of HIE. However, there was significant overlap in values between normal/mild and moderate/severe disability groups limiting predictive value of this measure⁴¹.

D. IMAGING BIOMARKERS OF OUTCOME FOLLOWING HIE

The CoolCap trial documented that brain injury was decreased following hypothermia for neonatal HIE⁴². In the NRN hypothermia RCT, 136 infants had neonatal MRI scans and outcome data at 18 months of age. A pattern of brain injury was described with each level reflecting a greater involvement of brain injury: 0, normal; 1A, minimal cerebral lesions with no involvement of basal ganglia or thalamus (BGT) or anterior or posterior limb of the internal capsule (ALIC, PLIC) and no watershed infarction; 1B, extensive cerebral lesions only; 2A any BGT, ALIC, PLIC or watershed involvement only, 2B: 2A and additional cerebral lesions and 3: cerebral hemispheric devastation. Normal scans were noted among 38

of 73 infants (52%) in the hypothermia group and 22 of 63 (35%) in the control group. Infants in the hypothermia group had significantly fewer areas of infarction (12%) compared to control infants (22%). Fifty one of 136 participants had death or moderate/severe disability at 18 months. The brain injury pattern described correlated with outcome of death or disability, and with disability among survivors. Each point increase in the severity of the pattern of brain injury was independently associated with a two fold increase of death or disability⁴³. The ICE trial evaluated 127 MRIs and noted reduced brain injury on T-1 and T2-weighted MRI studies and found abnormal MRI findings are prognostic of moderate/severe HIE at 2 years of age⁴⁴.

Recently the NRN hypothermia RCT data was used to examine ability of neonatal MRI imaging to predict death or IQ <70 at 6–7 years of age. Death or IQ <70 occurred in 4 of 50 (8%) of children with pattern 0, one of 6 (17%) with 1A, one of 4 (25%) with 1B, 3 of 8 (38%) with 2A, 32 of 49 (65%) with 2B and 7 of 7 (100%) with pattern 3, $p<0.001$; this association was also seen within hypothermia and control subgroups. IQ was 90+13 among the 46 children with a normal MRI and 69+25 among the 50 children with an abnormal MRI. In childhood, for a normal outcome, a normal neonatal MRI had a SENS of 61%, SPEC of 92%, a PPV of 92% and a NPV of 59%; for death or IQ <70, the 2B and 3 pattern combined had a SENS of 81%, SPEC of 78%, PPV of 70% and a NPV of 87%. Thus The NICHD NRN MRI pattern of neonatal brain injury is a biomarker of outcome at 6–7 years⁴⁵.

Summary of Biomarkers of Outcome Following HIE from the NICHD NRN—Our data has concluded the following: 1) Persistence of severe HIE following 72 hours of cooling and abnormal neurological examination at NICU discharge predict abnormal outcome in infancy; 2) the 18-month examination correlates with outcome at 6–7 years of age; 3) cognitive impairment can occur in the absence of CP and 4) neonatal MRI is predictive of outcome in childhood, although neurodevelopmental assessments still remain the gold standard of outcome.

Acknowledgments

Supported by grants from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

References

1. Busto R, Dietrich WD, Globus MY, et al. Small differences in intranscemic brain temperature critically determine the extent of ischemic neuronal injury. *J Cereb Blood Flow Metab.* 1987; 7:729–38. [PubMed: 3693428]
2. Coimbra C, Wieloch T. Moderate hypothermia mitigates neuronal damage in the rat brain when initiated several hours following transient cerebral ischemia. *Acta Neuropathol.* 1994; 87:325–331.
3. Thoresen M, Bagenholm R, Loberg EM, Apricena F, Kjellmer I. Posthypoxic cooling of neonatal rats provides protection against brain injury. *Arch Dis Child.* 1996; 74:F3–F9.
4. Gunn AJ, Gunn TR, Gunning MI, Williams CE, Gluckman PD. Neuroprotection with prolonged head cooling started before postischemic seizures in fetal sheep. *Pediatrics.* 1998; 102:1098–1106. [PubMed: 9794940]

5. Shankaran S, Laptook A, Wright LL, 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. [PubMed: 12165594]
6. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body Hypothermia for Neonates with Hypoxic-Ischemic Encephalopathy. *N Engl J Med*. 2005; 353:1574–1584. [PubMed: 16221780]
7. Gluckman PD, Wyatt J, Azzopardi DV, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicenter Randomised Trial. *Lancet*. 2005; 365:663–70. [PubMed: 15721471]
8. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med*. 2009; 361(14):1349–58. [PubMed: 19797281]
9. 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(4):e771–8. [PubMed: 20855387]
10. Zhou WH, Cheng GQ, Shao XM, 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(3):367–72. 372.e1–3. [PubMed: 20488453]
11. Jacobs SE, Morley CJ, Inder TE, 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(8):692–700. [PubMed: 21464374]
12. Shankaran S, Pappas A, Laptook AR, 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. [PubMed: 18829776]
13. Shankaran S, Pappas A, McDonald SA, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. *N Engl J Med*. 2012; 31(366):2085–92.
14. Guillet R, Edwards AD, Thoresen M, et al. Seven- to eight-year follow-up of the CoolCap trial of head cooling for neonatal encephalopathy. *Pediatr Res*. 2012; 71:205–9. [PubMed: 22258133]
15. Azzopardi D, Strohm B, Marlow N, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. *N Engl J Med*. 2014; 10(371):140–9.
16. Shankaran S, Laptook AR, Tyson JE, et al. Evolution of encephalopathy during whole body hypothermia for neonatal hypoxic-ischemic encephalopathy. *J Pediatr*. 2012; 160:567–572. e3. [PubMed: 22050871]
17. Wyatt JS, Gluckman PD, Liu PY, et al. Determinants of outcomes after head cooling for Neonatal Encephalopathy. *Pediatrics*. 2007; 119:912–921. [PubMed: 17473091]
18. Ambalavanan N, Carlo WA, Shankaran S, et al. Predicting outcomes of neonates diagnosed with hypoxemic-ischemic encephalopathy. *Pediatrics*. 2006; 118:2084–2093. [PubMed: 17079582]
19. Laptook AR, Shankaran S, Ambalavanan N, et al. Outcome of term infants using Apgar scores at 10 minutes following hypoxic-ischemic encephalopathy. *Pediatrics*. 2009; 124:1619–26. [PubMed: 19948631]
20. Natarajan G, Shankaran S, Laptook AR, et al. Apgar scores at 10 min and outcomes at 6–7 years following hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed*. 2013; 0:F1–F7.
21. Laptook A, Tyson J, Shankaran S, et al. Elevated temperature after hypoxc-ischemic encephalopathy: A risk factor for adverse outcome. *Pediatrics*. 2008; 122:491–9. [PubMed: 18762517]
22. Laptook AR, McDonald SA, Shankaran S, et al. Elevated temperature and 6- to 7-year outcome of neonatal encephalopathy. *Ann Neurol*. 2013; 73:520–8. [PubMed: 23595408]
23. Kwon JM, Guillet R, Shankaran S, 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]
24. Eicher DJ, Wagner CL, Katikaneni LP, et al. Moderate hypothermia in neonatal encephalopathy: Safety outcomes. *J Pediatr Neurol*. 2004; 32:18–24.
25. Natarajan G, Pappas A, Shankaran S, et al. Effect of inborn vs. outborn delivery on neurodevelopmental outcomes in infants with hypoxic-ischemic encephalopathy: secondary

- analyses of the NICHD whole-body cooling trial. *Pediatr Res*. 2012; 72:414–9. [PubMed: 22914450]
26. Shankaran S, Laptook AR, McDonald SA, et al. Temperature profile and outcomes of neonates undergoing whole body hypothermia for neonatal hypoxic-ischemic encephalopathy. *Pediatr Crit Care Med*. 2012; 13:53–9. [PubMed: 21499182]
 27. Sant'Anna G, Laptook AR, Shankaran S, et al. Phenobarbital and temperature profile during hypothermia for hypoxic-ischemic encephalopathy. *J Child Neurol*. 2012; 27:451–7. [PubMed: 21960671]
 28. Laptook AR, Kilbride H, Shepherd E, et al. Temperature control during therapeutic hypothermia for newborn encephalopathy using different Blanketrol devices. *Ther Hypothermia Temp Manag*. 2014; 4:193–200. [PubMed: 25285767]
 29. Pappas A, Shankaran S, Laptook AR, et al. Hypocarbica and adverse outcome in neonatal hypoxic-ischemic encephalopathy. *J Pediatr*. 2011; 158:752–8. [PubMed: 21146184]
 30. Eken P, Toet MC, Groenendaal F, de Vries LS. Predictive value of early neuroimaging, pulsed Doppler and neurophysiology in full term infants with hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed*. 1995; 73:F75–80. [PubMed: 7583610]
 31. Hellstrom-Westas L, Rosen I, Svenningsen NW. Predictive value of early continuous amplitude integrated EEG recordings on outcome after severe birth asphyxia in full term infants. *Arch Dis Child Fetal Neonatal Ed*. 1995; 72:F34–8. [PubMed: 7743282]
 32. Toet MC, Hellstrom-Westas L, Groenendaal F, Eken P, de Vries LS. Amplitude integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed*. 1999; 81:F19–23. [PubMed: 10375357]
 33. al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. *Pediatrics*. 1999; 103(6):1263–71. [PubMed: 10353940]
 34. Shalak LF, Laptook AR, Velaphi SC, Perlman JM. Amplitude-integrated electroencephalography coupled with an early neurologic examination enhances prediction of term infants at risk for persistent encephalopathy. *Pediatrics*. 2003; 111:351–7. [PubMed: 12563063]
 35. Shankaran S, Pappas A, McDonald SA, et al. Predictive value of an early amplitude integrated electroencephalogram and neurologic examination. *Pediatrics*. 2011; 128:e112–20. [PubMed: 21669899]
 36. Azzopardi D. TOBY study group. Predictive value of the amplitude integrated EEG in infants with hypoxic ischaemic encephalopathy: data from a randomised trial of therapeutic hypothermia. *Arch Dis Child Fetal Neonatal Ed*. 2014; 99:F80–2. [PubMed: 23800393]
 37. Natarajan G, Shankaran S, Pappas A, et al. Functional status at 18 months of age as a predictor of childhood disability after neonatal hypoxic-ischemic encephalopathy. *Dev Med Child Neurol*. 2014; 56:1052–58. [PubMed: 24957482]
 38. Vohr BR, Stephens B, McDonald SA, et al. Cerebral palsy and growth failure at 6 to 7 years. *Pediatrics*. 2013; 4:e905–14.
 39. Pappas A, Shankaran S, McDonald SA, et al. Cognitive outcomes after neonatal encephalopathy. *Pediatrics*. 2015; 135:e624–34. [PubMed: 25713280]
 40. Cotten MC, Goldstein RF, McDonald SA, et al. Apolipoprotein E genotype and outcome in infants with hypoxic-ischemic encephalopathy. *Pediatric Research*. 2014; 75:424–30. [PubMed: 24322171]
 41. Oh W, Perritt R, Shankaran S, et al. Association between urinary lactate to creatinine ratio and neurodevelopmental outcome in term infants with hypoxic-ischemic encephalopathy. *J Pediatr*. 2008; 153:375–8. [PubMed: 18534246]
 42. Rutherford M, Ramenghi LA, Edwards AD, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischemic encephalopathy: a nested substudy of a randomized controlled trial. *Lancet Neurology*. 2010; 9:39–45. [PubMed: 19896902]
 43. Shankaran S, Barnes PD, Hintz SR, et al. Brain injury following trial of hypothermia for neonatal hypoxic-ischemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed*. 2012; 97:F398–404. [PubMed: 23080477]

44. Cheong JLY, Coleman L, Hunt RW, et al. Prognostic utility of magnetic resonance imaging in neonatal hypoxic-ischemic encephalopathy. *Arch Pediatr Adolesc Med.* 2012; 166:634–40. [PubMed: 22751877]
45. Shankaran S, McDonald SA, Laptook AR, et al. Neonatal magnetic resonance imaging pattern of brain injury as a biomarker of childhood outcomes following a trial of hypothermia for neonatal hypoxic-ischemic encephalopathy. *J Pediatr.* 2015; 167:987–93. [PubMed: 26387012]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Hypothermia RCT's: Death or Disability at 18m

	Hypothermia	Control	OR (95%CI)
Cool Cap	55%	66%	0.61 (0.34–1.09)
NICHD	44%	62%	0.72 (0.54–0.95)
TOBY	45%	53%	0.86 (0.68–1.07)
Neo.nEURO	51%	83%	0.21 (0.09–0.54)
China	31%	49%	0.47 (0.26–0.84)
ICE	51%	66%	0.77 (0.62–0.98)

Table 2

Hypothermia RCT's: Rates of CP at 18m

	Hypothermia	Control	OR (95%CI)
Cool Cap	32%	43%	0.75 (0.48–1.16)
NICHD	19%	30%	0.68 (0.38–1.22)
TOBY	28%	41%	0.67 (0.47–0.96)
Neo.nEURO	12%	48%	0.15 (0.04–0.60)
China	14%	28%	0.40 (0.17–0.92)
ICE	27%	29%	0.92 (0.54–1.59)