



eNeonatal Review

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PROGRAM INFORMATION

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The focus of this issue is newborn encephalopathy secondary to hypoxia-ischemia (HIE). HIE represents a subset of infants with encephalopathy at birth and is distinguished from other etiologies of encephalopathy (eg. brain malformations, toxic exposures, in-utero infections, etc.) in that it may be amenable to treatment. At present there are no proven effective therapies for HIE and care is limited to supportive intensive care. There is now abundant experimental data that modest reduction in brain temperature (2-6°C) is an effective neuroprotective therapy.

In this month's issue, we present recent data on four areas relevant to potential treatment of HIE:

- The relationship between HIE and newborn encephalopathy
- Diagnosing encephalopathy in the first hours after birth
- The characteristics of an effective neuroprotective therapy
- The biologic basis and human pilot data for use of modest hypothermia as a treatment for newborns with HIE

Reviews & Commentary by:
Abbot R. Laptook, M.D.

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Guest Faculty Disclosure

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COMMENTARY

Newborn encephalopathy presents with difficulty initiating respirations at birth, and is accompanied by subnormal levels of activity, tone, reflexes, and consciousness, possibly with seizures. Newborn encephalopathy is a diagnosis of near- and term infants. It is usually not considered for preterm infants since neurologic features of prematurity can be similar to encephalopathy. Recognition is typically at birth or shortly thereafter, although symptoms may evolve following birth. The condition is a non-specific response to multiple events of which intrapartum hypoxia represents one specific event (evident in approximately 30% of newborns with encephalopathy). Using a prevalence of 2-4/1000 live births for newborn encephalopathy, moderate or severe encephalopathy associated with hypoxia-ischemia (HIE) is estimated to affect 2200-4400 term infants each year in the US. Sequelae of HIE include cerebral palsy; therefore there is a strong rationale to develop interventions for HIE, given that it is a) potentially modifiable, and b) that cerebral palsy has life long implications.

Early and accurate identification of newborns who would benefit from neuroprotective therapies is essential given the short therapeutic window (the time after an injury/event during which a therapy can be effectively initiated) and the potential risks of new therapies. Justification for brain-oriented therapies should include a high certainty of acute perinatal hypoxia-ischemia as well as a substantial risk for adverse outcome without intervention. However, categorizing neurological findings after birth is complex given transitional physiology, maternal medications, evolving neurological abnormalities, and other non-CNS conditions. While the Sarnat stages of encephalopathy used to categorize severity in neonates have been correlated with 1 year outcome, the studies used to establish the correlations relied on examinations later in the first week rather than within hours after birth. Therefore, the neurological examination shortly after birth may present abnormalities not easily classified by Sarnat stages, in particular for mild to moderate encephalopathy. In contrast, the amplitude integrated electroencephalogram (aEEG) has good prognostic ability for neurodevelopmental outcome after HIE. Thus, patient selection for neuroprotective therapies will probably combine criteria reflecting a history of placental gas exchange (intrapartum hypoxia-ischemia) with encephalopathy and aEEG abnormalities (evidence of injury).

Currently there are no proven neuroprotective therapies for HIE and treatment has focused on supportive intensive care with correction of physiologic abnormalities and treatment of seizures. In the research focused on potential treatments providing neuroprotection, modest hypothermia has the most compelling data for effectiveness, due to its impact on multiple pathways contributing to brain injury.

In newborn animals, modest hypothermia facilitates maintenance of brain high energy phosphorylated metabolites, improves the coupling between blood flow and oxidative metabolism, decreases the release of excitatory neurotransmitters, reduces nitric oxide production, and decreases apoptosis. Adult animal studies have demonstrated that modest hypothermia reduces free radical production, attenuates inflammation, and blocks inhibition of protein synthesis. Among the findings demonstrated for different species and across development are that modest hypothermia after hypoxia-ischemia (temperature reductions of 2-6°C) reduces histological brain injury, maintains EEG patterns, decreases brain edema, and improves neurological assessments. A key observation is that modest hypothermia is effective up to 6 hours following hypoxia-ischemia (1).

By next year published results will be available from multiple clinical trials testing modest reductions of brain temperature to reduce injury following HIE. The already completed Cool Cap trial combined selective head cooling with modest body cooling; although details await full publication, a preliminary report (2) supports benefit in infants with moderate but not severe HIE. As of early 2005, there are at least 3 randomized clinical trials of body cooling approaching completion, all with a primary outcome of neurodevelopment at 1-2 years.

Where are we headed for therapy directed at HIE? Much will depend on the first clinical trials of brain cooling; if beneficial, future studies may be directed at either optimizing the cooling regimen, or combining brain cooling with other potential therapies. Research on optimizing cooling regimens would involve identifying variables that may impact cooling efficacy, such as time of initiation, depth and duration of cooling. Evaluation of combining cooling and other therapies would involve assessing if hypothermia prolongs the therapeutic window for agents found less effective when used after a time delay (eg. allopurinol). In addition, there is promising work on potential treatments that target downfield events such as inflammation and apoptosis (eg. erythropoietin, minocycline, receptor antagonists of interleukins) which may be effective when combined with brain cooling.

1. Laptok AR, Corbett RJT, [The effects of temperature on hypoxic-ischemic brain injury](#). Clin Perinatol 29: 623-649,2002

2. Peter S. Gluckman, John S. Wyatt, Denis Azzopardi, Roberta Ballard, David Edwards, Donna M. Ferriero, Richard A. Polin, Charlene Robertson, Marianne Thoresen, Andrew Whitelaw, Alistair J. Gunn, the CollCap Study Group. [Selective Head Cooling with Mild Systemic Hypothermia to Improve Neurodevelopmental Outcome Following Neonatal Encephalopathy: The CoolCap Study](#). Pediatric Research, 55(4) page 582A, Abstract #3305, 2004

RISK FACTORS FOR NEWBORN ENCEPHALOPATHY

Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, Stanley FJ. Antepartum risk factors for newborn encephalopathy: The western Australian case-control study. BMJ 1998; 317:1549-1553

Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, Stanley FJ. Intrapartum risk factors for newborn encephalopathy: The western Australian case-control study. BMJ 1998; 317:1554-1558

Identifying predictors of newborn encephalopathy in term newborns.

This population-based, unmatched case-control study was performed in metropolitan Perth, Western Australia among term infants born between June 1993 and September 1995 to ascertain antepartum and intrapartum risk factors associated with newborn encephalopathy. The primary outcome was moderate or severe encephalopathy using a broad definition of encephalopathy modified from the Sarnat criteria. The authors performed daily exams on infants with encephalopathy and one exam on control infants at recruitment. Deaths in the first week of life were reviewed.

There were 164 infants with moderate or severe encephalopathy and 400 randomly selected

controls. The prevalence of moderate or severe newborn encephalopathy was 3.8/1000 live births. Examples of independent antepartum risk factors included socioeconomic status, maternal thyroid disease, severe pre-eclampsia, fetal growth restriction and post-dates. Intrapartum risk factors were maternal pyrexia, persistent occipital-posterior position, and acute intrapartum events (cord accident, ruptured uterus etc). Evidence of intrapartum hypoxia was based on a composite of an abnormal fetal heart rate pattern, passage of fresh meconium during labor, and low Apgar scores. Of infants with encephalopathy, the majority (69%) had evidence of only antepartum risk factors, while 25% had evidence of antepartum risk factors and intrapartum hypoxia, and 4% had only intrapartum hypoxia as risk factors for encephalopathy.

These results support the concept that there are multiple casual paths associated with encephalopathy. Given the frequent association with antepartum events, newborn encephalopathy may represent either a continuation of a causal path initiated long before labor, or a "double hit" sequence in which antepartum risk factors increase the vulnerability of the fetus to intrapartum events. Although the majority of newborns with encephalopathy do not have evidence of intrapartum hypoxia, hypoxia-ischemia may be a contributing factor in almost 30% of infants with encephalopathy.

Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, Pemberton PJ, Stanley FJ. Antepartum risk factors for newborn encephalopathy: The western Australian case-control study. *BMJ* 1998; 317:1549-1553

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aEEG IN INFANTS WITH HIE

Toet MC, Hellström-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

al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. *Pediatrics* 1999; 103:1263-1271

Shalak L, 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; 111:351-357

Assessing encephalopathy using amplitude integrated electroencephalography in newborns.

The amplitude integrated electroencephalogram (aEEG) records a limited number of channels from specific sites such as biparietal electrodes (as described for the Cerebral Function Monitor) and provides the electrical background activity of the brain. The latter is highly correlated with conventional EEG recordings.

Toet et al studied 73 term infants with asphyxia based on at least 3 of the following criteria;

fetal distress, cord pH < 7.1, delayed onset of respirations, low Apgar scores, or multi-organ failure. A single channel aEEG was recorded at 3 and 6 hours following birth and the recording was classified by pattern recognition (continuous normal voltage, discontinuous normal voltage, burst suppression, continuous low voltage, and a flat trace). Follow-up at more than 1 year was accomplished in 93% of the cohort. The ability to predict a normal outcome after a normal tracing was high. The sensitivity and specificity of abnormal patterns (burst suppression, continuous low voltage, and flat trace) for predicting poor outcomes was 85% and 77%, respectively, at 3 hours of age, and was 91% and 86%, respectively, at 6 hours of age.

al Naqeeb classified a single channel aEEG in a more simplified manner using voltage criteria that allowed characterization into a normal, moderately abnormal, and suppressed amplitude patterns. Consecutive cases of neonatal encephalopathy were studied but only a portion (24/56) were studied in the first 12 hours of age, and near 90% were suspected to be associated with asphyxia (evidence of fetal distress and either low Apgar scores and/or fetal acidemia). Neurodevelopmental outcome was assessed at 18-24 months. For the entire cohort 19 of 21 infants with a normal aEEG were normal on follow-up, whereas 27 of 35 infants with a moderate or suppressed amplitude aEEG died or developed neurological abnormalities. Among the infants evaluated within the first 12 hours of age, the aEEG patterns discriminated abnormal outcomes with a sensitivity of 1.0, specificity of .82, positive predictive value of .85, and a negative predictive value of 1.0.

Shalak et al compared the predictive characteristics of nearly simultaneous early neurological examinations and single channel aEEG recordings (average age of 5 hours) for a short term outcome of persistent encephalopathy beyond 5 days of age. Term infants (n= 50) with evidence of fetal distress, low Apgar scores and/or fetal acidemia were studied. An abnormal aEEG was more specific (89% vs 78%), had a greater positive predictive value (73% vs 58%), and had similar sensitivity (79% vs 78%) and negative predictive value (90% vs 91%) when compared with an abnormal early neurological examination. The presence of abnormalities of both the aEEG and examination had the highest specificity (94%) and positive predictive value (85%).

The observations from all three articles support the usefulness of the aEEG to predict subsequent brain injury.

Toet MC, Hellström-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

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Shalak L, 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; 111:351-357

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CHARACTERISTICS OF EFFECTIVE NEUROPROTECTIVE THERAPIES

Shankaran S, Laptook A. Challenge of conducting trials of neuroprotection in the asphyxiated term infant. Sem Perinatol 2003; 27:320-332

Presenting the specific challenges inherent in neuroprotective therapies implemented after birth.

Key observations by the authors regarding the characteristics of any intervention as successful brain-oriented therapy include:

- The intervention needs to target potential downstream events from the putative hypoxia-ischemia that are critical for the pathogenesis of tissue injury.
- Given the presence of a short therapeutic window (estimated to be 6 hours), and the need for therapies to be initiated as soon as possible after birth, treatments that are easier and faster to implement may impact efficacy. Pharmacologic therapies may therefore seem attractive, but the pharmacokinetics to maintain therapeutic drug concentrations in brain tissue can be complex given frequent hepatic and renal dysfunction following hypoxia-ischemia. Pharmacologic agents of high molecular weight may be less effective due to limited passage across the blood brain-barrier. In addition, concomitant non-pharmacologic interventions such as brain cooling may alter drug metabolism and clearance. Further, maturational differences between adults and neonates prohibit ready extrapolation across age.
- The duration that a neuroprotective intervention needs to be continued for optimal efficacy is unclear; however, what is certain is that delayed neuronal death and progression to irreversible injury can occur over a period of days (and potentially longer).
- An effective treatment must have a margin of safety to justify its use since the ability to predict at risk infants has limitations and may expose infants to unnecessary treatments.

Of all the therapies under investigation for neuroprotection, the one that best fulfills the above criteria is modest hypothermia. Modest hypothermia favorably affects multiple events along the pathways leading to brain injury. It can be initiated quickly and it can be easily maintained for days. Finally preliminary observations suggest that associated risks are no more frequent with hypothermia than those associated with HIE under normothermic conditions.

Shankaran S, Laptook A. Challenge of conducting trials of neuroprotection in the asphyxiated term infant. Sem Perinatol 2003; 27:320-332

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PILOT STUDIES IN BRAIN-COOLING

Gunn AJ, Gluckman PD, Gunn TR. Selective head cooling in newborn infants after perinatal asphyxia: A safety study. Pediatrics 1998; 102:885-892

Shankaran S, Laptook A, Wright LL, Ehrenkranz RA, Donovan EF, Fanaroff AA, Stark AR, Tyson JE, Poole K, Carlo WA, Lemons JA, Oh W, Stoll BJ, Papile LA, Bauer CR, Stevenson DK, Korones SB, McDonald S. Whole-body hypothermia for neonatal encephalopathy: Animal observations as a basis for a randomized, controlled pilot study in term infants. Pediatrics 2002; 110:377-385

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; 111:244-251

Results from three pilot studies randomizing newborn infants to normothermic conditions or brain cooling.

Gunn et al studied term infants with an umbilical artery pH <7.09 or Apgars ≤6 at five minutes and evidence of encephalopathy. Infants were maintained normothermic (n=10), or underwent systemic cooling to a rectal temperature of 36.3±0.2°C (n=6), or 35.7±0.2°C (n=6). Groups with lower systemic temperature were studied in a sequential manner for safety considerations. Each of the infants cooled systemically underwent head cooling by circulating water at 10°C through a home built coil of tubing around the head (held in place by a bonnet). Core body temperature was controlled by adjustments of overhead heaters. Rectal, fontanel, and nasopharyngeal temperatures were monitored. Cooling was initiated at approximately 4 hours of age and was maintained for up to 72 hours.

Shankaran et al used an animal model to evaluate a commercially available cooling system (Cincinnati Sub-Zero Blanketrol Hyper-Hypothermia system) and then applied these results to perform a pilot study of whole body hypothermia. Term infants were studied if they had evidence of encephalopathy in the presence of either an umbilical artery pH <7.0 or an acute perinatal event with respiratory depression at birth (low Apgars or need for ventilation). Infants were randomized to normothermia (n=10) or body cooling (n=9). Core body temperature was monitored using an esophageal temperature probe in both groups. Cooling was achieved by having infants lay on a blanket attached to the Blanketrol system with servo control of the esophageal site to 34.5°C. Body cooling was initiated at approximately 4.5 hours and was continued for 72 hours.

Battin et al studied 26 term infants with low Apgar scores and/or severe fetal acidemia (cord artery pH <7), and evidence of encephalopathy. Infants were randomized to receive selective head cooling with rectal temperatures at either 35°C (n=6) or 34.5°C (n=7), or were cared for under normothermic conditions (n=13). Cooling was achieved by circulating water at 10°C through a cap (either home built or commercially made, Olympic Medical) and was initiated at 5 hours of age and continued for 48-72 hours.

All three reports demonstrate the feasibility of performing a clinical trial with different modes of brain cooling among term infants with moderate or severe HIE. Within a 6 hour interval after birth, it was feasible to screen patients for eligibility, assess the neurological status, obtain informed consent, randomize, and initiate therapy. Whether one mode of cooling is more advantageous than another is not answered by these studies. Two of the pilots report the expected prominent drops in heart rate with cooling of the body; however, these cardiovascular changes were well tolerated. Although the numbers are small, there did not appear to be greater hazard to infants undergoing a cooling regimen compared to infants nursed under normothermia.

These reports provided the justification to proceed with the current clinical trials that are now completed or close to completion.

Gunn AJ, Gluckman PD, Gunn TR. Selective head cooling in newborn infants after perinatal asphyxia: A safety study. Pediatrics 1998; 102:885-892

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Shankaran S, Lupton A, Wright LL, Ehrenkranz RA, Donovan EF, Fanaroff AA, Stark AR, Tyson JE, Poole K, Carlo WA, Lemons JA, Oh W, Stoll BJ, Papile LA, Bauer CR, Stevenson DK, Korones SB, McDonald S. Whole-body hypothermia for neonatal encephalopathy: Animal observations as a basis for a randomized,

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Target Audience [back to top](#)

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Learning Objectives [back to top](#)

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity. At the conclusion of this activity, participants should be able to:

- Develop a better understanding of the conditions of intrapartum hypoxia-ischemia and newborn encephalopathy;
- Understand the characteristics of an effective neuroprotective therapy and the role of amplitude integrated EEG in selection of patients for treatment;
- Understand the rationale for modest hypothermia as a neuroprotective strategy.

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- Dr. Noguee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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