Therapeutic Hypothermia for Management of Neonatal Asphyxia: What Nurses Need to Know

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Birth asphyxia can induce a cascade of reactions that result in altered brain function known as hypoxic-ischemic encephalopathy. Possible outcomes for survivors of birth asphyxia vary widely, from a normal outcome to death, with a wide range of disabilities in between, including long-term neurodevelopmental disability, cerebral palsy, neuromotor delay, and developmental delay. Treatment of hypoxic-ischemic encephalopathy has centered on dampening or blocking the biochemical pathways that lead to death of neuronal cells. The reduction of body temperature by 3°C to 5°C less than normal body temperature can reduce cerebral injury. At Mount Sinai Hospital in Toronto, Ontario, the goal of therapeutic hypothermia is to achieve a rectal temperature of 33°C to 34°C, and the protocol is started within 6 hours after birth. The hypothermia is maintained for 72 hours, and then the infant is gradually warmed to normal body temperature (36.8°C-37°C). The protocol and nursing implications are presented. (*Critical Care Nurse.* 2011;31[3]:e1-e12)

Birth asphyxia is defined as inadequate oxygen delivery associated with impaired blood flow leading to poor gas exchange in the fetus and newborn before, during, and after delivery.[1] Causes of birth asphyxia include placental abruption, cord compression, intrauterine infections, ruptured uterus, birth trauma, congenital malformations, meconium aspiration, obstructed airway, and delay in establishing respiration.[2,3]

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Pathophysiology

Asphyxial injury leads to progressive hypoxemia, hypercapnia, and metabolic acidosis associated with anaerobic metabolism.[1(p11)] In this situation, blood is redirected to provide increased blood flow to the brain, heart, and adrenal glands and reduced blood flow to the intestines, skin, and kidneys. Concurrent release of epinephrine helps maintain and increase blood pressure. If the asphyxia persists, this initial coping mechanism begins to fail. Impaired myocardial function causes a decrease in blood pressure and a subsequent decrease in cerebral blood flow.[3(p400)]

The brain has limited sources of stored energy and relies on adequate blood flow to extract the needed energy supplies for neuronal cells. With reduced blood flow, neuronal cells cannot extract enough glucose to convert to energy-storing adenosine triphosphate (ATP). This decrease in ATP stimulates a cascade of biochemical reactions that lead to early neuronal cell death via ischemia and necrosis (primary energy failure) or cell death via apoptosis (secondary energy failure).[4] These reactions involve the destruction of cell membrane potentials as ATP levels decrease. Consequently, the control of movement of ions across the cell membrane is impaired. Accumulations of intracellular calcium, sodium, chloride, and water reach toxic levels, and the level of the excitatory neurotransmitter glutamate is elevated at the synaptic junction. Cell edema and lysis follow the influx of sodium and water.[5] Elevated levels of glutamate and intracellular calcium cause further cell damage by breaking down cell proteins and hydrolyzing lipids in

cell membranes, producing free radicals such as superoxide and nitric oxide.[5(p840),6] Superoxide in asphyxiated infants reacts with nitric oxide to form toxic reactive nitrogen species that cause mitochondrial damage and eventual cell death. In addition, cell damage signals inflammatory mediators that stimulate production of glutamate. Cell membranes damaged by the depletion of ATP stores cannot clear the accumulated glutamate, which reaches toxic levels, creating the environment for apoptosis.[1(p30),7]

Clinically, these reactions manifest themselves in altered brain function known as hypoxic-ischemic encephalopathy (HIE). Once an asphyxiated infant is resuscitated, although renewed blood flow restores the energy needs of the cells, it also triggers a secondary cascade of events that further contribute to apoptotic or delayed cell death.[8] This secondary reaction can occur from 6 to 48 hours after the initial injury. Hyperemia in reperfused areas causes inundation by neutrophils and inflammatory markers, which block microvessels, causing further ischemia. In addition, oxygen, which becomes available with reperfusion, metabolizes to produce reactive oxygen species, which further exacerbate the biochemical pathways outlined earlier, leading to cell death.[4(p515),8(p295)] Of note, encephalopathy or manifestation of brain dysfunction can be due to causes other than birth hypoxia, such as brain malformations, drugs, infections, and metabolic disease.[9(p225)] Thus, to correlate encephalopathy with asphyxia associated with birth, the American College of Obstetrics and Gynecology[10] has developed a policy statement that defines the criteria for the diagnosis of birth asphyxia (Table 1).

Table 1 Summary of the report of the American College of Obstetricians and Gynecologists[a]

Essential criteria to define birth asphyxia (must meet all 4)
1. Evidence of a metabolic acidosis according to blood gas analysis of fetal umbilical cord arterial blood obtained at delivery (pH <7 and base deficit = 12 mEq/L)
2. Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type
4. Exclusion of other identifiable causes of encephalopathy such as trauma, coagulation disorders, infectious conditions, or genetic disorders
Criteria that collectively suggest an intrapartum timing (close to time of labor and delivery, eg, 0-48 hours) but are nonspecific to asphyxial injuries
1. A sentinel (signal) hypoxic event occurring immediately before or during labour
2. A sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent, late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal
3. Apgar scores of 0-3 beyond 5 minutes
4. Onset of multisystem involvement within 72 hours of birth
5. Evidence of acute nonfocal cerebral abnormality on early imaging study

[a] Based on data from the Task Force of the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics.[10]

Incidence and Mortality

Globally, according to the World Health Organization,[11] for 2006 (the most recent data available), almost 4 million children died in the neonatal period. Among these, 7 deaths per 1000 births were attributed to birth asphyxia; the majority of the deaths occurred in underdeveloped and developing countries. In contrast, for the whole of the United States for 2005 (most recent data available),[12] the overall neonatal mortality rate was 4.54 deaths per 1000 live births. Death associated with birth asphyxia was 2.7% of the total infant mortality rate, or less than 1 death per 1000 live births.

Staging

In 1976, Sarnat and Sarnat[13] proposed an HIE staging system that classifies the degree of encephalopathy (stages 1, 2, and 3) on the basis of clinical assessment. In 1983, Fenichel[14] classified HIE on the basis of clinical signs and symptoms (mild, moderate, and severe). The 2 classification systems are quite similar, including definitions, and are often quoted interchangeably. To date, both systems are commonly used to define HIE (Table 2).

Outcome

Possible outcomes for survivors of birth asphyxia vary widely, from a normal outcome to death, with a wide range of disabilities in between.

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Table 2 Classification of hypoxic-ischemic encephalopathy[a]

	Classification of encephalopathy		
	Stage I Mild	Stage 2 Moderate	Stage 3 Severe
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Muscle tone	Normal	Mildly hypotonic	Flaccid
Myoclonus	Present	Present	Absent
Sucking reflex	Weak	Weak or absent	Absent
Moro embrace reflex	Strong	Weak or incomplete	Absent
Pupils	Dilated	Constricted	Variable/unequal
Heart rate	Tachycardic	Bradycardic	Variable
Salivary secretions	Sparse	Profuse	Variable
Seizures	None	Common: focal or multifocal	Uncommon
Duration	<24 h	2-14 d	Hours to weeks

[a] Based on data from Sarant and Sarnat[13] and Fenichel[14] staging system.

Cerebral palsy is a major outcome of HIE, but other outcomes have also been reported (Table 3).

In a prognostic model for term infants with HIE,[16] 3 independent predictors were highly significant ($P<.05$) for death or severe neurodevelopment disability (a developmental quotient of <70) in survivors: (1) administration of chest compressions for longer than 1 minute ($P=.004$); (2) base deficit, according to blood gas analysis (done within the first 4 hours of delivery), of more than 16 mmol/L ($P=.005$); and (3) onset of respirations 30 minutes or more after delivery ($P=.006$). When infants with HIE had these 3 characteristics, the probability of severe adverse outcomes was 93%. In contrast, if none of the 3 predictors was present, the probability of severe adverse outcome was 46%. Recently, amplitude-integrated electroencephalography (aEEG) has become available as a bedside tool for monitoring brain activity. Unlike traditional EEG machines, aEEG machines are small and portable. They record cerebroelectrical background activity in neonates via 2 electrodes placed on either side of the head and 1 electrode placed mid forehead that acts as ground. The signals received by the electrodes are compressed and displayed as background activity and microvoltage on the monitor.[17] Interpretation of the findings is based on pattern recognition of the bandwidth (called amplitude) produced by the compressed signals and the voltage measurement of the upper and lower limits of this bandwidth (Table 4).[17(p80)] Findings on aEEGs are predictive of later neurodevelopmental outcome. In a meta-analysis[18] of 8 studies, the sensitivity of aEEG for correct prediction of poor developmental outcome, defined as the presence of cerebral palsy and a developmental quotient of 85 or less on the Griffiths developmental scale,[19] varied from 73% to 100%. The specificity of aEEG for correct prediction of no

Table 3 Outcomes after hypoxic-ischemic encephalopathy[a]

A

Degree of encephalopathy[13,14]	Adverse outcomes, %[b]
Mild	0
Moderate	23.8-67
Severe	94.1-100

B

Degree of encephalopathy[13,14]	Presence of cerebral palsy, %[c,d]	Abnormal outcome without the presence of cerebral palsy, %[e]
Moderate to severe	58	42

[a] Part A based on data from Pin et al[9] and B based on data from Al-Macki et al.[15]
[b] Death or cerebral palsy or motor/cognitive impairment more than 2 standard deviations below the norm.
[c] Cerebral palsy comprising spastic quadriplegia, hemiplegia, monoplegia, and mixed type.
[d] Severe microcephaly, occurrence of more than 1 episode of seizures, use of phenytoin, and use of antiepileptic medication at discharge significant for later presence of cerebral palsy ($P \leq .05$)
[e] Global developmental delays, attention deficit hyperactivity, developmental language impairment, autism spectrum disorder, epilepsy, and secondary microcephaly.

Table 4 Categories of amplitude-integrated electroencephalograms and associated outcomes

Background activity	Lower margin, μV	Upper margin, μV	Outcomes in term infants
Continuous	5-10	10-25	Normal
Discontinuous	Variable but <5	>10	Normal if present only during first 6-12 h after asphyxia
Burst suppression	No variability; 0-1 Low voltage, intermixed with higher amplitude	>25	Abnormal outcome; some infants with normal outcome if tracing becomes continuous within 12-24 hours
Low voltage	Continuous pattern; around or <5	<10	Abnormal outcome
Inactive	Isoelectric tracing; <5		Abnormal outcome
Seizure	Abrupt rise in lower margin	Simultaneous rise in upper margin	Outcome dependent on background activity

[a] Based on data from Hellstrom-Westas et al[17] and Spitzmiller et al.[18]

neurodevelopmental deficit also ranged from 73% to 100%. The aEEG patterns associated with poor outcomes were burst suppression, continuous low voltage, flat tracing, and single or repetitive epileptiform activity tracings. Continuous and discontinuous aEEG tracings were associated with no neurodevelopmental deficit. In further studies,[20,21] 60% of infants in whom a repeat aEEG showed recovery from burst suppression, flat tracings, and low voltage within 24 hours after an asphyxia event had mild disability or normal neurodevelopmental outcomes on follow-up.

Treatment

Treatment of HIE has centered on dampening or blocking the biochemical pathways that lead to neuronal death. Allopurinol has been used to prevent formation of free radicals. However, Chaudhari and McGuire[22] were unable to determine if allopurinol has a beneficial effect after HIE and called for larger trials of allopurinol therapy.

Another treatment, which has been studied widely, initially in animals[23,24] and then in neonates,[25-30] is therapeutic hypothermia. The reduction of body temperature by 3°C to 5°C less than normal body temperature during reperfusion before secondary energy failure occurs, can reduce cerebral injury. How this reduction is achieved is not altogether clear. Most likely the cooling reduces the hyperemia during reperfusion and decreases neuronal metabolic rate, therefore reducing the need for ATP, interrupting the excitotoxic cascade of glutamate and the inflammatory response, thus blocking neuronal cell death by apoptosis.[6(p295),8(p64)] In studies on therapeutic hypothermia, the decrease in body temperature was achieved by head cooling only, with a special cap with circulating cold water placed on the head of the neonate, or by systemic whole-body cooling with either a thermostatically controlled cooling blanket or hot/cold gel packs placed under or around the neonate.

Meta-analysis of Trials

In a review of 8 studies with a total patient population of 638 infants, Jacobs et al[31] analyzed (1) the effects of therapeutic hypothermia on mortality, long-term neurodevelopmental disability, cerebral palsy, neuromotor delay, and developmental delay (as indicated by scores on the Bayley Scale of Infant Development[32]) and (2) clinically important side effects. The 8 studies were published during the period 1998 to 2005. The infants were greater than 35 weeks of gestation and weighed more than 2000 g. All the studies had well-defined criteria for birth asphyxia. In 4 studies, hypothermia was achieved by using both head cooling and whole-body cooling; in the other 4 studies, whole-body cooling alone was used. Hypothermia was started by the time the infants were 6 hours old, and target temperature varied from 32.5°C to 36.5°C. Duration of hypothermia was from 48 to 72 hours. The rate of rewarming varied from 0.5°C per hour to 0.5°C every second hour, and the procedure required 8 to 12 hours. Composite outcomes of the studies indicated that therapeutic hypothermia was beneficial for term infants with HIE.

Compared with infants who received standard care, those treated with hypothermia had a significant reduction in death or major neurodevelopmental disability ($P < .001$; 95% confidence interval [CI], 0.65-0.89). Mortality rates were 24% in the hypothermia group and 33% in infants who had standard care ($P = .01$; 95% CI, 0.58-0.94). Neurodevelopmental disability in survivors was 28% in the hypothermia group and 42% in the standard care group ($P = .01$; 95% CI, 0.51-0.92). Cerebral palsy rates were 25% in the hypothermia group and 34% in the standard care group; this difference was not significant ($P = .09$; 95% CI, 0.52-1.05). The most important adverse outcomes were sinus bradycardia, hypotension requiring

Case Study

A 32-year-old gravida 1, para 0 woman expecting twins was essentially healthy and had an uneventful pregnancy. However, at 35 weeks 5 days gestational age, labor had to be induced because of increased blood pressure and decreased amniotic fluid for twin A. Artificial rupture of membranes 15 hours before delivery yielded clear fluid. During the induction of labor, the woman experienced a fever (body temperature >38°C). Fetal tachycardia (heart rate >160/min) also occurred, necessitating treatment with antibiotics. Worsening decelerations and a sudden fetal bradycardia on fetal tracing of twin A led to an emergency cesarean delivery. Twin B was delivered without incident.

Twin A, a 2820-g girl, was delivered with no audible heart rate. After immediate intubation, cardiac compressions, 3 doses of epinephrine, and a sodium bicarbonate bolus, a sustained heart rate greater than 100/min was achieved at 10 minutes of life. An umbilical arterial catheter and a peripheral arterial catheter were placed. A full sepsis workup consisting of complete blood cell count and cultures of blood and cerebrospinal fluid was completed. The infant was given ampicillin and gentamicin. Apgar scores were 0, 0, 2, 4, and 7 at 1, 5, 10, 15, and 20 minutes, respectively. Results of blood gas analysis of cord blood were not available. At 43 minutes of age, twin A began treatment with mechanical ventilation with settings as follows: respirations 30/min, peak inspiratory pressure 16 mm Hg, positive end-expiratory pressure 6 mm Hg, and 70% oxygen. Results of blood gas analysis of a blood sample obtained when the infant was 20 minutes old were pH 7.16, P_{CO_2} 30 mm Hg, P_{O_2} 95 mm Hg, bicarbonate 10 mEq/L, base excess -17.9 mEq/L, lactate 207 mg/dL (to convert to millimoles per liter, multiply by 0.111), and glucose 88.3 mg/dL (to convert to millimoles per liter, multiply by 0.0555). The first hemoglobin value was 17.7 g/dL, with white blood cell count 23 360/mm^3 and platelet count 134 000/mm^3. At 1 hour 3 minutes of age, twin A began clonic movements and lip smacking. At 1 hour 48 minutes of life, further suspicious mouthing and jaw movements were witnessed. The first of several doses of phenobarbital was given at 1 hour 55 minutes of life. An overall initial examination revealed no visible dysmorphic features. However, the infant had large fontanelles, splayed sutures, facial edema, lethargy, no reflexes, poor muscle tone, no spontaneous movements, constriction of pupils bilaterally, jitteriness (shaking movements) of limbs and lower jaw, and hematomas to the limbs, head, and chest, presumably from delivery. From the onset, twin A was nursed on an open radiant warmer bed.

During the initial week and up to the first 10 days, platelet count fluctuated between 57 000/μL and 167 000/μL, despite infusion of 2 units of fresh-frozen plasma, 2 units of platelets, and 1 unit of cryoprecipate and 4 separate injections of vitamin K. The initial prothrombin time was 15.2 seconds, with an activated partial thromboplastin time of 42 seconds and an international normalized ratio of 1.5. The values for these 3 parameters did normalize when the infant was about 48 hours old. Neurologically, the infant received numerous doses of phenobarbital while hospitalized and was discharged home on a maintenance dose.

Because of the initial resuscitation, results of blood gas analysis, ongoing hypotonia, seizures, and decreases in platelet count, twin A overwhelming met the criteria for whole-body therapeutic hypothermia (WBTH). However, the infant's gestational age was initially recorded as 35 weeks, which did not meet the strict definition of the inclusion criteria. WBTH was started only after arrival of the attending neonatologist and discussion with the parents, who wanted everything to be done despite the elapsed time and the shortfall of the infant's gestational age by 1 day.

When the infant was 11 hours old, the cooling procedure was begun. The radiant warmer was turned off. A rectal probe was inserted and secured to the inner part of the infant's thigh. The rectal temperature was continuously displayed on the monitor. The thermistor probe that was part of the electronic feedback system (servocontrol) used to regulate the heat output of the radiant warmer was kept on the infant as a way to follow skin temperature during the cooling process. Once the skin temperature was less than 35°C, the probe was removed. The initial axillary temperature was 37.1°C; the initial rectal temperature was 37.3°C. The goal was to achieve

inotropic support, and increases in thrombocytopenia.

Despite evidence on the efficacy of hypothermia in mitigating the adverse outcomes of HIE, questions about hypothermia still remained,[33] including the method of achieving hypothermia, the duration of sustained hypothermia, the optimal hypothermia temperature, the optimal age of starting hypothermia, methods of rewarming, and how to determine best which infants will benefit most.

In a more recent meta-analysis that included studies completed after those reviewed by Jacobs et al,[31] Shah[34] analyzed 13 trials from the period 1998 to 2009 with a combined population of 1440 infants. In 6 studies, selective head cooling

a rectal temperature of 34°C while maintaining an overall rectal temperature of 33°C to 34°C throughout the 72-hour cooling phase. Cool packs were placed beside the infant and under her legs. The diaper remained under the infant and not traditionally "on."

Within 1 hour 25 minutes, the rectal temperature was 34°C. The infant had some spontaneous movements during that time; her toes and feet became cyanotic and she was pale overall. Findings on an electrocardiogram done at this time were normal. After 2 hours of therapy, the rectal temperature was 33°C. At this time the cool packs were removed. During the next 6 hours, the rectal temperature continued to decrease, necessitating the need for a hat and blankets. Once the rectal temperature was 32.1°C, the infant appeared to start shivering and was overall dusky and cyanotic. At this time the radiant warmer was turned on, and the infant was slowly warmed until the rectal temperature was 33°C. Twelve hours into the cooling phase, the infant was extubated, and treatment with low flow oxygen by nasal prongs was started. Three hours after extubation, distinctive cycling movements were witnessed, and a dose of phenobarbital was given. During the next 12 hours, the infant was irritable and had marked decreases in oxygen saturations, hypertonic and stiffening posturing, and tremors and/or shivering that required further doses of phenobarbital. Thirty-six hours after the cooling phase was initiated, the decision was made to move the infant to an isolation room to provide not only a quiet environment, thereby potentially reducing irritability, but also an environment that would better enable control of the ambient temperature. Allowing the parents quiet visiting time with the infant was also important. Once the infant was settled in the isolation room, the rectal temperature increased slightly to 34.2°C. Again, cool packs were placed along the sides of the infant's body until a temperature of 33°C was achieved. On the same day, the first of 2 electroencephalograms (EEGs) was obtained, but because of the infant's shivering, irritability, and subtle seizure behavior, the results were inconclusive.

After 72 hours of cooling, the warming process was started. The goal was to increase core temperature no faster than 0.5°C every hour. The warmer was turned on to 10% output, and the percentage was gradually increased manually during the next several hours. Within 6 hours of the time warming began, the infant experienced apneic episodes, decreases in oxygen saturations, and irregular breathing, necessitating positive pressure ventilation with oxygen. After 14 hours of warming, a rectal temperature of 36.6°C was maintained. After the infant's care was normalized, magnetic resonance imaging was done, which required reintubation, a fentanyl infusion, and sedation. The images revealed changes in the basal ganglia suggesting a degree of ischemia. After the imaging, the infant was quickly extubated, and during the next few hours and the following few days, she had episodes of severe decreases in oxygen saturations with subsequent decreases in heart rate requiring positive pressure ventilation, phenobarbital infusions, and eventually a daily maintenance dose of phenobarbital.

In the days that followed, an EEG revealed patterns more consistent with those of an infant at 28 to 30 weeks' gestation. The patterns of twin A were primitive, discontinuous, and asynchronous at times. Evoked-potential examinations were carried out on days 6 and 24 of life. The day 24 examination showed mild immature signals in visual evoked potentials for a near-term baby.

On day 6 of life, feedings were introduced. After a few unsuccessful attempts with nasogastric feeding, feeding was tolerated by day 12 of life. Attempts to breastfeed were unsuccessful because the infant was sleepy. An occupational therapist was consulted to assess the sucking reflex. The infant's parents, physicians, nurses, occupational therapist, and lactation consultants agreed to offer the infant bottles of expressed breast milk to better gauge volumes and hopefully improve sucking. Within 1 week after bottles were started, the infant was on an ad lib/demand schedule, gaining weight, and responsive, with a normal cry, normal tone, and strong reflexes.

On day 27 of life, twin A was discharged home. The parents' goal to bring their baby home was achieved. Twin A continues to thrive at home. At follow-up assessments at the tertiary neonatal follow-up clinic, spastic quadriplegia was diagnosed. The infant has no hearing or vision deficit. She is able to hold herself up, sit without support, and walk with the help of a walker. She is currently working with occupational therapists and a physiotherapist to improve her fine motor skills.

along with whole-body cooling was used to achieve hypothermia; in the other 7 studies, hypothermia was achieved by whole-body cooling alone. The target temperature varied from 33°C to 36.5°C, and core temperature was measured via the rectum, esophagus, and nasopharynx. Gestational ages varied from more than 35 weeks to 37 weeks or more.

Table 5 Summary of outcomes of neonatal therapeutic hypothermia from 2 systematic reviews[a]

Outcomes	Relative risk (95% confidence interval)	
	Jacobs et al[31]	Shah[34]
Death or major disability	0.76 (0.65-0.89)[b]	0.74 (0.65-0.83)[b]
Selective head cooling with systemic hypothermia	0.85 (0.69-1.05)	0.69 (0.56-0.84)[b]
Whole-body cooling	0.69 (0.55-0.86)[b]	0.77 (0.66-0.90)[b]
Temperature >34°C	NA	0.84 (0.67-1.04)
Temperature <34°C	NA	0.70 (0.60-0.82)[b]
Mortality	0.74 (0.58-0.94)[b]	0.78 (0.65-0.92)[b]
Selective head cooling with systemic hypothermia	0.83 (0.59-1.16)	0.77 (0.58-1.03)
Whole-body cooling	0.66 (0.47-0.93)[b]	0.78 (0.63-0.96)[b]
Temperature >34°C	NA	0.87 (0.62-1,21)
Temperature <34°C	NA	0.75 (0.62-0.91)[b]
Neurodevelopmental disability	0.68 (0.51-0.92)[b]	0.67 (0.54-0.88)[b]
Selective head cooling with systemic hypothermia	0.77 (0.51-1.17)	0.66 (0.46-0.95)[b]
Whole-body cooling	0.60 (0.40-0.92)[b]	0.68 (0.51-0.90)[b]
Temperature >34°C	NA	0.73 (0.48-1.11)
Temperature <34°C	NA	0.65 (0.50-0.90)[b]
Cerebral palsy	0.74 (0.52-1.05)	0.65 (0.48-0.88)[b]
Selective head cooling with systemic hypothermia	0.80 (0.52-1.22)	0.63 (0.35-1.14)
Whole-body cooling	0.66 (0.36-1.18)	0.65 (0.46-0.93)[b]
Temperature >34°C	NA	0.63 (0.35-1.14)
Temperature <34°C	NA	0.65 (0.43-0.93)[b]
PDI <70 disability[c]	0.73 (0.53-1.00)	0.70 (0.54-0.90)[b]
Selective head cooling with systemic hypothermia	0.81 (0.51-1.29)	0.74 (0.46-1.19)
Whole-body cooling	0.66 (0.42-1.02)	0.68 (0.50-0.92)[b]
Temperature >34°C	NA	0.76 (0.47-1.23)
Temperature <34°C	NA	0.67 (0.50-0.90)
MDI <70 disability[d]	0.74 (0.53-1.02)	0.70 (0.54-0.90)[b]
Selective head cooling with systemic hypothermia	0.86 (0.54-1.36)	0.76 (0.47-1.23)
Whole-body cooling	0.64 (0.41-1.00)	0.67 (0.50-0.90)[b]
Temperature >34°C	NA	0.74 (0.46-1.19)
Temperature <34°C	NA	0.68 (0.50-0.92)[b]

Abbreviations: MDI, Mental Developmental Index; NA, not available; PDI, Psychomotor Developmental Index.
[a] Based on data from Jacobs et al[31] and Shah.[34]
[b] $P \leq .05$.
[c] PDI measured by using the Bayley Scale of Infant Development, Psychomotor Developmental Index.
[d] MDI measured by using the Bayley Scale of Infant Development, Mental Developmental Index.

Compared with the normothermia group, the hypothermia group had a significant reduction in the combined risk of mortality or moderate to severe neurodevelopmental disability (relative risk, 0.74; 95% CI, 0.65-0.83). However, more importantly, Shah addressed some of the outstanding questions about therapeutic hypothermia. The meta-analysis indicated that selective head cooling (relative risk, 0.69; 95% CI, 0.56-0.84) and whole-body cooling (relative risk, 0.77; 95% CI, 0.66-0.90) were equally effective in reducing mortality or moderate to severe disability and neurodevelopmental disability among survivors. Whereas whole-body cooling was effective ($P < .05$) in reducing the mental developmental index to less than 70, the psychomotor developmental index to less than 70, and the occurrence of cerebral palsy, selective head cooling was not. Temperatures less than 34°C reduced the combined mortality and neurodevelopmental disability rate, the mental developmental index to less than 70, the psychomotor developmental index to less than 70, and the occurrence of cerebral palsy, whereas temperatures greater than 34°C did not. The most important side effects were cardiac arrhythmias and thrombocytopenia. Tables 5 and 6 provide a comparison of outcomes and side effects reported in these 2 meta-analyses.

Hypothermia Protocol and Nursing Care

After careful analysis, review of evidence, and discussion with experts in the field, whole-body therapeutic hypothermia (WBTH)

Table 6 Summary of side effects of neonatal therapeutic hypothermia from 2 systematic reviews[a]

	Relative risk (95% confidence interval)	
Adverse effect	**Jacobs et al[31]**	**Shah[34]**
Visual deficit/blindness	0.57 (0.30-1.08)	0.59 (0.35-0.98)[b]
Hearing deficit/deafness	0.93 (0.37-2.34)	0.75 (0.36-1.55)
Bradycardia	0.96 (2.15-16.49)[b]	
Hypotension	1.17 (1.00-1.38)[b]	1.03 (0.93-1.13)
Arrhythmia	1.04 (0.07-16.39)	4.08 (1.55-10.74)[b]
Thrombocytopenia	1.55 (1.14-2.11)[b]	1.28 (1.07-1.52)[b]
Coagulopathy	0.83 (0.31-2.24)	0.96 (0.80-1.15)
Sepsis	0.86 (0.42-1.76)	0.86 (0.40-1.88)
Seizures	0.96 (0.84-1.10)	0.96 (0.86-1.06)

[a] Based on data from Jacobs et al[31] and Shah.[34]
[b] $P \leq .05$.

Table 7 Eligibility criteria for whole-body hypothermia

Infants who are 35 weeks plus 6 days or more gestational age and meet any 2 of the following criteria:
- Apgar score <5 at 10 minutes
- Cord pH or postnatal blood gas pH <7 within 1 hour of birth
- Base deficit >16 mEq/L on blood gas analysis of cord blood or on any postnatal arterial blood gas analysis done within 1 hour of birth
- At least 10 minutes of positive pressure ventilation

AND

Evidence of moderate to severe encephalopathy defined as clinical seizures **OR** presence of at least 1 sign in at least 3 of these 6 categories:

	Degree of encephalopathy	
Category	**Moderate**	**Severe**
Level of consciousness	Lethargy	Stupor/coma
Spontaneous activity	Decreased activity	No activity
Posture	Distal flexion, full extension	Arms extended and internally rotated, legs extended with feet in forced plantar flexion
Tone	Hypotonic	Flaccid
Primitive reflexes	Weak sucking reflex Incomplete Moro embrace reflex	Absent sucking reflex Absent Moro embrace reflex
Autonomic system	Constricted pupils Bradycardia Periodic breathing	Deviated pupils/nonreactive to light/dilated Variable heart rate Apnea

Exclusion criteria:
a. Presence of known lethal chromosomal anomaly
b. Severe intrauterine growth restriction
c. Infants in severe condition for which no additional intensive therapy can be offered, after discussion with parents and the attending neonatologist
d. Presence of congenital anorectal anomaly (eg, imperforate anus) on visual inspection
e. Evidence of head trauma or intracranial hemorrhage

was adopted as a standard of care in our neonatal intensive care unit. Table 7 gives the inclusion and exclusion criteria. The goal is to achieve a rectal temperature of 33°C to 34°C, and the protocol (Table 8) is to be started within 6 hours after birth. The therapeutic hypothermia is maintained for 72 hours, and then the infant is gradually warmed to normal body temperature (36.8°C-37°C). Because the emphasis of therapeutic hypothermia is reduction of core temperature, we opted to use cool packs to achieve WBTH. We also established an interprofessional "cool crew" to review each case, so that deficiencies can be identified and rectified. Even though WBTH is a standard of care, each infant's parents must be informed of the infant's diagnosis, prognosis, expectant management, and the role of WBTH. Nurses in our unit are an integral part of the resuscitation team. Along with the neonatologist, they play a valuable role in the initial identification of infants in need of WBTH and later at the bedside, by providing the physical and emotional support to the infant and the infant's family.

Nursing Implications

Our WBTH protocol does not require specialized equipment. Although the use of simple alternatives, such as bottles filled with cool water,[36] has been recognized as effective in other settings, achieving and maintaining hypothermia with cool packs required the nurses' constant attention and vigilance to ensure that the temperature remained within the prescribed range. In our experience, the temperature decreased to lower than the prescribed parameters,

Table 8 Nursing protocol for whole-body therapeutic hypothermia (WBTH)

Before starting WBTH	Achieving WBTH	During WBTH	Rewarming phase (after 72 hours)[35(p1351)]
Place infant on a radiant warmer with the power turned off[30 (p1576)]	Aim for rectal temperatures of 33°C-34°C[28(p19),25(p1351)]	Maintain temperature between 33°C-34°C	Turn on the radiant warmer
Assist in the placement of a peripheral or umbilical arterial catheter for monitoring blood pressure and collection of blood samples for laboratory tests	Monitor temperature every 15 minutes[30(p1576)]; infants can have body temperature decrease spontaneously just by having the radiant warmer off	Parents may touch and interact with the infant, but skin to skin care is discouraged at this time, as that may disrupt the cooling process	Set the desired skin temperature on the warmer to 0.5°C higher than the rectal temperature
Insert a peripheral intravenous catheter or assist in the placement of an umbilical venous catheter as needed	If after 60 minutes, temperature remains >35.5°C, apply cool packs[27(p835)] around infant to aid in lowering temperature	Record ongoing nursing assessment of neurological status, vital signs, blood pressure, and arrhythmias every 30 minutes; report any variances and intervene as appropriate	Increase temperature of the warmer by 0.5°C to rewarm infant at a rate no faster than 0.5°C every hour[30(p1577)]
Infuse the prescribed intravenous solution		If infant is intubated, maintain gas humidity at 35°C-40°C as per unit protocol	Monitor temperature every 30 minutes to ensure that rewarming is not occurring at a fast rate
Call for and obtain a 12-lead electrocardiogram to determine if any arrhythmias are present		Monitor for pain by using measurement/assessment tools such as the Premature Infant Pain Profile (PIPP); report any signs of pain	Keep rewarming until axillary temperature is 36.8°C and rectal temperature is 37°C; this process should be slow and may take up to 8 hours
Obtain complete blood cell count, serum electrolyte levels (sodium, potassium, chloride), lactate level, coagulation studies (prothrombin, partial thromboplastin times), glucose level, creatinine level, and liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) for baseline results and report them		Attach a cerebral function monitor to record amplitude-integrated electroencephalogram (aEEG) to recognize any abnormal patterns that might warrant medical intervention	Remove rectal probe after rewarming and maintain temperature thereafter in normal range
Insert the rectal probe[35] no deeper than 1.27 cm (0.5 in.) to avoid irritation/perforation and tape it to the thigh to monitor core temperature accurately		Obtain computed tomography, magnetic resonance imaging, and EEG studies on basis of infant's condition and aEEG findings; maintain cooling during these procedures	Set heart rate alarms back to the standard range per unit protocol
Place the radiant warmer's temperature probe on the infant's abdomen to monitor the skin temperature		Check stools and report presence of frank or occult blood; other than necrotizing enterocolitis, blood may be due to gut ischemia from the initial asphyxia event or even to the presence of the rectal probe and requires further investigation	Obtain complete blood cell count, serum electrolyte levels (sodium, potassium, chloride), lactate level, coagulation studies (prothrombin, partial thromboplastin times), glucose level, creatinine level, and liver function tests (ALT, AST) 72 hours after birth; report abnormal values and implement interventions as ordered

Continued

Table 8 *Continued*

Before starting WBTH	Achieving WBTH	During WBTH	Rewarming phase (after 72 hours)[35(p1351)]
Obtain and record vital signs		Adjust alarms limits on the cardiorespiratory monitor; cooled infants have lower pulse rates of 90-140/min	Once baby is rewarmed, reevaluate need for computed tomography, magnetic resonance imaging, visual evoked potentials, and somatosensory evoked potentials; magnetic resonance images obtained between 48 and 120 hours after asphyxial injury can determine the timing and extent of cerebral injury
Remove blankets and head coverings and keep infant naked during breastfeeding or bottle feeding to provide better visual assessment and minimize heat retention		Obtain complete blood cell count, serum levels of electrolytes (sodium, potassium, chloride), lactate level, coagulation studies (prothrombin, partialthromboplastin times), glucose level, creatinine level, and liver function tests (ALT, AST) at 24 and 48 hours after birth; report abnormal values and implement interventions as ordered	Be cautious in the introduction of feedings; infant can be at high risk for necrotizing enterocolitis because of reduced flow to the gut during hypothermia

requiring the warmer to be turned on briefly or use of a hat and blankets to avoid severe hypothermia (<32°C). Further, during WBTH, the infant can feel cold to the touch and look dusky because of decreased blood flow to the extremities. These changes are considered normal so long as oxygen saturation is in the required zone (94%-98%).

Tremors observed in twin A after the start of anticonvulsive therapy could have been due to either shivering or ongoing seizure activity. Expertise with the use of the cerebral function monitor could have helped the nurses and the medical teams differentiate between shivering and ongoing seizure activity. If a cerebral function monitor is not available, an EEG can be helpful for diagnosing seizures and beginning appropriate anticonvulsive therapy.

In our experience, pain scores in a sedated infant are not helpful in determining if hypothermia is painful, and this area needs further exploration. Nurses must be aware of subtle clues that can indicate pain and must advocate for appropriate interventions.

Parents can feel helpless when they see their infant shivering or shaking and will need reassurances and support. In our experience, use of a separate quiet room is welcomed by parents and nurses, because it provides an opportunity for privacy and parental bonding and allows for more environmental control of ambient temperature. However, use of a separate quiet room may be a challenge in units that have an open floor plan. Maintaining therapeutic relationships with an infant's family, keeping the family members informed and involved in the infant's care plan, encouraging breast pumping, and judicially referring the parents to support services are important aspects of the nursing care plan for WBTH and are much appreciated by the infants' parents.

Therapeutic hypothermia has now become a standard of care in many other units beside ours. As mentioned previously, some questions still need to be answered.[33(pp943, 946),37] Do gestational age and the time hypothermia is started have an effect on outcomes? Most studies on therapeutic hypothermia have been done with term infants, and treatment has been started within 6 hours of birth. In our case study, because the infant was 1 day short of the gestational age specified in the WBTH protocol, the cooling process did not begin until 11 hours after her birth.

Also not known is the optimal rate of cooling and rewarming. As noted, we had some difficulty in keeping rectal temperature at 33°C to 34°C.

Who benefits most from therapeutic hypothermia and what is the best way of answering that question? Although a cerebral function monitor was recently introduced in the unit, staff members were not familiar with its use, and so it was not used in the treatment of twin A. Subsequently, we had difficulty assessing actual seizure activity vs shivering vs pain response. Because twin A was born during the night shift, we were also unable to get an EEG before we began the cooling process because in-house EEG technicians are not available during the night shift. These deviations from the standard cooling protocol raise questions about the ultimate effect of these variables on outcome. With the help of the cool crew, these deviations and deficiencies were identified, and resources were allocated for the education and availability of appropriate personnel to avoid these problems in the future. Thankfully, birth asphyxia and HIE are rare conditions. However, this rarity also prevents nurses and physicians from becoming experts in the management and application of WBTH.

Does the availability of this WBTH influence a clinician's decision to offer redirection of care toward palliation or withdrawal of medical treatment? A meta-analysis[34(p7)] detected no difference in the risk of withdrawal of life support between infants who underwent therapeutic hypothermia and infants who were normothermic. Even so, this point could have played a role in our case study, because palliation or withdrawal of medical treatment was not discussed with the parents. Each new neonatal therapy is associated with the risk of pushing the established limits without firm answers to all outstanding questions. Because of the disastrous effects of birth asphyxia, the limitations of treatment options, and the chance of improving the odds with WBTH, our experience suggests that parents would urge clinicians to take that risk. CCN

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Financial Disclosures
None reported.

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