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Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy

An Updated Systematic Review and Meta-analysis

Mohamed A. Tagin, MB BCh; Christy G. Woolcott, PhD; Michael J. Vincer, MD; Robin K. Whyte, MB; Dora A. Stinson, MD

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Objective: To establish the evidence of therapeutic hypothermia for newborns with hypoxic ischemic encephalopathy (HIE).

Data Sources: Cochrane Central Register of Controlled Trials, Oxford Database of Perinatal Trials, MEDLINE, EMBASE, and previous reviews.

Study Selection: Randomized controlled trials that compared therapeutic hypothermia to normothermia for newborns with HIE.

Intervention: Therapeutic hypothermia.

Main Outcome Measures: Death or major neurodevelopmental disability at 18 months.

Results: Seven trials including 1214 newborns were identified. Therapeutic hypothermia resulted in a reduction in the risk of death or major neurodevelopmental disability (risk ratio [RR], 0.76; 95% CI, 0.69-0.84) and increase in the rate of survival with normal neurological function (1.63; 1.36-1.95) at age 18 months. Hypothermia reduced the risk of death or major neurodevelopmental disability at age 18 months in newborns with moderate HIE (RR, 0.67; 95% CI, 0.56-0.81) and in newborns with severe HIE (0.83; 0.74-0.92). Both total body cooling and selective head cooling resulted in reduction in the risk of death or major neurodevelopmental disability (RR, 0.75; 95% CI, 0.66-0.85 and 0.77; 0.65-0.93, respectively).

Conclusion: Hypothermia improves survival and neurodevelopment in newborns with moderate to severe HIE. Total body cooling and selective head cooling are effective methods in treating newborns with HIE. Clinicians should consider offering therapeutic hypothermia as part of routine clinical care to these newborns.

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Author Affiliations: Department of Paediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario (Dr Tagin), and Perinatal Epidemiology Research Unit (Dr Woolcott) and Department of Pediatrics (Drs Vincer, Whyte, and Stinson), IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada.

GLOBAL ESTIMATES FOR ASphyxia-related neonatal deaths vary from 0.7 to 1.2 million annually.[1] Peripartum asphyxia remains an important cause of long-term sensorineural impairments and disabilities.[2-4]

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During the last 2 decades, evidence from experimental and clinical studies suggests that therapeutic hypothermia reduces cerebral injury and improves neurological outcome.[5-14] Experts and clinicians have been hesitant about these findings with the supposition that the evidence is yet insufficient to support widespread implementation of therapeutic hypothermia outside the limits of controlled trials.[15-18] A Cochrane review of therapeutic hypothermia including 638 term newborns with moderate to severe encephalopathy and evidence of intrapartum asphyxia showed significant benefits in newborns with severe encephalopathy, but the benefits for newborns with moderate encephalopathy were unclear.[8] Two more recent reviews[14,19] showed significant benefits for newborns with moderate encephalopathy, but the benefits for newborns with severe encephalopathy were not signifi-

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cant. There are more studies published since the previous reviews.[20-22] The primary objective of this review was to use all the available data, including those from the most recently published randomized trials, to evaluate the effectiveness of therapeutic hypothermia for newborns with hypoxic ischemic encephalopathy (HIE).

METHODS

DATA SOURCE

To identify all the relevant studies, the search strategy of the Cochrane systematic review, "Cooling for Newborns With Hypoxic Ischaemic Encephalopathy"[8] (last edited in June 2007), was reproduced from June 2007 to May 2011. Relevant studies were identified from the Cochrane Central Register of Controlled Trials, the Oxford Database of Perinatal Trials, MEDLINE, and EMBASE using the following strategy: {Silver Platter–June 2007 to May 2011: Infant, Newborn (explode) [MeSH heading] and Asphyxia (explode) [MeSH heading] or Hypoxic Ischaemic Encephalopathy and Hypothermia (explode) [MeSH heading]}. References from previous reviews were cross-referenced. No language restrictions were applied.

ELIGIBILITY CRITERIA

Randomized controlled trials that compared therapeutic hypothermia (either systemic or selective head cooling) to normothermia to treat newborns with HIE were included. Studies were selected only if they included data on death or disability at 18 months or older. Randomized controlled trials that had significant methodological limitations were excluded.

STUDY IDENTIFICATION AND DATA EXTRACTION

All titles and abstracts identified as potentially relevant by the literature search were assessed for inclusion in the review. The full texts for potentially eligible studies were reviewed against the predefined criteria. Data were extracted on a predefined data extraction form by the primary author (M.A.T.). The selection of relevant studies was by consensus. Whenever necessary, additional information and clarification of published data were requested from the authors of the individual trials.[13,20-22]

CRITICAL APPRAISAL

The methodological quality of the studies was assessed using the risk of bias assessment tool as recommended by the Cochrane Neonatal Review Group except for the criterion of blinding of intervention (methods of cooling cannot be masked).[23] The domains of assessment included sequence generation, allocation concealment, blinding of outcome assessment, completeness of assessment, selective reporting bias, and the likelihood of other biases. The methodological quality of the studies previously reported in the Cochrane review was reassessed.[8]

OUTCOMES MEASURES

The primary outcome was a composite of death or long-term (≥18 months) major neurodevelopmental disability (cerebral palsy; developmental delay [<2 SDs] below the mean in Mental Developmental Index (MDI) score in Bayley Scales of Infant Development II [BSID-II],[24] a Cognitive Scale score or a Language Composite Scale score on the BSID-III,[24,25] Griffiths assessment,[26] Brunet-Lézine quotient,[27] or Gesell Child Development Age Scale[28]; or intellectual impairment [IQ <2 SDs below mean], blindness [vision <6/60 in both eyes], or sensorineural deafness requiring amplification). Secondary outcomes included examining each component of the primary outcome independently, survival with normal neurological function (no cerebral palsy, normal development [not <1 SD below the mean on the aforementioned standardized tests], normal vision, and normal hearing). Furthermore, we determined if the severity of encephalopathy or the method of cooling modified the effect of hypothermia on the composite outcome of death or major disability. Grade of encephalopathy was assessed on the basis of clinical examination[29] or amplitude-integrated electroencephalography (aEEG),[30] both of which were considered equivalent.

DATA ANALYSIS

Meta-analysis was performed with Review Manager software (RevMan, version 5.0; Nordic Cochrane Centre) using the Mantel-Haenszel method and a fixed-effect model.[31] Risk ratios (RRs) and the number needed to treat (NNT) with 95% CIs were calculated. The χ^2 test was applied to detect between-study heterogeneity, and I^2 values were calculated to assess statistical heterogeneity.

RESULTS

Fourteen trials were evaluated for eligibility (eFigure 1; http://www.archpediatrics.com). Seven trials fulfilled the inclusion criteria; their details are shown in **Table 1**, with additional details noted in the eAppendix. The 7 studies that were excluded along with reasons for exclusion are shown in **Table 2**.[7,9,33-37] The 2007 Cochrane review identified 9 randomized controlled trials[7-10,12,32-34,36]; only 3 trials reported data on death or major disability at 18 months or longer.[10,12,32] Database searching between June 2007 and May 2011 identified 6 additional randomized controlled trials (eFigure 1),[13,20-22,35,37] of which only 4 satisfied the inclusion criteria (Table 1).[13,20-22] The trial by Shankaran et al[12] reported moderate or severe disability in their outcome. In fact, most newborns in this trial had severe disability (43 of 45 in the hypothermia group and 62 of 64 in the normothermia group either died or had an MDI of less than 70 at follow-up at 18-22 months). Therefore, the numbers reported in this trial for moderate or severe disability were used to define major disability in this review.

CLINICAL HETEROGENEITY ASSESSMENT AMONG INCLUDED STUDIES

A total of 1214 newborns with moderate to severe HIE were randomized in the included trials. Newborns who were reported to have mild HIE were excluded from this review. The included trials had similar enrollment criteria including evidence of birth asphyxia and moderate to severe HIE (Table 1). Three trials also included abnormal aEEG as an enrollment criterion.[10,13,21] Newborns were at least 35 weeks gestation in 1 trial,[20] at least 36 weeks in 4 trials,[10,12,13,21] and at least 37 weeks in the other 2 trials.[22,32] Four trials used total body cooling[12,13,20,21] and 3 trials used selective head cooling with mild systemic hypothermia.[10,22,32] In all the included trials,

Table 1. Details of Included Trials[a]

Source	Characteristics	Description
Azzopradi et al,[13] 2009	Inclusion	GA≥36 weeks with PHI, moderate to severe encephalopathy, and abnormal background on aEEG
	Exclusion	Major congenital abnormalities or >6 h of age
	Intervention	Hypothermia group (n=163): cooling blanket to maintain rectal temperature 33°C-34°C Control group (n=162): radiant heaters to maintain rectal temperature 37.0°C±0.2°C
	Primary outcome	Death or severe neurodevelopmental disability in survivors at 18 mo of age
Gluckman et al,[10] 2005	Inclusion	GA≥36 weeks with PHI, moderate to severe encephalopathy, and abnormal background on aEEG
	Exclusion	Major congenital abnormalities, >5.5 h of age, received prophylactic anticonvulsants, BW<1800 g, HC<2 SD for gestation if BW and length>−2 SD, or critically ill and unlikely to benefit from intensive care
	Intervention	Hypothermia group (n=116): cooling cap to maintain rectal temperature 34°C-35°C Control group (n=118): radiant warmer to maintain rectal temperature 36.8°C-37.2°C
	Primary outcome	Mortality and severe neurodevelopmental disability in survivors at 18 mo of age
Gunn et al,[32] 1998	Inclusion	GA≥37 weeks with PHI and encephalopathy
	Exclusion	Major congenital abnormality or metabolic diseases
	Intervention	Hypothermia group (n=18): cooling cap with sequential randomization of rectal temperature to 36.0°C-36.5°C (n=6), then to 35.5°C-35.9°C (n=6), then to 34.5°C-35.4°C (n=6) Control group (n=13): radiant warmer to maintain rectal temperature 36.8°C-37.2°C
	Primary outcome	Acute adverse effects, long-term neurodevelopmental outcomes were also reported
Jacobs et al,[20] 2011	Inclusion	GA≥35 weeks with PHI and moderate or severe encephalopathy
	Exclusion	Major congenital abnormalities, >6 h of age, BW<2 kg, overt bleeding, required >80% oxygen, death was imminent, or therapeutic hypothermia had commenced before assessment
	Intervention	Hypothermia group (n=110): refrigerated gel packs to maintain rectal temperature 33°C-34°C Control group (n=111): radiant warmer to maintain rectal temperature 36.8°C-37.3°C
	Primary outcome	Mortality or major sensorineural disability in survivors at 2 y of age
Shankaran et al,[12] 2005	Inclusion	GA≥36 weeks with PHI, <6 h of age, and encephalopathy or seizures
	Exclusion	Major congenital abnormalities, BW≤1800 g, or >6 h of age
	Intervention	Hypothermia group (n=102): cooling blanket to maintain esophageal temperature 33°C-34°C Control group (n=106): standard care to maintain esophageal temperature 36.5°C-37.0°C
	Primary outcome	Death or moderate or severe disability in survivors at 18 to 22 mo of age
Simbruner et al,[21] 2010	Inclusion	GA≥36 weeks, PHI, encephalopathy, and abnormal EEG or aEEG findings
	Exclusion	Major congenital malformations, >5.5 h of age, received anticonvulsant therapy, BW<1800 g, HC less than the third percentile for GA if BW and length are greater than the third percentile, imperforate anus, or gross hemorrhage
	Intervention	Hypothermia group (n=64): cooling mattress to maintain rectal temperature 33°C-34°C Control group (n=65): an open care unit to maintain rectal temperature 36.5°C-37.5°C
	Primary outcome	Death or severe disability in survivors at 18 to 21 mo of age
Zhou et al,[22] 2010	Inclusion	GA≥37 weeks, BW≥2500 g, PHI, and encephalopathy
	Exclusion	Major congenital abnormalities, signs of infection, other causes of encephalopathy or severe anemia
	Intervention	Hypothermia group (n=119): cooling cap to maintain nasopharyngeal temperature 34°C±0.2°C and rectal temperature 34.5°C-35°C Control group (n=116): radiant warmer to maintain rectal temperature 36.0°C-37.5°C
	Primary outcome	Death and severe disability at 18 mo of age

Abbreviations: aEEG, amplitude-integrated electroencephalogram; BW, birth weight; EEG, electroencephalogram; GA, gestational age; HC, head circumference; PHI, peripartum hypoxia-ischemia.

[a]The included studies provided therapeutic hypothermia for 72 h except in the trial reported by Gunn et al,[32] where cooling was discontinued between 48 and 72 h if newborns recovered neurologically. Newborns with mild encephalopathy were excluded from the analysis.

random allocation and hypothermia were initiated within 6 hours after birth. Therapeutic hypothermia was maintained for 72 hours except in the trial by Gunn et al,[32] in which cooling was discontinued between 48 and 72 hours if the newborn recovered neurologically. Rewarming was gradual at no more than 0.5°C per hour until the temperature was normalized in 5 trials[10,12,13,20,21]; passive rewarming was allowed in 1 trial.[22] The rewarming process was unclear in the trial conducted by Gunn et al.[32] Total body cooling was achieved either by cooling blankets placed under the newborns[12,13,21] or by gel packs,[20] and selective head cooling was achieved by a cooling cap[10,22,32] (Table 1).

METHODOLOGICAL QUALITY OF THE INCLUDED STUDIES

All the included studies used appropriate methodology following the Cochrane review guidelines.[23] Assessment of the risk of bias among the included studies is reported in **Table 3**. Overall, the methodology of the 7 studies was strong, particularly in the 3 largest completed trials[10,12,13] and the 2 trials that were stopped early due to the loss of clinical equipoise as assessed by independent data monitoring committees.[20,21] Two trials had moderate methodological quality. The trial by Gunn et al[32] was limited by a small sample size. It also had addi-

tional newborns randomized in other reports.[38,39] The trial by Zhou et al[22] may not be generalizable because of the higher proportion of males included (87% in the selective head-cooling group and 83% in the control group) and is weakened by high attrition (17% lost to follow-up). Also in the trial report by Zhou et al,[22] the outcome of 5% of the subjects was assessed by pediatricians in local hospitals rather than by blinded-certified neurologists. In none of the trials were caregivers blinded to the treatment assignment. The study protocol was violated in 2 trials with the inclusion of 19% to 20% of newborns with mild HIE.[20,22] The assessment of publication bias using funnel plots indicated no substantial evidence of publication bias in the primary outcome of death or severe disability in newborns with moderate or severe HIE (**Figure 1**).[40] More details about the methodological quality of the included trials are reported in the eAppendix.

PRIMARY OUTCOME: COMPOSITE OF DEATH OR MAJOR NEURODEVELOPMENTAL DISABILITY AT 18 MONTHS

The primary outcome was assessed in all 7 trials included in this review, representing 1214 newborns (Table 1). Therapeutic hypothermia reduced the risk of the composite outcome of death or major neurodevelopmental disability at age 18 months (RR, 0.76; 95% CI, 0.69-0.84; and NNT, 7; 95% CI, 5-10; I^2=0%; **Figure 2**).

SECONDARY OUTCOMES

Each component of the composite primary outcome was examined. Hypothermia reduced the risk of death at age 18 months (RR, 0.75; 95% CI, 0.63-0.88; NNT, 11; 95% CI, 7-26; I^2=0%; **Figure 3**). Among newborns who survived to 18 months, those treated with hypothermia had significantly lower rates of major disability (RR, 0.68; 95% CI, 0.56-0.83; NNT, 8; 95% CI, 5-16; I^2=12%; Figure 3), cerebral palsy (0.62; 0.49-0.78; 8; 6-16; 33%; Figure 3), developmental delay (0.66; 0.52-0.82; 8; 5-18; 25%; Figure 3), and blindness (0.56; 0.33-0.94; 23; 12-207; 0%; Figure 3). The rate of deafness was 3.7% in newborns treated with hypothermia and 5.8% in newborns treated with normothermia, suggesting a protective effect of hypothermia that was not statistically significant (RR, 0.64; 95% CI, 0.32-1.27; I^2=0%; Figure 3). Therapeutic hypothermia increased survival with normal neurological function (RR, 1.63; 95% CI, 1.36-1.95; NNT, 7; 95% CI, 5-11; I^2=0%; **Figure 4**). Hypothermia reduced the risk of death or major disability both in newborns with moderate HIE (RR, 0.67; 95% CI, 0.56-0.81; NNT, 6; 95% CI, 4-11; I^2=0%; **Figure 5**) and in newborns with severe HIE (0.83; 0.74-0.92; 7; 5-16; 0%; Figure 5). The risk of mortality or major neurodevelopmental disability was reduced by both total body cooling (RR, 0.75; 95% CI, 0.66-0.85; NNT, 6; 95% CI, 4-11; **Figure 6**) and selective head cooling (0.77; 0.65-0.93; 7; 4-21; Figure 6) when compared with normothermia. Statistical heterogeneity by I^2 was not significant for any of the analyses, indicating homogeneity among the included studies.

Table 2. List of Excluded Studies With Reasons for Exclusion

Source	Reason for Exclusion
Akisu et al,[33] 2003	Reported outcomes only to hospital discharge
Eicher et al,[9] 2005	Only 12-mo neuromotor outcome reported
Inder et al,[34] 2004	Reported outcomes only to hospital discharge
Li et al,[35] 2009	Significant methodological limitation including Less than transparent allocation method, although described as "random assignment" Nonblinded assessor of outcome measurement (at 18 mo of age) Internal validity issues where the included newborns do not represent moderately to severely asphyxiated newborns (have normal PH, less base deficits, and better Apgar scores from what was stated in the inclusion criteria)
Lin et al,[36] 2006	Reported follow-up to 10 d of age
Robertson et al,[37] 2008	Reported the outcomes only at 17 d of age
Shankaran et al,[7] 2002	Reported outcomes only to hospital discharge

SENSITIVITY ANALYSES

The trial conducted by Simbruner et al[21] was terminated early due to ethical concerns regarding controls (normothermia group); 14% of the randomized subjects were not included in the final analysis of this trial. Therefore, sensitivity analysis was performed assuming an extreme scenario (all the newborns lost to follow-up in the hypothermia group were affected with the primary outcome and all the newborns lost to follow-up in the normothermia group were unaffected). In this extreme scenario, the evidence remained in favor of the hypothermia group (RR, 0.76; 95% CI, 0.59-0.99).

Due to the methodological concerns in the trial by Zhou et al[22] discussed earlier, a sensitivity analysis excluding the data from this study was carried out the conclusion did not change in that the combined rate of death or major disability was lower in the hypothermia group compared with the normothermia group (RR, 0.77; 95% CI, 0.70-0.86; NNT, 7; 95% CI, 5-12) (eFigure 2). The sensitivity of the results to the exclusion of this trial was also examined in the subgroup analysis in newborns with moderate (n=557) and severe HIE (n=480); the results remained significantly in favor of hypothermia in newborns with moderate HIE (RR, 0.70; 95% CI, 0.58-0.84; NNT, 6; 95% CI, 4-13) (eFigure 3) and in newborns with severe HIE (0.84; 0.75-0.94; 8; 5-21) (eFigure 4).

COMMENT

This updated systematic review of the randomized controlled trials conducted in newborns with HIE supports that therapeutic hypothermia is effective in reducing the risk of death or major disability at age 18 months in newborns with either moderate or severe HIE. An important outcome of this review is that hypothermia re-

Table 3. Risk of Bias Assessment Among the Included Studies

	Azzopradi et al,[13] 2009	Gluckman et al,[10] 2005	Gunn et al,[32] 1998	Jacobs et al,[20] 2011	Shankaran et al,[12] 2005	Simbruner et al,[21] 2010	Zhou et al,[22] 2010
Sequence generation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Allocation concealment	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blinding of outcome assessment	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
Incomplete data addressed	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Free of selective reporting	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Free of other bias	Yes	Yes	No	No	Yes	No	No
Overall bias assessment	Unlikely	Unlikely	Moderate	Low	Unlikely	Low	Moderate

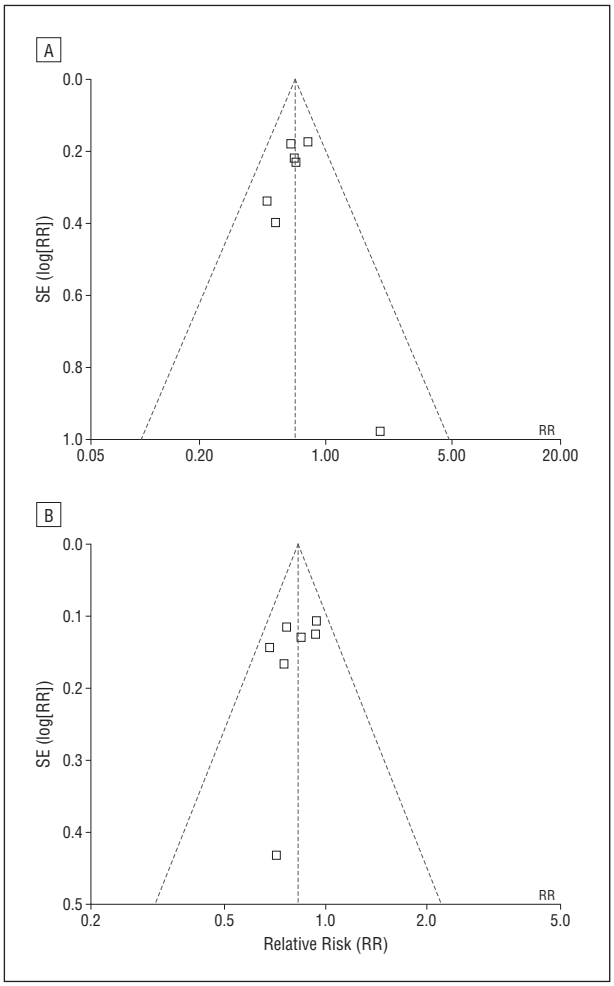

Figure 1. Publication bias funnel plots for the primary outcome. A, Publication bias funnel plot for death or severe disability in newborns with moderate hypoxic ischemic encephalopathy. B, Publication bias funnel plot for death or severe disability in newborns with severe hypoxic ischemic encephalopathy.

duced the mortality rate without increasing the disability rate in asphyxiated newborns. This outcome was indicated by a decrease in the rate of major disability and an increase in the rate of survival with normal neurological function.

The homogeneity of the included studies (patient inclusion and exclusion criteria, study design, methodological quality, and length of follow-up) increases the confidence that therapeutic hypothermia improves the long-term outcomes at 18 months in different clinical settings. The homogeneity also allowed us to use the fixed-effects model in the analysis where it was appropriate. Had the included studies been heterogeneous, the random-effects model would have been a more appropriate method.

Experimental and clinical evidence had previously suggested that outcomes after hypothermic treatment were strongly influenced by the severity of HIE, with less effective neuroprotection following severe HIE.[41,42] Severe HIE is associated with a shorter latent phase (the period between reestablishment of apparently normal cerebral metabolism after HIE and the start of secondary energy failure and its irreversible neurotoxic cascade), worse secondary energy failures and more cortical-gray matter neuronal death.[41] The extensive brain injury in severe HIE involving the basal ganglia and thalami are often associated with abnormalities in specific cortical and subcortical white matter.[43] Moderate and severe lesions in the basal ganglia and thalami and severe white matter lesions are associated with cerebral palsy.[44-46] Although the evidence from this review suggests that newborns with severe HIE will benefit, therapeutic hypothermia seems to be more beneficial to newborns with moderate HIE than newborns with severe HIE (relative risk reduction, 33% vs 17%). The diversity in the timing and magnitude of the brain injury in newborns with moderate and severe HIE may have led to a differential treatment effect.

Although hypothermia decreases rates of death or disability, newborns who are profoundly asphyxiated will not likely benefit from hypothermic therapy. Identifying newborns who are untreatable can be a challenge; therefore, early predictors of nonresponders are required to individualize treatment decision. Six moderately asphyxiated newborns or 7 severely asphyxiated newborns need to be treated to save 1 newborn from death or major disability.

Edwards et al[19] in a recent meta-analysis estimated that the RR of composite outcome of death or major disability reached statistical significance in newborns with moderate HIE (RR, 0.73; 95% CI, 0.58-0.92) and did not reach statistical significance in newborns with severe HIE (0.87; 0.75-1.01). Based on their results, these authors recommended that " . . . clinicians make individual decisions on whether to treat newborns with severe encephalopathy."[19] Their review did not include 3 recent trials.[20-22] With the inclusion of these trials and the higher number of newborns available for analysis, it is clear that newborns with severe HIE also benefit from therapeutic hypothermia.

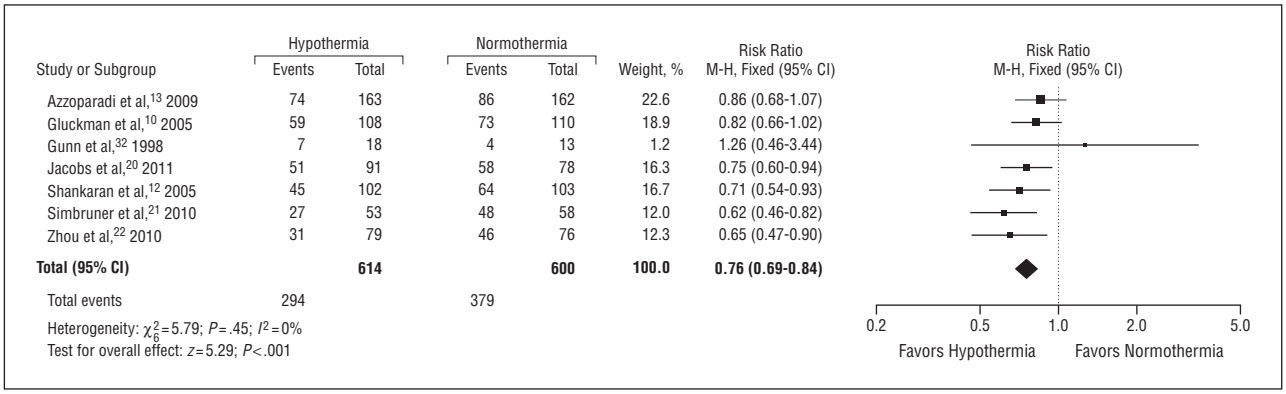

Figure 2. Forest plot of the composite primary outcome of death or major disability in survivors. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI). M-H indicates Mantel-Haenzel test.

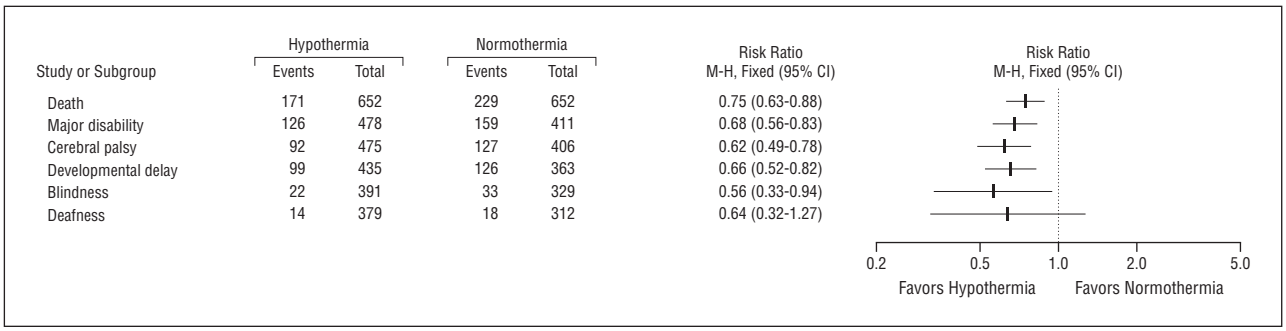

Figure 3. Forest plot of components of the composite primary outcome. Blindness and deafness were not reported in the study by Zhou et al.[22] M-H indicates Mantel-Haenzel test.

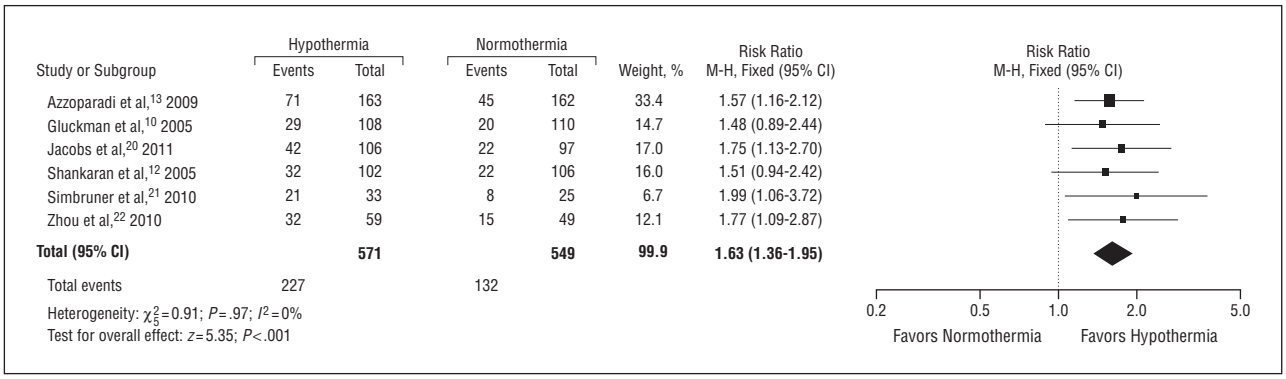

Figure 4. Forest plot of survival with normal neurological function ("events"). Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI). M-H indicates Mantel-Haenzel test.

The assessment of the severity of encephalopathy is difficult, imprecise, and subjective when based on clinical evaluation alone. Two of the included trials that used clinical criteria alone violated their protocol and included newborns with mild HIE.[20,22] Newborns with mild HIE were not expected to benefit from hypothermia.[47] None of the adverse events of death or severe disability occurred in newborns with mild HIE in the trial reported by Zhou et al.[22] However, in the trial by Jacobs et al,[20] 33% and 25% of newborns with mild HIE in the control and cooled groups, respectively, died or had severe disability; the authors related the recruitment of newborns with mild HIE to the lack of a standardized neurological assessment tool to assess encephalopathy. One may speculate that newborns may be misclassified in regard to their degree of encephalopathy and subsequently receive suboptimal treatment decisions. The combination of the aEEG and the neurological examination shortly after birth enhances the ability to identify high-risk newborns and limits the number of newborns who would be falsely identified when they are assessed with either evaluation alone.[48]

The realistic therapeutic window of hypothermia is uncertain.[41,49] Experimental evidence suggests that the neuroprotective response of hypothermia is influenced by the timing of initiation of therapy.[50,51] In all included trials, the timing of initiation of hypothermia was no more than 6 hours after birth. Li et al[35] suggested that delaying the onset of therapy by 6 to 10 hours after birth did not negatively affect the rate of moderate to severe disability and

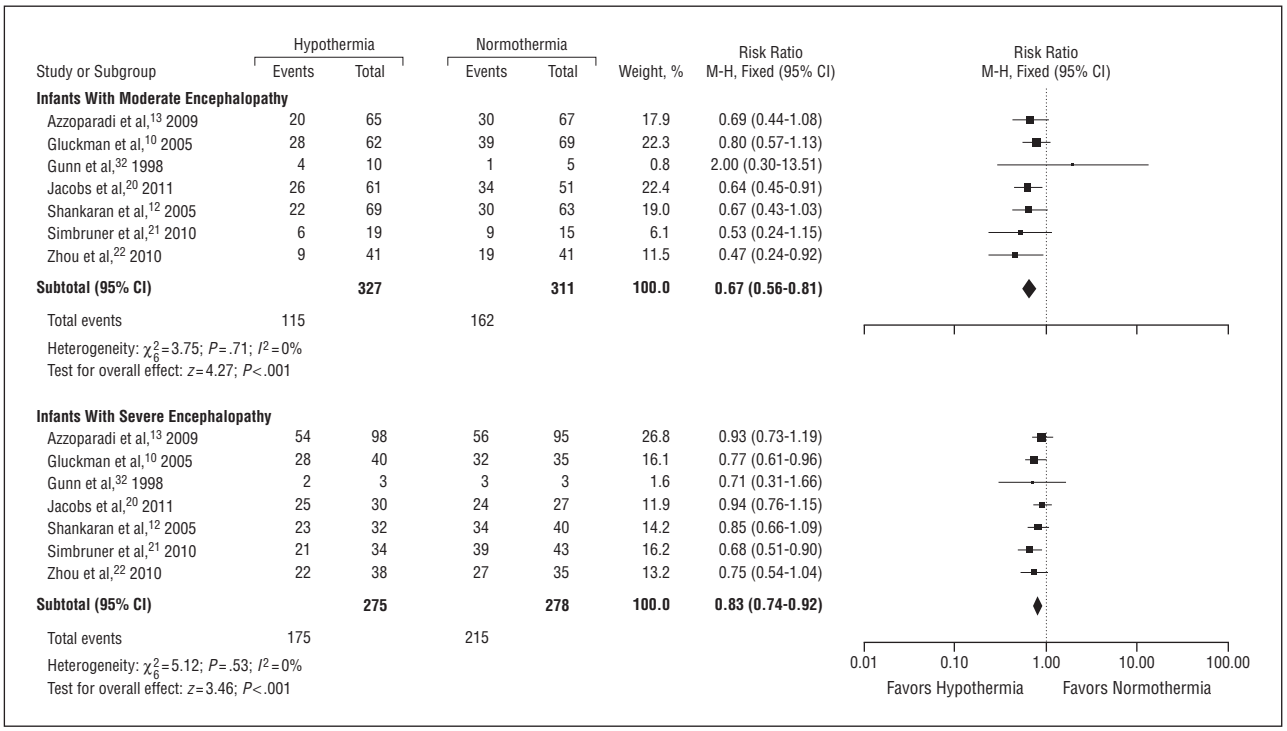

Figure 5. Forest plot of the primary outcome of death or major disability in survivors in newborns with moderate to severe hypoxic ischemic encephalopathy. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI). M-H indicates Mantel-Haenzel test.

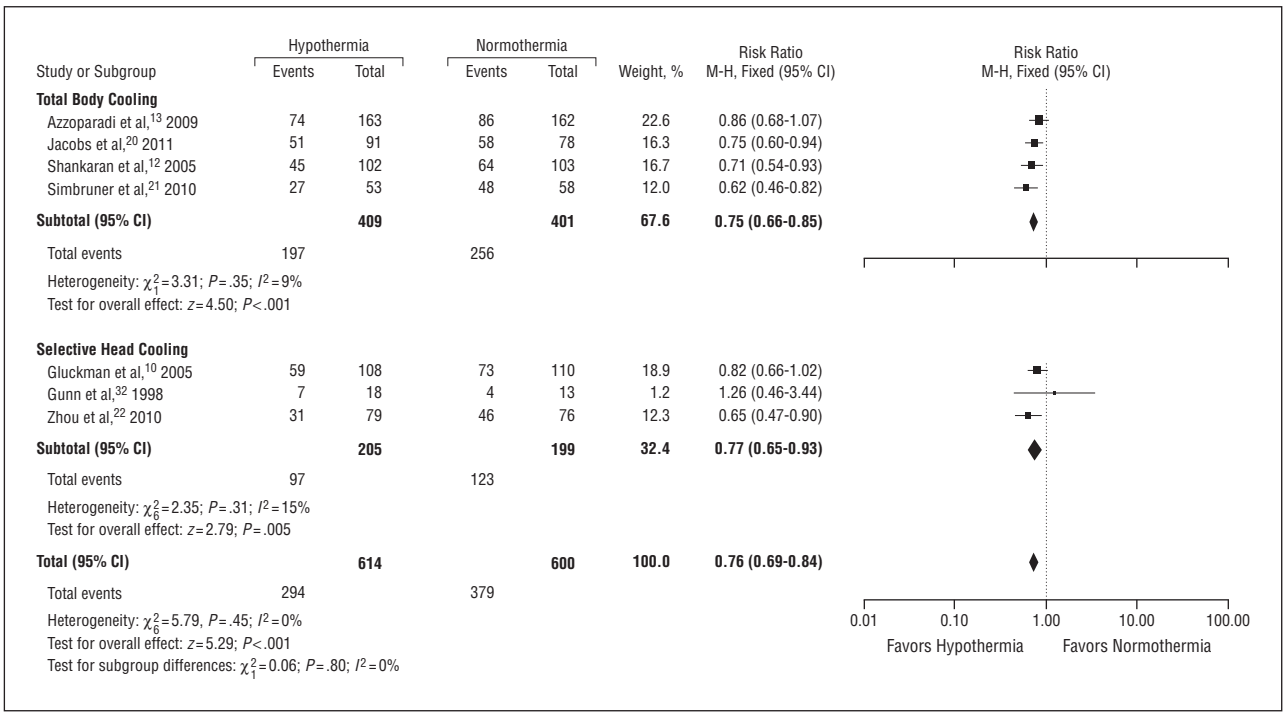

Figure 6. Forest plot for the primary outcome of death or major disability by method of cooling in newborns with moderate to severe encephalopathy. Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI). M-H indicates Mantel-Haenzel test.

death when compared with newborns treated within 6 hours after birth. The National Institute of Child Health and Human Development is evaluating late hypothermia for newborns with HIE initiated between 6 and 24 hours of age (ClinicalTrials.gov Identifier: NCT00614744). Until further evidence is available, it seems prudent to initiate therapeutic hypothermia as soon after birth as possible for newborns with moderate to severe HIE.

The strengths of this updated systematic review are the inclusion of recent trials, increased power based on increased sample size, detailed subgroup analyses, and sensitivity analyses. The current analysis was able to re-

fine the confidence with which clinicians should offer therapeutic hypothermia in newborns with moderate to severe HIE.

The unblinded nature of the included studies will remain the major limitation of the available evidence about therapeutic hypothermia. The current evidence is limited to 18-month follow-up data; therefore, it remains appropriate for clinicians to be conservative when counseling parents about longer-term neurological function. Long-term follow-up of the newborns in the trials reported to date will provide data to examine if neurological data recorded at 18 months accurately predict long-term neurological function.[19] As the outcome of birth asphyxia is devastating, work should continue to find adjuvant therapy to hypothermia.

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Correspondence: Mohamed A. Tagin, MB, BCh, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario M5G 1X8, Canada (mohamed.tagin@utoronto.ca).
Author Contributions: Drs Tagin, Vincer, and Whyte had full access to all the data in this review and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Tagin. *Acquisition of data:* Tagin. *Analysis and interpretation of data:* Tagin, Woolcott, Vincer, Whyte, and Stinson. *Drafting of the manuscript:* Tagin. *Critical revision of the manuscript for important intellectual content:* Tagin, Woolcott, Vincer, Whyte, and Stinson. *Statistical analysis:* Tagin. *Study supervision:* Whyte.
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REFERENCES

1. Lawn J, Shibuya K, Stein C. No cry at birth: global estimates of intrapartum stillbirths and intrapartum-related neonatal deaths. *Bull World Health Organ*. 2005;83(6):409-417.
2. Gonzalez FF, Miller SP. Does perinatal asphyxia impair cognitive function without cerebral palsy? *Arch Dis Child Fetal Neonatal Ed*. 2006;91(6):F454-F459.
3. Marlow N, Rose AS, Rands CE, Draper ES. Neuropsychological and educational problems at school age associated with neonatal encephalopathy. *Arch Dis Child Fetal Neonatal Ed*. 2005;90(5):F380-F387.
4. van Handel M, Swaab H, de Vries LS, Jongmans MJ. Long-term cognitive and behavioral consequences of neonatal encephalopathy following perinatal asphyxia: a review. *Eur J Pediatr*. 2007;166(7):645-654.
5. Gunn AJ, Gunn TR, de Haan HH, Williams CE, Gluckman PD. Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs. *J Clin Invest*. 1997;99(2):248-256.
6. Gunn AJ, Gunn TR. The 'pharmacology' of neuronal rescue with cerebral hypothermia. *Early Hum Dev*. 1998;53(1):19-35.
7. 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(2, pt 1):377-385.
8. Jacobs S, Hunt R, Tarnow-Mordi W, Inder T, Davis P. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev*. 2007;(4):CD003311.
9. Eicher DJ, Wagner CL, Katikaneni LP, et al. Moderate hypothermia in neonatal encephalopathy: efficacy outcomes. *Pediatr Neurol*. 2005;32(1):11-17.
10. Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet*. 2005;365(9460):663-670.
11. Shah PS, Ohlsson A, Perlman M. Hypothermia to treat neonatal hypoxic ischemic encephalopathy: systematic review. *Arch Pediatr Adolesc Med*. 2007;161(10):951-958.
12. Shankaran S, Laptook AR, Ehrenkranz RA, et al; National Institute of Child Health and Human Development Neonatal Research Network. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med*. 2005;353(15):1574-1584.
13. Azzopardi DV, Strohm B, Edwards AD, et al; TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med*. 2009;361(14):1349-1358.
14. Shah PS. Hypothermia: a systematic review and meta-analysis of clinical trials. *Semin Fetal Neonatal Med*. 2010;15(5):238-246.
15. Higgins RD, Raju TNK, Perlman J, et al. Hypothermia and perinatal asphyxia: executive summary of the National Institute of Child Health and Human Development workshop. *J Pediatr*. 2006;148(2):170-175.
16. 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(3):942-948.
17. Kirpalani H, Barks J, Thorlund K, Guyatt G. Cooling for neonatal hypoxic ischemic encephalopathy: do we have the answer? *Pediatrics*. 2007;120(5):1126-1130.
18. Wilkinson DJ, Casalaz D, Watkins A, Andersen CC, Duke T. Hypothermia: a neuroprotective therapy for neonatal hypoxic-ischemic encephalopathy. *Pediatrics*. 2007;119(2):422-423. doi:10.1542/peds.2006-1253.
19. Edwards AD, Brocklehurst P, Gunn AJ, 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. doi:10.1136/bmj.c363.
20. Jacobs SE, Morley CJ, Inder TE, et al; Infant Cooling Evaluation Collaboration. 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. doi:10.1001/archpediatrics.2011.43.
21. Simbruner G, Mittal RA, Rohlmann F, et al. Systemic hypothermia after neonatal encephalopathy: outcomes of neo.nEURO.network RCT [published online September 20, 2010]. *Pediatrics*. doi:10.1542/peds.2009-2441.
22. 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):367-372.
23. Higgins JP Green S, ed. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. the Cochrane collaboration, 2011.
24. Bayley N. *Bayley Scales of Infant Development*. 2nd ed. San Antonio, TX: Psycholgical Corp; 1993.
25. Bayley N. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Psychological Corp; 2006.
26. Griffiths R.. *The Griffiths Mental Development Scales, 1996 revision*. Henley: Association for Research in Infant and Child Development, Test Agency.
27. Brunet O, Lézine I. *Le développement psychologique de la première enfance*. Paris, France: Editions et Applications Psychologiques; *1983*.
28. Gesell AL. *Gesell and Amatruda's Developmental Diagnosis: The Evaluation and Management of Normal and Abnormal Neuropsychologic Development in Infancy and Early Childhood*. 3rd ed. Hagerstown, MD: Harper & Row; 1974.
29. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol*. 1976;33(10):696-705.
30. Al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. *Pediatrics*. 1999;103(6, pt 1):1263-1271.
31. Review Manager (RevMan) [computer program]. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.
32. Gunn AJ, Gluckman PD, Gunn TR. Selective head cooling in newborn infants after perinatal asphyxia: a safety study. *Pediatrics*. 1998;102(4, pt 1):885-892.
33. Akisu M, Huseyinov A, Yalaz M, Cetin H, Kultursay N. Selective head cooling with hypothermia suppresses the generation of platelet-activating factor in cerebrospinal fluid of newborn infants with perinatal asphyxia. *Prostaglandins Leukot Essent Fatty Acids*. 2003;69(1):45-50.
34. Inder TE, Hunt RW, Morley CJ, et al. Randomized trial of systemic hypothermia selectively protects the cortex on MRI in term hypoxic-ischemic encephalopathy. *J Pediatr*. 2004;145(6):835-837.
35. Li T, Xu F, Cheng X, et al. Systemic hypothermia induced within 10 hours after birth improved neurological outcome in newborns with hypoxic-ischemic encephalopathy. *Hosp Pract (Minneap)*. 2009;37(1):147-152. doi:10.3810/hp.2009.12.269.

36. 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(3):180-184.
37. Robertson NJ, Nakakeeto M, Hagmann C, et al. Therapeutic hypothermia for birth asphyxia in low-resource settings: a pilot randomised controlled trial. *Lancet*. 2008;372(9641):801-803.
38. Battin MR, Dezoete JA, Gunn TR, Gluckman PD, Gunn AJ. Neurodevelopmental outcome of infants treated with head cooling and mild hypothermia after perinatal asphyxia. *Pediatrics*. 2001;107(3):480-484.
39. Battin MR, Penrice J, Gunn TR, Gunn AJ. Treatment of term infants with head cooling and mild systemic hypothermia (35.0° C and 34.5° C) after perinatal asphyxia. *Pediatrics*. 2003;111(2):244-251.
40. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
41. Iwata O, Iwata S, Thornton JS, et al. "Therapeutic time window" duration decreases with increasing severity of cerebral hypoxia-ischaemia under normothermia and delayed hypothermia in newborn piglets. *Brain Res*. 2007;1154(1):173-180.
42. Wyatt JS, Gluckman PD, Liu PY, et al; CoolCap Study Group. Determinants of outcomes after head cooling for neonatal encephalopathy. *Pediatrics*. 2007; 119(5):912-921.
43. Okereafor A, Allsop J, Counsell SJ, et al. Patterns of brain injury in neonates exposed to perinatal sentinel events. *Pediatrics*. 2008;121(5):906-914. doi:10.1542/peds.2007-0770.
44. Cowan F, Rutherford M, Groenendaal F, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. *Lancet*. 2003;361(9359):736-742. doi:10.1016/S0140-6736(03)12658-X.
45. Miller SP, Ramaswamy V, Michelson D, et al. Patterns of brain injury in term neonatal encephalopathy. *J Pediatr*. 2005;146(4):453-460. doi:10.1016/j.jpeds.2004.12.026.
46. Barkovich AJ, Miller SP, Bartha A, et al. MR imaging, MR spectroscopy, and diffusion tensor imaging of sequential studies in neonates with encephalopathy. *AJNR Am J Neuroradiol*. 2006;27(3):533-547.
47. Robertson CMT, Finer NN, Grace MGA. School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term. *J Pediatr*. 1989; 114(5):753-760.
48. 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(2):351-357.
49. Taylor DL, Mehmet H, Cady EB, Edwards AD. Improved neuroprotection with hypothermia delayed by 6 hours following cerebral hypoxia-ischemia in the 14-day-old rat. *Pediatr Res*. 2002;51(1):13-19.
50. 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(5):1098-1106.
51. Gunn AJ, Bennet L, Gunning MI, Gluckman PD, Gunn TR. Cerebral hypothermia is not neuroprotective when started after postischemic seizures in fetal sheep. *Pediatr Res*. 1999;46(3):274-280.