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CLINICAL REPORT

# Hypothermia and Neonatal Encephalopathy

## abstract

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Data from large randomized clinical trials indicate that therapeutic hypothermia, using either selective head cooling or systemic cooling, is an effective therapy for neonatal encephalopathy. Infants selected for cooling must meet the criteria outlined in published clinical trials. The implementation of cooling needs to be performed at centers that have the capability to manage medically complex infants. Because the majority of infants who have neonatal encephalopathy are born at community hospitals, centers that perform cooling should work with their referring hospitals to implement education programs focused on increasing the awareness and identification of infants at risk for encephalopathy, and the initial clinical management of affected infants. *Pediatrics* 2014;133:1146–1150

COMMITTEE ON FETUS AND NEWBORN

**KEY WORDS**

hypothermia, hyperthermia, neonatal encephalopathy, infant, head cooling

**ABBREVIATIONS**

aEEG—amplitude-integrated electroencephalography
EEG—electroencephalography
CI—confidence interval
NICHD—National Institute of Child Health and Human Development
RR—relative risk

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## BACKGROUND

In 2005, the National Institute of Child Health and Human Development (NICHD) convened a workshop to evaluate the status of knowledge regarding the safety and efficacy of hypothermia as a neuroprotective therapy for neonatal hypoxic-ischemic encephalopathy.[1] Shortly thereafter, the Committee on Fetus and Newborn of the American Academy of Pediatrics published a commentary supporting the recommendation of the workshop that the widespread implementation of hypothermia outside the limits of controlled trials was premature.[2] In 2010, the *Eunice Kennedy Shriver* NICHD organized a follow-up to the 2005 workshop to review available evidence.[3] The purpose of this clinical report is to review briefly the current knowledge regarding the efficacy and safety of therapeutic hypothermia, to point out major gaps in knowledge that were identified at the 2010 workshop, and to suggest a framework for the implementation of hypothermia. The intended audience is neonatal/perinatal medicine practitioners.

## PRELIMINARY STUDIES

Neuronal rescue of encephalopathic newborn infants using induced hypothermia is one of the few therapeutic modalities in neonatology that was studied extensively in animal models before clinical application in humans. From animal studies, it was noted that cooling the brain to approximately 32°C to 34°C starting within 5.5 hours after a hypoxic/ischemic insult and continuing to cool for 12 to 72 hours resulted in improved neuropathologic and functional outcomes.[4] After showing consistent benefit in animal models, the safety, feasibility, and practicality of using induced hypothermia in infants who have neonatal encephalopathy were investigated in



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several small studies. Data from these preliminary clinical studies indicated that reducing body temperature by 2°C to 3°C for a prolonged period of time was possible and that the changes in blood pressure, heart rate, and cardiac output noted were of little clinical significance.[5–7]

## Large Randomized Clinical Trials of Hypothermic Neural Rescue (Table 1)

Six large randomized clinical trials of induced hypothermia for neonatal encephalopathy were published from 2005 to 2011.[8–13] Although there were some differences in the method of cooling and selection of subjects, in all trials infants were at least 35 weeks' gestation at birth; randomization was completed within 6 hours of birth; the target temperature was 33.5°C to 34.5°C; the intervention period was 72 hours, followed by slow rewarming (0.5°C/hour); and the primary outcome measure was the combined rate of death or disability, assessed at 18 to 22 months of age. Some trials used preferential head cooling with mild body cooling,[8,11] and others used whole-body cooling[9,10,12,13]; however, all trials continuously monitored both the degree of cooling and core body temperature. In addition, 3 trials used either amplitude-integrated electroencephalography (aEEG) or electroencephalography (EEG) for the assessment of severity of encephalopathy and enrollment of infants.[8,10,12]

**TABLE 1** Therapeutic Hypothermia Clinical Trials

| Clinical Trial | Entry Criteria |
|---|---|
| CoolCap | Gestational age ≥36 weeks and ≤6 hours of age<br>AND<br>Apgar score ≤5 at 10 minutes after birth<br>OR<br>Continued need for resuscitation at 10 minutes after birth<br>OR<br>pH <7.00 or base deficit ≥16 mmol/L or more on an umbilical cord blood sample or an arterial or venous blood sample obtained within 60 minutes of birth<br>AND<br>Moderate or severe encephalopathy on clinical examination<br>AND<br>Moderately or severely abnormal background of at least 20 minutes' duration or seizure activity on amplitude integrated electroencephalogram (aEEG) after one hour of age |
| Whole Body Cooling | Gestational age ≥36 weeks and ≤6 hours of age<br>AND<br>pH ≤7.00 or base deficit ≥16 mmol/L in an umbilical cord blood sampleor any blood sample obtained within the first hour after birth[a]<br>AND<br>Moderate or severe encephalopathy on clinical examination |
| TOBY | Gestational age ≥36 weeks and ≤6 hours of age<br>AND<br>Apgar score ≤5 at 10 minutes after birth<br>OR<br>Continued need for resuscitation 10 minutes after birth<br>OR<br>pH <7.00 or base deficit ≥16 mmol/L on umbilical cord or arterial or capillary blood sample obtained within 60 minutes after birth<br>AND<br>Moderate or severe encephalopathy on clinical examination<br>AND<br>Abnormal background activity of at least 30 minutes' duration or seizures on amplitude integrated electroencephalogram (aEEG) |

[a] If blood gas is not available or pH is between 7.01 and 7.15 or base deficit is between 10 and 15.9 mmol/L on blood sample obtained within the first hour of birth, two additional criteria are needed: a history of an acute perinatal event (eg, cord prolapse, fetal heart rate decelerations) and either the need for assisted ventilation initiated at birth and continued for 10 minutes or an Apgar score ≤5 at 10 minutes after birth.

Each of the 6 published trials was powered to detect a difference in the primary composite outcome of death or disability at 18 to 24 months of age, and all showed a benefit with cooling; in 4 of the 6 studies, this reached statistical significance. Rates of death or disability were similar in the control groups for 4 of the 6 studies, suggesting that patient selection and treatment were likely similar in these trials.[8–10,13] A published meta-analysis that included a small pilot study[5] as well as the 6 large published clinical trials demonstrated a reduction in the relative risk (RR) of the composite outcome of death or major neurodevelopmental disability at 18 to 24 months of age by 24% (RR, 0.76; 95% confidence interval [CI], 0.69–0.84).[14] A beneficial effect was noted both in infants who had moderate encephalopathy (RR, 0.67; 95% CI, 0.56–0.81) and those who had severe encephalopathy (RR 0.83; 95% CI, 0.74–0.92). The number of infants who need to be treated to prevent 1 infant from dying or becoming disabled is 6 for infants who have moderate encephalopathy and 7 for those who have severe encephalopathy. A review by the Cochrane collaboration that included 11 randomized controlled trials comprising 1505 term and late preterm infants who had moderate/severe encephalopathy demonstrated similar results.[15] The reduction in death or major neurodevelopmental disability to 18 months of age for treated infants was 25% overall; 32% for infants who had moderate encephalopathy and


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18% for those who had severe encephalopathy.

Follow-up beyond infancy has been reported for subjects enrolled in the CoolCap trial and the NICHD Whole-Body Cooling trial.[16,17] Because the follow-up rate at 7 to 8 years of age was only 50% in the CoolCap trial, there were insufficient data to ascertain the long-term risk or benefits of selective head cooling. In the NICHD follow-up study, there was no statistical difference in the composite primary outcome of death or IQ <70 at 6 to 7 years of age between the treated and usual care cohorts ($P$ = .06). Hypothermia treatment was associated with a reduction in the secondary outcomes of death (RR, 0.66; 95% CI, 0.45–0.97) and death or cerebral palsy (RR, 0.71; 95% CI, 0.54–0.95).

## Observations From Large Clinical Trials

Adverse effects observed with hypothermia were infrequent in the target temperature ranges used in published clinical trials. The most common adverse effects were sinus bradycardia and prolongation of the QT interval on electrocardiogram, both of which are physiologic responses to hypothermia. Reddening or hardening of the skin (systemic hypothermia) and on the scalp (selective head cooling) and subcutaneous fat necrosis occurred rarely. The reported rates of coagulopathy, sepsis, and pneumonia were essentially the same in treated and control infants. When published studies were aggregated in a meta-analysis, the adverse effects of hypothermia included an increase in sinus bradycardia and a significant increase in thrombocytopenia (platelet count <150 000/mm$^3$).[15]

Both the TOBY and NICHD trial noted an adverse effect of pyrexia on neurologic outcome among infants allocated to standard care.[18,19] In both trials, approximately 30% of the control group had a rectal or esophageal temperature greater than 38°C recorded on at least 1 occasion. The risk for death or disability among infants who had an elevated rectal temperature was increased by threefold in the TOBY trial, whereas in the NICHD trial, the risk for adverse outcome was increased threefold to fourfold, with each degree Celsius increase in the highest quartile of esophageal temperature. It is not known whether the elevated temperatures observed in the 2 trials caused additional brain injury or whether the elevated temperatures were the manifestation of existing hypoxic-ischemic brain injury.

## Knowledge Gained From Large Clinical Trials

Approximately 1200 infants were enrolled in the 6 large clinical trials of therapeutic hypothermia. Analyses of aggregate data, as well as data from registries, indicate that moderate hypothermia initiated within 6 hours of birth and continued for 72 hours is a safe and modestly effective neural rescue strategy for infants born at greater than 35 weeks of gestational age who have clinical evidence of moderate or severe neonatal encephalopathy.

## Areas of Uncertainty

Because there was little variability among published clinical trials, questions remain regarding the optimal timing for the initiation of cooling and the depth and duration of therapy. There are several ongoing randomized clinical trials that are designed to assess the efficacy of initiating cooling between 6 and 12 hours of age, using a deeper depth of cooling (32°C), or cooling for a longer duration (120 hours) (NCT 01192776, NCT 00614744). In addition, information regarding the safety and efficacy of cooling treatment of encephalopathic infants born at less than 35 weeks of gestational age is lacking, but preliminary information may be available in the near future (NCT 1793129).

There is also uncertainty regarding the safety and efficacy of initiating cooling before transfer to a center offering therapeutic hypothermia. However, data from the Vermont Oxford Encephalopathic Registry indicate that as many as a third of encephalopathic infants, many of whom were born in other facilities, were not admitted to a neonatal ICU until after 6 hours of age.[20] In a study in which active cooling with cool packs was started on arrival of the transport team at the referring center, approximately one-third of the 35 infants had a rectal temperature below 32°C on arrival at the cooling center.[21] A similar rate of excessive cooling on arrival was noted when passive cooling was used (3 of 18 infants).[22] Using a carefully designed protocol for passive cooling at the referral hospital and on transport, Kendall et al noted that 67% of the 39 infants were within target temperature range (33°C–34°C) on arrival at the cooling center, and 11% had a rectal temperature below 32°C.[23] There have been 2 observational studies from the United Kingdom of servo-controlled cooling in the field.[24,25] Application of this mode of cooling led to significantly less overcooling and greater success in maintaining rectal temperature in the target range when compared with passive cooling.

## Clinical Trials of Adjuvant Therapies for Neonatal Encephalopathy

Because the incidence of death and disability remains high after treatment with cooling (approximately 40%), there is an urgent need for additional therapies to further improve outcomes of infants who have acute encephalopathy. Promising neuroprotective agents include antiepileptic drugs, erythropoietin,


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melatonin, and xenon. Phase I and II trials of xenon (NCT 00934700, NCT 01545271) and topiramate (NCT 01241019, NCT 01765218) as adjuvant therapy to hypothermia are underway. A phase II study of erythropoietin using doses of 1000 U/kg intravenously in infants undergoing cooling is planned (NCT 01913340) and a phase I and II study of darbepoetin as concurrent therapy with cooling is in progress.[26] There is also a phase I–II study assessing the safety and efficacy of clonidine therapy during cooling for neonatal encephalopathy (NCT 01862250).

## CONCLUSIONS

1. Medical centers offering hypothermia should be capable of providing comprehensive clinical care, including mechanical ventilation; physiologic (vital signs, temperature) and biochemical (blood gas) monitoring; neuroimaging, including MRI; seizure detection and monitoring with aEEG or EEG; neurologic consultation; and a system in place for monitoring longitudinal neurodevelopmental outcome.
2. Infants offered hypothermia should meet inclusion criteria outlined in published clinical trials (see Table 1). Eligibility criteria include a pH of $\leq$7.0 or a base deficit of $\geq$16 mmol/L in a sample of umbilical cord blood or blood obtained during the first hour after birth, history of an acute perinatal event, a 10-minute Apgar score of <5, or assisted ventilation initiated at birth and continued for at least 10 minutes. In addition, a neurologic examination demonstrating moderate to severe encephalopathy is essential. If preferential head cooling is used, an abnormal background activity on either EEG or aEEG also is required.
3. Training programs and infrastructure need to be established and maintained in a highly organized and reproducible manner to ensure patient safety. Each center offering hypothermia therapy needs to develop a written protocol and monitor management and outcomes. Training needs to include awareness and timely identification of infants at risk for encephalopathy and an appropriate assessment of infants who have encephalopathy. Educational endeavors need to involve obstetric care providers; labor, delivery, nursery, and postpartum personnel; and pediatric care providers.
4. Outreach education to community hospitals needs to be implemented. Specific issues include the awareness and timely identification of infants at risk for encephalopathy and prevention of extreme hypothermia and hyperthermia.
5. Cooling infants who are born at less than 35 weeks' gestation or those who have mild encephalopathy, cooling for longer than 72 hours, cooling at a temperature lower than that used in published clinical trials, and the use of adjuvant therapies should only be performed in a research setting and with informed parental consent.


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