Current Management of the Infant Who Presents with Neonatal Encephalopathy

Elena V. Wachtel, MD, MPH, FAAP, and
Karen D. Hendricks-Muñoz, MD, MPH, FAAP

Neonatal encephalopathy after perinatal hypoxic-ischemic insult is a major contributor to global child mortality and morbidity. Brain injury in term infants in response to hypoxic-ischemic insult is a complex process evolving over hours to days, which provides a unique window of opportunity for neuroprotective treatment interventions. Advances in neuroimaging, brain monitoring techniques, and tissue biomarkers have improved the ability to diagnose, monitor, and care for newborn infants with neonatal encephalopathy as well as predict their outcome. However, challenges remain in early identification of infants at risk for neonatal encephalopathy, determination of timing and extent of hypoxic-ischemic brain injury, as well as optimal management and treatment duration. Therapeutic hypothermia is the most promising neuroprotective intervention to date for infants with moderate to severe neonatal encephalopathy after perinatal asphyxia and has currently been incorporated in many neonatal intensive care units in developed countries. However, only 1 in 6 babies with encephalopathy will benefit from hypothermia therapy; many infants still develop significant adverse outcomes. To enhance the outcome, specific diagnostic predictors are needed to identify patients likely to benefit from hypothermia treatment. Studies are needed to determine the efficacy of combined therapeutic strategies with hypothermia therapy to achieve maximal neuroprotective effect. This review focuses on important concepts in the pathophysiology, diagnosis, and management of infants with neonatal encephalopathy due to perinatal asphyxia, including an overview of recently introduced novel therapies.

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Neonatal encephalopathy continues to be an important cause of death and disability in newborn infants.[1,2] Because of advances in obstetrical and neonatal care, survival rate and early outcomes have improved; however, the incidence of developmental disabilities has not significantly declined.[3] The risk for brain injury can occur at any time during gestation, labor, and delivery and often is difficult to accurately identify. Neonatal encephalopathy, also identified as perinatal hypoxia-ischemia, has multiple etiologies and continues to be a common underlying cause of brain injury and subsequent neurologic disability.[4] Additionally, the disorder imposes a major burden on the individual, family, and society, accounting for 15-28% of children with cerebral palsy and 25% of all cases of developmental delay.[5,6] This review focuses on important concepts in the pathophysiology, diagnosis, and management of infants with neonatal encephalopathy due to perinatal asphyxia, including an overview of recently introduced novel therapies.

From the Department of Pediatrics, Division of Neonatology, New York University School of Medicine, New York, NY.
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Definition

Neonatal encephalopathy is a clinical syndrome of "disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness, and often seizures."[7] Encephalopathy is a nonspecific response of the brain to injury, which may occur via multiple casual pathways. Recognition of the cause of neonatal neurologic illness remains challenging with today's current diagnostic criteria.[8] During the perinatal period, hypoxemia, ischemia, or both occur because of asphyxia, an impairment in the exchange of respiratory gases. The American College of Obstetrics and Gynecology defines encephalopathy as an acute

TABLE 1. Distinguishing features of the 3 clinical stages of postanoxic encephalopathy in the full-term newborn infant

	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems decreased
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivarysecretions	Spars	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)
Electroencephalogram findings	Normal (awake)	Early low-voltage continuous delta and theta. Later, periodic pattern (awake). Seizures: focal 1- to 1.5-Hz spike- and -wave	Early: periodic pattern with isopotential phases. Later: totally isopotential
Duration	Less than 24 h	2-14 d	Hours to weeks

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intrapartum event sufficient to cause neuronal injury evidenced by a metabolic acidosis (pH <7 and base deficit ≥ 12) in fetal umbilical cord arterial blood obtained at the delivery.[9] Development of early encephalopathy (hours to days after birth) is considered essential to be confident about an underlying perinatal insult. Therefore, newborn infants with evidence of an acute intrapartum insult and/or difficult transition from fetal to neonatal life requiring resuscitation at birth should be carefully monitored for abnormal neurological symptoms as well as clinical seizures. The Sarnat 3 stage grading system of mild (stage 1), moderate (stage 2), and severe neonatal encephalopathy (stage 3), based on clinical symptoms and electroencephalogram (EEG) evaluation, is widely accepted (Table 1).[10] The grading system considers the responses of the neonate to handling, level of consciousness, changes in muscle tone and reflexes, presence of seizures, and the duration of the symptoms within 7 days after birth. Neonatal seizures are defined clinically as abnormal, stereotyped, paroxysmal alterations in neurological function.[11] Challenges in diagnosis and treatment are discussed later in the article.

Recognition of the cause of neonatal neurologic illness remains challenging with today's current diagnostic criteria.[8]

Epidemiology

Neonatal encephalopathy after perinatal hypoxic-ischemic insult is of great public health importance as a major contributor to global child mortality and morbidity. Global estimates for asphyxia-related deaths vary from 0.7 to 1.2 million newborns out of 4 million of all neonatal deaths. Almost 99% of neonatal deaths arise in developing (low- and middle-income) countries, in contrast to 1% of deaths in developed countries.[12,13] The incidence of neonatal encephalopathy in the USA is 2-3 per 1000 live term births.[14] With an annual birth rate of 4 million infants it is expected that 8000-12,000 infants will be diagnosed with this disorder each year. Most common etiologies include brain hemorrhage, focal cerebral infarction, and injury because of hypoxia-ischemia.[15] Much less frequently, neonatal encephalopathy is the result of metabolic or congenital abnormalities, meningitis, hypoglycemia, and hyperbilirubinemia. Neonatal encephalopathy does not always progress to permanent neurologic impairment. As many as 20% of term newborn infants with encephalopathy after perinatal asphyxia will die during the neonatal period and 25% of those who survive will have permanent neurologic disability.[16] Outcome of infants with mild encephalopathy is generally normal, including normal cogni-

tive function at school age.[17,18] A moderate degree of neonatal encephalopathy can be associated with a spectrum of long-term disabilities ranging from normal outcome to significant motor or cognitive disabilities. Up to 40% of infants with moderate neonatal encephalopathy after perinatal asphyxia and 100% of those with severe encephalopathy die or develop neurosensory impairments, including cerebral palsy, mental retardation, and hearing loss.[19] Cerebral palsy is a neurodevelopmental disability historically linked with intrapartum asphyxia and refers to a group of permanent disorders affecting the development of movement and posture that result in activity limitation attribute to nonprogressive disturbances in early life.[20,21] The prevalence of cerebral palsy among term deliveries has remained constant, approximating 2.0 per 1000 live births despite advances in obstetrical and neonatal care.[22] Long-term outcome is found to depend on the severity of neonatal encephalopathy and condition.[16,19] Cognitive deficit in children after neonatal encephalopathy, such as intellectual limitation, language problems, impairments in learning and in executive function, or social skills, have been reported in the literature.[23] In a review by Gonzalez and Miller[24] it was evident that survivors of moderate to severe neonatal encephalopathy after perinatal asphyxia are also at risk for cognitive deficits, with or without diagnosis of cerebral palsy. Thus, early brain injury frequently results in lifelong permanent disability and imposes a major burden on the individual, family, and society. Clinicians need awareness of the spectrum of abnormal neurological outcomes in infants with neonatal encephalopathy after perinatal asphyxia for prognostication, available treatment options, and counseling of parents. An extended period of neurodevelopmental follow-up of these high-risk infants is also required.

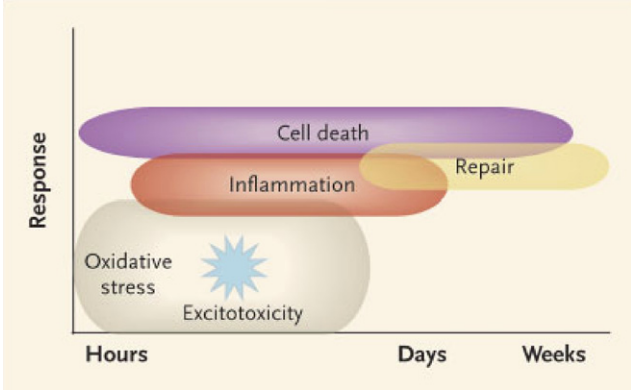

FIG 1. Evolution of brain injury in neonates after perinatal hypoxic-ischemic insult. (Reproduced with permission from Ferriero DM.[1]) (Color version of figure is available online.)

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Pathophysiology of Neonatal Encephalopathy

The underlying mechanism for perinatal brain injury is an interruption of placental blood flow followed by impaired gas exchange that leads to cerebral deficits in oxygen and substrates.[11] Infant gestational age, as well as the nature, severity, and duration of the hypoxic-ischemic insult, will determine the extent and locations of neuronal injury. The main mechanisms of fetal defense against hypoxia-ischemia, described in animal studies, include peripheral vasoconstriction and redistribution of blood flow to the brain and heart at the expense of visceral organs and skeletal muscle.[25,26] However, this protective ability is overwhelmed if hypoxia-ischemia continues.

Perinatal brain injury is a complex evolving process initiated during the insult and extending into a recovery period (Fig 1). Following a reversible perinatal hypoxia-ischemia, 2 major phases occur when neuronal death has been identified.[27,28] The primary phase of neuronal brain injury occurs during a hypoxic-ischemic insult, which, if uninterrupted, initiates a cascade of deleterious biochemical events and necrotic cell death. This phase, primarily related to cellular hypoxia, precludes oxidative phosphorylation and leads to depletion of high-energy phosphate reserves (eg, phosphocreatine) followed by a fall in intracellular pH. In response to a switch to this anaerobic state, glycolysis becomes the sole source of adenosine triphosphate (ATP) production in the brain. Unlike oxidative phosphorylation, which produces 36 molecules of ATP for every molecule of glucose consumed, glycolysis is an inefficient method to generate ATP by substrate phosphorylation, generating only 2 molecules of ATP per molecule of

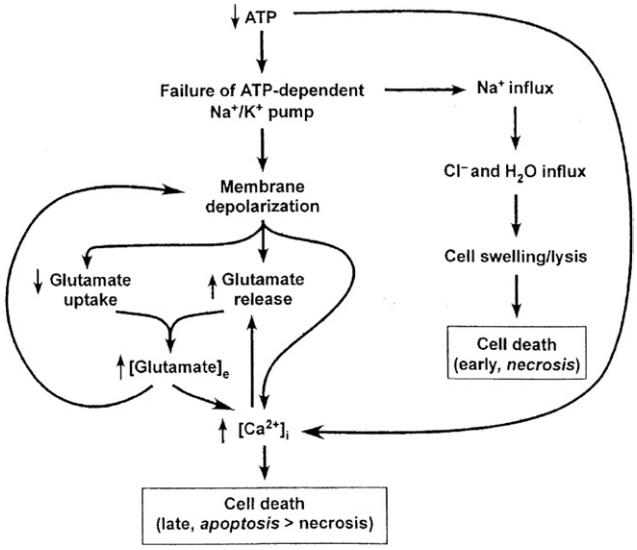

FIG 2. Relation between energy depletion and neuronal cell death. Early cell death is primarily necrosis, and more important, later cell death is primarily apoptotic. (Reproduced with permission from Volpe J.[11])

glucose consumed. This primary energy failure results in neuronal membrane depolarization and loss of membrane ionic homeostasis. ATP must fall below 25% before neuronal injury begins to occur and injury becomes irreversible if ATP levels fall below 10%.[29] At this point, synaptic function and neuronal conductivity cease and cellular influx of sodium (Na^+), followed by chloride (Cl^-) and water influx, leads to osmotic (cytotoxic) edema and necrotic cell death (Fig 2). In the more typical, less severe insult, cellular efflux of potassium (K^+) induces a release of glutamate into the synaptic cleft and because of a failure of energy-dependent reuptake, a massive accumulation of glutamate occurs.[30] Glutamate is the most common excitatory neurotransmitter and in small amounts it is essential for neuronal function. However, when glutamate accumulates in large amounts, it exhibits neuronal toxicity and under these conditions it has been called an excitotoxin.[31] Glutamate stimulates the N-methyl-D-aspartate receptor-channel complex leading to calcium (Ca^{2+}) influx into neuronal cells.[32,33] Simultaneously, because intracellular Ca^{2+} removal is an energy-dependent process of the Na^+–Ca^{2+} pump, removal of Ca^{2+} is also impaired. This massive accumulation of Ca^{2+} within the cell cytoplasm induces production of nitric oxide (NO) by activation of NO synthase. NO adversely affects neurons by reacting with superoxide to form peroxynitrite, a toxic free-radical that is known to alter cell membranes by increasing the activity of Ca^{2+} ATPase leading to further intracellular accumulation of Ca^{2+}.[34] Excessive intracellular Ca^{2+} also activates catabolic enzymes, such as proteases, phospholipases, and endonucleases. Free radicals and catabolic enzymes destroy structural proteins, nucleic acids, and other cellular contents, causing neuronal necrosis. The type of cell death is dependent on severity of the insult and accumulated Ca^{2+} concentrations. Indeed, cellular necrosis occurs with higher levels of intracellular Ca^{2+} than those observed in apoptosis.[35] Furthermore, an elevation of lactate levels in cerebral tissue indicates global impairment of perfusion and is consistent with hypoxia as well as eventual poor neurologic outcome.[36,37] The marked increase in cerebral lactic acid levels damages not only neurons but also glial and mesenchymal cells.

Perinatal brain injury is a complex evolving process initiated during the insult and extending into a recovery period

Following successful resuscitation and restoration of cerebral blood flow, oxygen, and glucose delivery, the concentration of phosphorus metabolites and intracellular pH normalizes with transient improvement of cytotoxic edema. These events herald the "latent phase" and correspond to a therapeutic window for neuroprotective interventions, discussed later in this article. The reperfusion is necessary for the reversal of deleterious events leading to necrotic neuronal death during the primary phase of injury; however, reperfusion can simultaneously cause additional (delayed) injury by attracting monocytes and subsequent inflammatory response to the site of injury. The secondary phase of brain injury does not occur in all infants with perinatal asphyxia and is primarily determined by several factors, such as duration and severity of hypoxic-ischemic insult, preconditioning events, substrate availability, body temperature, and gestational maturation. The secondary phase of injury occurs slowly (hours to days) and with a normal intracellular pH and stable cardiorespiratory status[38]; however, the cellular response during this phase of neuronal injury is similar to the primary phase of injury. This phase is also characterized by a decrease in the ratio of phosphocreatine/inorganic phosphate leading to a secondary energy failure. Additionally,

the cascade of pathologic processes following reperfusion triggers accumulation of excitotoxic amino acids, increased cytosolic Ca^{2+}, generation of free radicals, and activation of phospholipases as well as other metabolic events leading to further neuronal cell injury.[39] Increased intracellular Ca^{2+} also activates a cascade of proteolytic enzymes. These proteolytic enzymes, especially caspases or cystein proteases, will eventually trigger cellular nuclear fragmentation.[40-43] Additionally, microglial activation after hypoxia-ischemia and reperfusion promotes release of reactive oxygen and nitrogen species as well as cytokines, especially IL-1 and TNF-alpha.[11] Therefore, the mechanism involved in the secondary phase of injury includes excitotoxicity, inflammation, mitochondrial failure, apoptosis, and cytotoxic actions of activated microglia. It appears that the secondary energy failure is a consequence of the cascade of these events rather than a result of cellular destruction. Indeed, the severity of the secondary energy failure has been shown to be associated with seizures and adverse neurological outcome.[44]

Patterns of Brain Injury and Neuroimaging

Brain injury of term infants in response to hypoxic-ischemic insult is a complex process. Selective neuronal necrosis is the most commonly observed pattern of brain injury in neonates with hypoxic-ischemic encephalopathy and is dependent on the severity and temporal characteristics of the insult.[11] The final pattern of neuronal injury also depends greatly on the gestational age of the infant at the time of the perinatal hypoxia-ischemia and is most likely influenced by immaturity of newborn brain structures and neuronal cells.[45] Three major regional patterns of selective neuronal necrosis in full-term infants with neonatal encephalopathy have been identified.[46-48] Severe prolonged hypoxic-ischemic insults result in diffuse neuronal injury. With moderate to severe relatively prolonged insults, a predominance of cerebral cortical-deep nuclear neuronal injury is most commonly observed. It involves injury within the deep cortical gray matter structures of the basal ganglia and thalamus. With severe abrupt hypoxia-ischemia, deep nuclear brain-stem neuronal injury predominance occurs.[11] This abrupt insult possibly precludes an adaptive mechanism of diversion of blood flow from the cerebral hemispheres to the most vital deep nuclear structures. Another common pattern of perinatal brain injury in term infants after hypoxia-ischemia occurs in the parasagittal end artery regions of the 3 major cerebral arteries, frequently referred to as a "watershed injury" (Fig 3). This includes cerebral cortex and the underlying subcortical white matter in the parasagittal regions and is bilateral in distribution.

Computerized tomography can be used to define the site and extent of the injury and provide useful prognostic information.[49,50] Because of advances in neuroimaging, magnetic resonance imaging (MRI) techniques using diffusion weighted and diffusion tensor imaging allow greater delineation of brain tissue, including detailed integrative neuronal pathways. Therefore, MRI has become the primary and most sensitive method for evaluation of brain injury patterns, determination of timing of injury, and prognostication in newborn infants with encephalopathy.[51-54] The predominant pattern of brain injury found to be most strongly associated with long-term outcome, more so than the severity of injury in any given region, is injury to the basal ganglia and thalamus. In the study by Miller et al,[47] injury to basal ganglia and thalamus in term neonates with hypoxic-ischemic encephalopathy had an unfavorable neurological outcome compared with injury patterns in the parasagittal watershed area. Abnormal signal intensity in the posterior limb of the internal capsule was also a strong predictor of impaired neurodevelopment by 12 months of age.[55] Magnetic resonance spectroscopy (MRS), either proton or phosphorus variety, is able to evaluate cerebral tissue metabolic status, offering a complementary diagnostic value to conventional MRI.[56] Within the first 18 hours of brain injury or shortly thereafter, MRS can detect elevated cerebral lactate and a decline in high-energy phosphate compounds that correspond to secondary energy failure in infants with encephalopathy after hypoxic-ischemic

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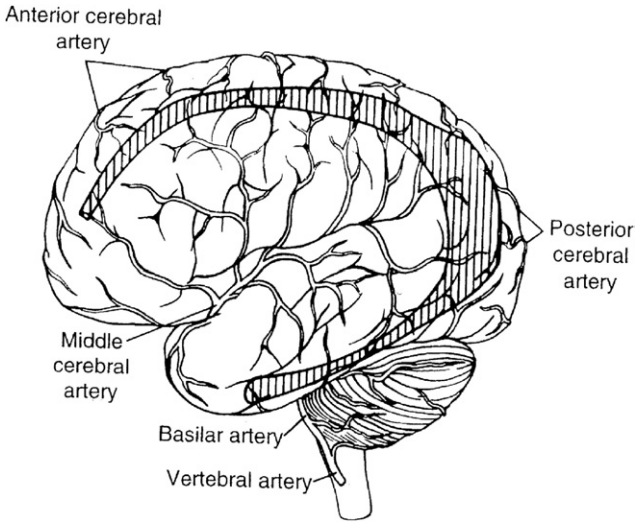

FIG 3. Parasagittal cerebral injury showing distribution of major cerebral arteries, lateral view. (Reproduced with permission from Volpe J.[11])

insult. The elevation in lactate correlates with the severity of neonatal encephalopathy and neurological outcome.[54,57,58] Changes in metabolic ratios can be used to diagnose the severity of encephalopathy and approximate timing of injury. N-acetyl-aspartate (NAA), one of the main cerebral metabolites, a marker for neurons/axons, is reduced in immature newborn brain tissue and after hypoxic-ischemic neuronal injury.[56] In a recently published meta-analysis by Thayyil et al[59] that included 32 neuroimaging studies of newborn infants with neonatal encephalopathy, they demonstrated that MRS was more specific and sensitive for determination of neurodevelopmental outcome than MRI. The elevation of lactate/NAA peak–area ratio in the basal ganglia was found to be the most useful in identification of infants with a severe stage of encephalopathy as well as a higher specificity of 95% (95% CI: 88%-99%) and sensitivity of 82% (95% CI: 74%-89%), compared with MRI in prognostigation of unfavorable neurodevelopmental outcome. The authors concluded that the lactate/NAA ratio is the most accurate quantitative MRS biomarker for prediction of neurodevelopmental outcome after neonatal encephalopathy and can be useful in early clinical management decisions in infants with severe neonatal encephalopathy.

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Diagnosis and Biomarkers

Diagnosis of neonatal encephalopathy and prediction of the long-term outcome can be challenging. Assessing the proportion of neonatal encephalopathy that is due to perinatal asphyxia is difficult because of problems in identifying asphyxia and in recognizing the cause of neonatal neurologic illness.[8] Encephalopathy can develop because of causes other than hypoxia-ischemia and rapid determination to exclude these causes is equally important to afford any opportunity for successful intervention. Accurate diagnosis relies on a combination of biomarkers suggestive of perinatal asphyxia as well as development of clinical symptoms of encephalopathy early after birth. According to the ACOG Committee on Obstetric Practice, "Umbilical cord blood gas and acid–base assessment are the most objective determinations of the fetal metabolic condition at the moment of birth." The presence of other acute perinatal events, such as placental abruption, hemorrhage, prolapsed umbilical cord, abnormal fetal heart rate tracings, as well as abnormal Apgar scores and need for resuscitation after birth, may also be important indicators in establishing hypoxic-ischemic etiology of encephalopathy.[60] However, these biomarkers are not always available or reliable and most studies have found them to be absent in a large majority of neurologically symptomatic neonates.[61-63] Therefore, determination of the timing of injury remains challenging given that much of the injury occurs before birth and may be the result of more than a single injury.[64,65] At present, there is no universal agreement on objective laboratory markers as a gold standard to support the diagnosis of term intrapartum asphyxia.[66] Evidence of multiorgan failure in infants with severe encephalopathy is helpful and used as an additional diagnostic criterion in the recognition of the hypoxic-ischemic insult[67]; however it is not specific or essential.[9]

Several tissue biomarkers suggestive of hypoxic-ischemic brain injury in term infants with neonatal encephalopathy have also been identified in the systematic review by Ramaswamy et al.[68] A meta-analysis of 22 studies demonstrated an association between serum and cerebrospinal fluid interleukin-1b, serum interleukin-6, and CSF neuron-specific enolase with poor outcome of death or disability. Other biomarkers identified in this review, such as urine lactate/creatinine ratio, first urine S100, and umbilical cord IL-6, also were shown to be associated with poor outcome, although only in single studies. Despite these results, the author concluded that because of study limitations larger multicenter trials are needed to validate biomarkers as useful in clinical practice.

Clinical Presentation

Challenges remain in early identification of high-risk infants with neonatal encephalopathy. Badawi et al in a West Australian case-control study demonstrated that almost 70% of cases had no clear evidence of adverse intrapartum events, 24% had antepartum and intrapartum risk factors, and 5% of cases had only intrapartum risk factors.[64,65] The severity of a perinatal hypoxic-ischemic insult is difficult to quantitate and many infants may only have transitory neurologic signs of neonatal encephalopathy at the time of birth and complete recovery after stabilization. Clinical presentation of infants with neonatal encephalopathy of varying etiologies can overlap and therefore make it difficult to identify etiology through the use of neurological examination alone. Thus, it is very important to exclude other causes of neonatal encephalopathy in symptomatic patients with unclear perinatal history risk factors. Clinical presentation of infants with neonatal encephalopathy after perinatal asphyxia can range from subtle, with a hyperalert state or mild hypotonia, to severe, consisting of stupor, coma, profound hypotonia, and absent reflexes (Table 1). Importantly, clinical subtle signs and symptoms of neonatal encephalopathy as well as difficulties in neonatal seizure recognition may lead to a delay in the diagnosis and proper neuroprotective intervention. Neonatal seizures affect 1.5-3.5 per 1000 live term births in the US and are more common in the neonatal period than at any other time in life.[11] Furthermore, seizures are very common among infants with neonatal encephalopathy because of hypoxia-ischemia. The widely accepted classification of clinical seizures proposed by Volpe[11] includes subtle, clonic, tonic, and myoclonic seizures, which can be focal, multifocal, or generalized. They are often classified as being either electroclinical, when electrographic changes and clinical symptoms occur, or electrographic and clinically silent.[69] It can be challenging for the clinician to diagnose neonatal seizures. In fact, only approximately 20-30% of electrographic neonatal seizures provoke obvious clinical signs.[70-72] Electrographic seizures in neonates have also been correlated with the subsequent development of cerebral palsy and microcephaly.[73] When prolonged, seizures may also exacerbate brain injury initiated by the precipitating acute hypoxic-ischemic injury. Thus, accurate diagnosis, monitoring, and effective treatment of neonatal seizures are crucial. Recently, the cerebral function monitor, a single- or double-channel amplitude-integrated EEG (aEEG), has been introduced for the brain monitoring of neonates with suspected encephalopathy and used primarily to define selection criteria for hypothermia therapy among infants with neonatal encephalopathy. The aEEG provides the clinician with a method to identify the presence of brain injury and determine the severity of encephalopathy and outcome.[69] Continuous monitoring with cerebral function monitor/aEEG has become helpful to monitor for seizure activity during the 72 hours of the cooling process, to monitor responses to antiepileptic drugs, and to identify changes in brain function over time. The severity of clinical encephalopathy has been shown to be a strong predictor of neurodevelopmental outcome.[74] However, clinically, it can be difficult to predict outcome for infants with encephalopathy, especially those with Sarnat stage 2 symptomatology. Infants with Sarnat stage 2 encephalopathy, which presents with clinical seizures, have a 50% risk of subsequent neurological impairment.[16]

Assessing the proportion of neonatal encephalopathy that is due to perinatal asphyxia is difficult because of problems in identifying asphyxia and in recognizing the cause of neonatal neurologic illness.[8]

Thus, duration of the abnormal neurological symptoms and aEEG/conventional EEG changes has been helpful in prognostigation. Infants who will not progress to Sarnat stage 3 and who have clinical signs of moderate encephalopathy for less than 5 days will generally have a normal outcome. Persistence of Sarnat stage 2 symptoms for more than 7 days or abnormal cerebral background activity on aEEG/conventional EEG is frequently associated with later neurologic impairments. Murray et al[75] found that normal or mildly abnormal video EEG results within 6 hours after birth were associated with normal neurodevelopmental outcomes at 24 months of age. In contrast, clinical factors, such as more severe grade of encephalopathy, a higher number of neonatal seizures, use of the anticonvulsant medication phenytoin, diffuse abnormalities on radiologic imaging, and abnormal findings on neurologic examination at discharge, are significantly associated with abnormal neurologic outcome by 2 years of age in infants with intrapartum asphyxia.[76] Clinical evaluation of the infant with neonatal encephalopathy in assessment of outcome has the most important value and should be used together with other specialized diagnostic approaches. Indeed, the best early (within several hours of life) predictors of outcome in infants with encephalopathy are the identified severity of deficits on clinical examination coupled with the degree of abnormal EEG background activity (eg, sustained low-voltage, iso-electric, burst suppression patterns).[77,78]

Current Therapies

Management in the Delivery Room

The treatment of depressed infants after intrapartum asphyxia includes resuscitation in the delivery room that follows the latest Neonatal Resuscitation Program guidelines.[79] Because of the compelling evidence outlining the deleterious effects of hyperoxia,[80-82] recent recommendation for resuscitation of term newborn infants supports use of room air rather than 100% oxygen.[83,84] After hypoxia-ischemia and primary energy failure, generation of energy for production of ATP will depend on oxygen and glucose supply necessary for oxidative phosphorylation. Therefore, conditions that may delay the recovery from the primary phase of brain injury, such as hypoxia, hypoglycemia, hypotension, and blood loss/anemia, must be corrected as soon as possible. Newborn infants with severe acidemia at birth (pH <7.0) and hypoglycemia (initial blood glucose ≤ 40 mg/dL) are 18 times more likely to develop moderate to severe encephalopathy compared with severely acidemic infants with normal glucose levels.[85] In the course of resuscitation, routine measures include warming. However, it should be noted that hyperthermia has been shown to be associated with worsening brain injury and should be avoided.[86] Laptook et al found that the odds of death and disability in infants with moderate to severe encephalopathy was increased fourfold for each 1°C increase in the highest quartile of skin or esophageal temperature.[87,88] Additionally, excessive hypothermia (cold stress) should be avoided. Therefore, after establishment of adequate ventilation and circulation, newborns with suspected hypoxic-ischemic perinatal event should be transferred urgently to a neonatal intensive care unit (NICU) capable of initiation of hypothermia treatment and close monitoring and care of systemic and cerebral function. If there is evidence of hypoxic-ischemic encephalopathy, referral to the nearest cooling center should be arranged as soon as possible given the short (6 hour) therapeutic window for initiation of neuroprotective hypothermia therapy (Table 2). In consultation with our cooling center, we recommend that the radiant warmer be switched off to achieve passive hypothermia while maintaining core temperatures of 35°C + 0.5°C in preparation for the transport.

If there is evidence of an acute hypoxic-ischemic perinatal insult, referral to the nearest cooling center should be arranged as soon as possible given the short (6 hour) therapeutic window for initiation of neuroprotective hypothermia therapy

Supportive Care

Postresuscitative management of infants with neonatal encephalopathy due to perinatal asphyxia is complex and requires careful monitoring and immediate provision of anticipatory care. Because many infants with encephalopathy will develop multiorgan dysfunction and alterations in the ability to maintain physiological homeostasis, prompt recognition and interven-

TABLE 2. Guide for the delivery room management of depressed infants at risk for the neonatal encephalopathy after perinatal hypoxic-ischemic insult

Guide	Specific Responses
Follow Neonatal Resuscitation Program Guidelines	Establish adequate ventilation/oxygenation and circulation
Oxygen	For babies born at term it is best to begin resuscitation with air rather than 100% oxygen.[83,84] If despite effective ventilation there is no increase in heart rate or if oxygenation remains unacceptable, use of higher concentration of oxygen should be considered
Ventilation	Avoid hypocapnia or hypercapnia
Glucose	Correct hypoglycemia
Metabolic acidosis	Correct severe metabolic acidosis
Temperature	Avoid hyperthermia
Referral to the Cooling Center	In the presence of 1 of the following criteria: Severe acidemia; pH <7 and/or base deficit >16[a] 10 min Apgar score <5 Continued need for resuscitation, including respiratory support by 10 min of life

[a]Measured in umbilical cord blood sample or any blood sample within 60 minutes of birth (arterial or venous).

tion to support organ function can have a significant effect on outcome and should be provided in a NICU. General principles of supportive care after resuscitation include continued cardiorespiratory support, correction of hypoglycemia, severe metabolic acidosis, and electrolyte abnormalities as well as prompt treatment of hypotension and seizures.

Respiratory Management. Ventilatory support is frequently required for infants with neonatal encephalopathy because of respiratory depression, apnea with seizures, and respiratory distress, if concurrent conditions, such as sepsis, meconium aspiration, and/or persistent pulmonary hypertension, are present. It is important to ensure adequate ventilation as changes in PCO_2 can affect cerebral blood flow. If allowed to occur, hypocapnia because of overventilation can cause cerebral vasoconstriction and compromise oxygen and glucose delivery to the brain. The association of hypocapnia and periventricular leukomalacia in preterm infants has been reported in the literature.[89,90] In a study by Vannucci et al,[91] immature animals subjected to global ischemia and normocapnia had less severe evidence of brain injury compared with the same animals exposed to hypocapnia. Interestingly, elevation of PCO_2 to 50-55 mm Hg with hypoxia-ischemia associated with better outcome than when PCO_2 was within normal limits or in the mid 30 mm Hg range. However, significant hypercapnia can also be harmful to the brain tissue after hypoxia-ischemia. A recent review by Fritz and Delivoria-Papadopoulos summarized studies on newborn piglets and mechanisms of the newborn brain injury.[92] Exposure for 6 hours to PCO_2 of either 65 mm Hg or 80 mm Hg resulted in a decrease in cellular energy metabolism, including a decrease in high energy phosphates, alterations in nuclear enzyme activity, and apoptotic protein expression in the cerebral cortex of these animals. Thus, extrapolating to the human infant, careful monitoring of blood gases and/or end-tidal PCO_2 levels to maintain normocapnia is of particular importance in the management of neonatal encephalopathy.

After perinatal hypoxic-ischemic insults, newborn infants have serious impairment of cerebrovascular autoregulation.

Additionally, monitoring perfusion and oxygenation in infants with neonatal encephalopathy is of equal importance. After perinatal hypoxic-ischemic insults, newborn infants have serious impairment of cerebrovascular autoregulation. Hypoxia may further exacerbate ischemic cerebral injury by inducing pressure-passive cerebral circulation with only moderate decreases in arterial blood pressure.[11] Cerebral tissue hypoxia leads to expression of apoptotic proteins and other deleterious events that may further contribute to neuronal cell death as described earlier (see the pathogenesis of neonatal encephalopathy, above). Hyperoxia can also worsen brain injury after perinatal asphyxia and ultimate outcome through reperfusion and exacerbation of oxidative injury.[93,94] Oxygen free radicals are produced from hypoxanthine, a degra-

dation product of ATP, during reperfusion with high concentrations of oxygen in the presence of xanthine oxidase.[95] Formation of oxygen free radicals lead to a chain of reactions that injure cellular membranes by lipid peroxidation. In term infants with neonatal encephalopathy, hyperoxia in the first hours of life was found to be an independent factor for poor neurological outcome.[80,81] It is therefore prudent to avoid both hypoxia and hyperoxia in infants with encephalopathy after perinatal asphyxia and maintain P_aO_2 levels within normal ranges of 60-90 mm Hg.

Cardiovascular Management. Infants with neonatal encephalopathy frequently experience hypotension. Most commonly it is related to left ventricular dysfunction following hypoxic-ischemic insult,[96] endothelial cell damage, and less frequently blood/volume loss because of placental abruption/uterine rupture. Impaired autoregulation of cerebral blood flow has been demonstrated in severely asphyxiated newborns.[97] Cerebral circulation after hypoxia-ischemia appears to be pressure passive[11]; thus, blood pressure must be monitored continuously and diligently to avoid systemic hypotension or hypertension which may cause hemorrhage. Treatment should be targeted toward the underlying cause of hypotension: if there is reduced myocardial contractility, inotropic support is warranted (eg, dobutamine); if the infant is hypovolemic, volume replacement/transfusion should be implemented; if hypotension not because of myocardial dysfunction or hypovolemia, dopamine would be the drug of choice. These interventions, along with continuous blood pressure and central venous pressure monitoring, are vital in accomplishing the goal of maintaining the arterial blood pressure within the normal range for gestational and chronological age.

Fluid-Electrolytes/Glucose Management. Infants with encephalopathy are at risk for developing cerebral edema, swelling accompanied by increased intracranial pressure, as well as syndrome of inappropriate antidiuretic hormone (SIADH) secretion in the first few days after birth. SIADH will manifest with fluid retention, weight gain, hyponatremia, and corresponding concentrated urine. Infants who have sustained renal tubular injury may develop renal failure as well as salt wasting. As a result, it is imperative to frequently monitor levels of sodium and other electrolytes, daily fluid balance, the weight of the infant, and urine output. Treatment includes restriction of fluids and replacement of electrolytes by the second day of life or as indicated. Calcium and magnesium levels are usually low in the infant with birth asphyxia and likewise closely monitored and supplemented accordingly. Hypoglycemia should be avoided at any time during the care of the infant with neonatal encephalopathy.[85,98] Neurons require a continuous source of energy, produced by breakdown of glucose into pyruvate, which enters into the citric acid cycle to produce ATP under aerobic condition. Hyperglycemia, by contrast, can induce excessive production of tissue lactic acid and associated derangement in pH homeostasis.[99,100] Hyperglycemia is found to accentuate neuronal injury in adult experimental models but not in immature animals after hypoxia-ischemia[101-103] and is most likely related to maturation differences in the rate of cerebral glucose uptake and metabolism.[104] Hyperglycemia can cause a hyperosmolar effect and consequent hemorrhage. Thus, until further evidence is recommended, it is best to maintain a blood glucose concentration within normal ranges (75-100 mg/mL).[11]

Hypoglycemia should be avoided at any time during the care of the infant with neonatal encephalopathy.[85,98]

Last, adequate nutritional support to reduce tissue catabolism, negative nitrogen balance, and acidosis must be a mainstay of the supportive treatment in these infants.

Treatment of Seizures. Although some controversy still exists regarding the contribution of brief seizures to ongoing brain injury, seizures as a symptomatic expression of an acute hypoxic-ischemic neuronal injury may also be an exacerbating factor in causing brain injury.[105-107] Seizures are known to be associated with a marked increase in metabolic rate, a consequent rapid fall in brain glucose, an increase in lactate, an excitatory amino acid release, and a decrease in high-energy phosphates.[108] After perinatal asphyxia, neonates who had clinical seizures had an increased lactate/choline ratio and decreased NAA, which was assessed by MRS.[109] Seizures are known to have deleterious effects with reduction of cellular proliferation, differentiation, and migration as well as alteration in myelination and formation of synapses.[110] Whether clinical manifestations are present or not, electrographic seizures correlate with increased morbidity and mortality.[111,112] It is therefore recommended to treat neonatal seizures aggressively after hypoxia-

ischemia to reduce the possibility of further brain injury. Common anticonvulsant therapy includes the following: phenobarbital, phosphenytoin, or lorazepam.[113] There is no strong evidence that prophylactic anticonvulsant use prevents morbidity and mortality in neonates with encephalopathy.[114] Because the secondary phase of brain injury and cerebral edema generally resolves within the first several days after perinatal asphyxia, seizures generally resolve as well, and anticonvulsant therapy frequently can be discontinued before discharge, in consultation with the pediatric neurologist. Unfortunately, the efficacy of these antiepileptic drugs is limited and there are known potential side effects. Control of seizures with monotherapy phenobarbital or phenytoin has been reported to be only 50% effective and when other agents are added control of seizures has been achieved only in approximately 60% of neonates.[115] Also, antiepileptic drugs can produce electroclinical dissociation of seizures (electrographic seizures persist despite the disappearance of the clinical seizures), providing false clinical impression and reassurance.[116] Newer antiepileptic drugs to treat neonatal seizures, such as topiramate, levetiracetam, and bumetanide,[117-120] have shown safety and good efficacy in the pediatric population to treat epilepsy, but randomized controlled trial (RCTs), including long-term outcome results, are needed before these therapies can be recommended in neonates with encephalopathy.

Whether clinical manifestations are present or not, electrographic seizures correlate with increased morbidity and mortality.[111,112]

Other Management

Disseminated intravascular coagulation (DIC) is frequently observed in infants with severe encephalopathy after hypoxia-ischemia. DIC is a secondary process associated with endothelial vascular cell damage and derangements in homeostasis after perinatal asphyxia. DIC is manifested by diffuse fibrin deposition in the microvasculature, consumption of coagulation factors, and clinical bleeding.[121,122] Careful monitoring of the infant's coagulation profile, including complete blood count as well as prompt treatment with fresh frozen plasma, coagulation factors, platelets, and vitamin K, could be necessary to prevent adverse hemorrhage.

Polycythemia and hyperviscosity may also occur in infants with neonatal encephalopathy.[11] Furthermore, during moderate hypothermia therapy, discussed in the following section, blood flow slows down because of decreased heart rate and cardiac output,[28] which can further compromise cerebral blood flow. Thus, in the setting of hypothermia therapy, partial exchange transfusion treatment of associated polycythemia should be initiated at a lower hematocrit threshold (Hct $\geq$60%).

Therapeutic Hypothermia

Before publication of RCTs over the last several years demonstrating the efficacy of hypothermia therapy, treatment of neonates with encephalopathy after perinatal asphyxia was primarily supportive. The knowledge that brain injury after hypoxia-ischemia is an evolving process has provided a "window of opportunity" for therapeutic interventions that may arrest or ameliorate secondary brain injury. Therapeutic hypothermia aims to lower the temperature of the vulnerable deep brain structure to 32°C-34°C. Therapeutic hypothermia derives most of its protective effect from a graded reduction in metabolism, decreased energy use, reduced accumulation of excitotoxic amino acids, reduced nitric oxide production, suppression of free radical activity, suppression of the inflammatory cascade and inhibition of apoptosis with resultant reduction in the extension of brain injury.[38,123-127]

There are two methods of hypothermia therapy currently available for the neonate with encephalopathy: whole-body cooling (placing the infant on the cooling blanket or mattress circulated with coolant fluid to maintain esophageal/rectal temperature of 33°C-34°C) and selective head cooling with mild systemic hypothermia (circulating cold water in a cap fitted around the head with mild body hypothermia to 34°C-35°C rectal temperature). To date, both methods of therapeutic hypothermia have generally been found to be equally safe and effective, although a small study by Rutherford et al reported a decrease in the incidence of severe cortical lesions on MRI in infants with encephalopathy treated with selective head cooling compared with infants treated with whole-body cooling.[128] These results could be due to differential temperature gradients demonstrated with selective

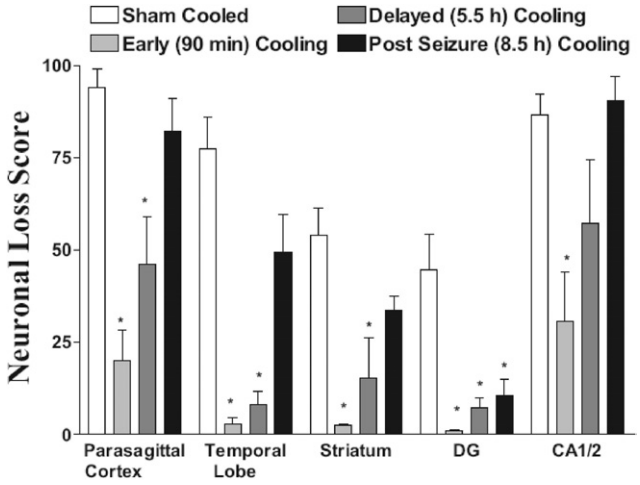

FIG 4. The results of the studies performed by Gun et al[132-134] to determine the effect of time of initiation of cooling on neuronal loss. Y axis shows percent neuronal loss, encompassing different regions of the brain. Initiation of hypothermia is effective, but efficacy decreases as duration of time following ischemia increases. Cooling starting at 8.5 hours following ischemia was not effective. Asterisks indicate differences ($P < .005$) compared with sham-cooled animals. (Reproduced with permission. AR Laptook, et al: Use of Therapeutic Hypothermia for Term Infants with Hypoxic-Ischemic Encephalopathy. Pediatr Clin N Am 2009;56:601-16.)

head cooling with associated colder temperature in the cortex.[129,130] Nevertheless, presently more research is needed to demonstrate whether one of these cooling methods is superior.

The currently recommended timing for initiation and duration of cooling treatment was derived from the studies of Gunn et al[131-133] in fetal sheep exposed to 30 minutes of cerebral ischemia. These studies showed a neuroprotective effect of selective head cooling for up to 72 hours. Prolonged hypothermia prevented secondary cytotoxic cerebral edema and had a significant protective effect on neuronal loss in fetal sheep. This effect was only observed if cooling started before the development of the secondary phase of injury or before the onset of postischemic seizures. Neuroprotection was most significant when cooling started 90 minutes after induced cerebral ischemia as well as when the delay in initiating cooling was extended to 5.5 hours, but not if cooling was started as late at 8.5 hours after cerebral ischemia (Fig 4). Taken together, studies in fetal sheep subjected to hypoxia-ischemia suggest that the potential window for treatment in animal models seems to be up to 6 hours post injury. Thus, in translation from preclinical animal studies, clinical trials in humans incorporated a 6-hour therapeutic window into clinical protocols to maximize the neuroprotective effect of hypothermia therapy. A clinical trial in humans (National Institute of Child Health and Human Development trial (NICHD); 16 centers participating) is currently under way to explore if therapeutic hypothermia initiated after 6 hours of life may be beneficial in reducing brain injury.

Evidence from Clinical Trials of Hypothermia on Infants with Neonatal Encephalopathy

To determine the impact of hypothermia treatment on the human infant, several small feasibility studies assessed hypothermia as a treatment for neonatal encephalopathy secondary to acute hypoxic ischemic perinatal events.[134-137] The safety of mild hypothermia has been well established, as no serious adverse safety issues (eg, cardiac arrhythmia, persistent metabolic acidosis, pulmonary hypertension, thrombocytopenia, coagulopathy, and increased risk of infections) have been reported in these trials. Reversible cardiovascular side effects, such as sinus bradycardia and hypotension, as well as an increase in late coagulopathy were reported. Most initial small trials noted improvements in neurological outcome but these studies were not adequately powered to achieve statistical significance. These pilot studies led to the initiation of several RCTs, 4 of which have been published to date: the Eicher et al trial,[138] the CoolCap trial,[139] the NICHD trial,[140] and the Total Body Hypothermia for Neonatal encephalopathy trial (TOBY).[141] An additional RCT, the Australian Infant Cooling Evaluation trial, is expected to publish long-term outcome data by the end of 2010. The entry criteria in the RCTs, although slightly varied, included recruitment of infants of similar severity (moderate to severe encephalopathy) with identified evidence of intrapartum asphyxia, such as low Apgar score, acidosis (pH <7.0), or significant base deficit (≥ 16) on a sample of umbilical or infant blood obtained within 60 minutes of life, and need for resuscitation. Two studies[138,140] also required aEEG assessment of background cerebral activity to determine the degree of encephalopathy and/or evidence of electrographic seizures as additional inclusion criteria.

In a multicenter, relatively small RCT, Eicher et al[138] reported neurologic outcome in 65 term newborns with moderate to severe encephalopathy ran-

domized to either moderate systemic hypothermia (n = 32) vs normothermia/supportive care (n = 33). Whole-body hypothermia for outborn newborn infants was initiated with icepacks (for 2 hours) and then continued for 48 hours with a servo-controlled cooling blanket to maintain rectal temperature at 33 ± 0.5°C. Therefore, the mean time to target temperature for outborn infants was only 111 ± 78 minutes. The primary outcome of death or severe motor disability by 12 months occurred in 52% of hypothermia group compared with 84% of the normothermic controls ($P = 0.019$). Of note, 77% of the infants recruited for the study had severe encephalopathy. Reported adverse events related to whole-body hypothermia in this study were bradycardia, higher prothrombin time, longer dependence on pressors, and more transfusions with fresh frozen plasma and platelets.

The NICHD Neonatal Research Network Centers Trial was a multicenter RCT that prospectively enrolled 208 term newborn infants with moderate to severe encephalopathy.[140] Subjects were randomized to treatment with whole-body cooling achieved by placing an infant on a servo-controlled blanket to esophageal temperature at 33.5 ± 0.5°C for 72 hours (102 infants), or to normothermia (106 infants). Adverse events were similar in both groups. Death or moderate to severe disability occurred in 44% of the hypothermia group and 62% of the control group, resulting in a relative risk (RR) for hypothermia of 0.72 (95% CI 0.54-0.95, $P = 0.01$) and a number needed to treat (NNT) of 6 infants.

Gluckman et al conducted the CoolCap trial,[139] an international RCT that enrolled 234 term infants with moderate to severe encephalopathy. In this trial, subjects were randomized to either selective head cooling with target rectal temperature of 34°C-35°C or conventional normothermic care. The primary outcome was death or severe disability in survivors at 18 months of age. In addition, aEEG was included to further select eligible patients and more precisely define the severity of the encephalopathy. Of the 218 enrolled infants for whom follow-up data were available, 55% of infants in the hypothermia group died or developed severe disability compared with 66% of infants in the control group, OR: 0.61 (95% CI 0.34-1.09; $P = 0.10$). However, after adjustment for illness severity which included the Apgar and modified Sarnat scores, as well as the aEEG background and presence of seizures, there was a significant overall effect of hypothermia therapy for the entire cohort, OR: 0.52 (95% CI 0.28-0.70; $P = 0.04$).[142] Further subgroup analysis suggested that head cooling was beneficial in infants with less severe aEEG changes consistent with moderate encephalopathy, but not those with the most severe aEEG changes ($P = 0.009$).

In 2009, Azzopardi et al published results of the TOBY trial,[141] a multicenter RCT in which 325 newborn infants ≥36 weeks gestation, less than 6 hours of age with evidence of moderate or severe encephalopathy, were randomized to intensive care and whole-body cooling (163 infants) or intensive care alone (162 infants). The inclusion criteria were the same as in previous trials, including aEEG evaluation for severity of encephalopathy. The primary outcome was death or severe disability at 18 months and the secondary outcome was survival without severe disability and specific neurologic outcomes (eg, cerebral palsy, Bayley Scales of Infant Development II scores, hearing loss, seizures, microcephaly, cortical visual impairment, multiple or severe neurodevelopmental abnormalities, etc). Results of the study showed that hypothermia therapy of infants who had perinatal asphyxia did not significantly reduce the combined rate of death or severe disability but resulted in improved neurologic outcomes in survivors (NNT was 6 infants). Infants in the hypothermia group had an increased rate of survival without neurologic abnormality (RR: 1.57; 95% CI, 1.16-2.12; $P = 0.003$). Additionally, cooling resulted in a reduced risk of cerebral palsy in survivors (RR: 0.67; 95% CI, 0.47-0.96; $P = 0.03$) and improved scores on Mental Developmental Index (MDI), Psychomotor Developmental Index (PDI) ($P \leq 0.03$ for each), and the Gross Motor Function Classification system ($P \leq 0.01$). In this study, there were no significant adverse events associated with cooling. Prior concerns that cooling might result in increased survival of infants with

The knowledge that brain injury after hypoxia-ischemia is an evolving process has provided a "window of opportunity" for therapeutic interventions that may arrest or ameliorate secondary brain injury.

TABLE 3. Neurodevelopmental outcome and severe hearing and visual impairment in survivors from the CoolCap, NICHD, and TOBY Trials (18-22 months of age)

Neurodevelopmental Outcomes in Survivors	CoolCap Trial		NICHD Trial		Toby Trial	
	Cooled (n = 112)	Control (n = 118)	Cooled (n = 102)	Control (n = 106)	Cooled (n = 163)	Control (n = 162)
MDI <70	30%	39%	21%[a] 41%[b]	30%[a] 67%[b]	24%	35%
DI <70	30%	41%	NA	NA	24%	34%
MDI >85	NA	NA	52%	40%	70%	55%[c]
PDI >85	NA	NA	NA	NA	68%	53%[c]
Cerebral palsy[d]	19%	31%	19%	30%	28%	41%
Severe neurologic disability[e]	19%	31%	24%	38%	27%	36%
Multiple neurodevelopmental disability	21%	31%	15% 35%	20% 56%	19%	30%[c]
No neurological abnormality	NA	NA	39%[a] 16%[b]	32%[a] 8%[b]	44%	28%[c]
Severe hearing impairment	8%	6%	4%	6%	4%	6%
Blindness	10%	17%	7%	14%	7%	11%

[a]Infants with moderate hypoxic-ischemic encephalopathy.
[b]Infants with severe hypoxic-ischemic encephalopathy.
[c]$P \leq 0.05$.
[d]Diagnosis of cerebral palsy is based on a gross motor performance score of 3-5 in whole-body cooling trials and a classification of neuromotor disability in the CoolCap trial.
[e]Severe neurologic disability include any of the following: Bayley MDI <70, gross motor function level of 3-5, or bilateral cortical visual impairment.

severe neurodevelopmental disability or other adverse outcomes have not been demonstrated in any of the largest RCTs (Table 3). To the contrary, the results of these trials support the benefits of hypothermia treatment (Fig 5), despite the relatively late initiation of cooling (mean time of enrollment: 4.8 hours in the CoolCap trial, 4.3 hours in NICHD trial, and 4.7 hours in TOBY trial).

Prior concerns that cooling might result in increased survival of infants with severe neurodevelopmental disability or other adverse outcomes have not been demonstrated in any of the largest RCTs

Compelling evidence of the effect of hypothermia therapy on brain tissue injury was further demonstrated in a nested substudy of the TOBY trial by Rutherford et al.[143] This study assessed brain tissue injury after moderate hypothermia by MRI and found significant reduction in cerebral lesions characteristic of hypoxic-ischemic encephalopathy, including lesions that predict later neurodevelopmental impairments (eg, basal ganglia/thalamus, posterior limb of the internal capsule, extensive cortical, or white matter lesions). Moderate hypothermia therapy was associated with statistically significant reduction in lesions in basal ganglia or thalamus, OR: 0.36 (95% CI 0.15-0.84, $P = 0.02$), white matter, OR: 0.30 (95% CI 0.12-0.77, $P = 0.01$), and abnormal signal intensity in posterior limb of the internal capsule, OR: 0.38 (95% CI 0.17-0.85, $P = 0.02$). The author concluded that therapeutic hypothermia resulted in significantly less brain tissue injury in infants with hypoxic-ischemic encephalopathy and that the predictive value of MRI for subsequent neurological impairment is not affected by hypothermia.

Current Recommendations for Hypothermia Therapy

In 2005, the American Academy of Pediatrics (AAP) Committee on the Fetus and Newborn recommended that, "Therapeutic hypothermia is a promising therapy that should be considered investigational until the short-term safety and efficacy have been confirmed in the additional human trials underway. Long-term safety and efficacy remain to be defined."[144] Shortly after, the NICHD workshop concluded that hypothermia therapy is "potentially promising"; however, "long-term efficacy and safety are yet to be established."[145] As such, the NICHD also stated that hypothermia treatment should continue to be considered an investigational alternative therapy for the

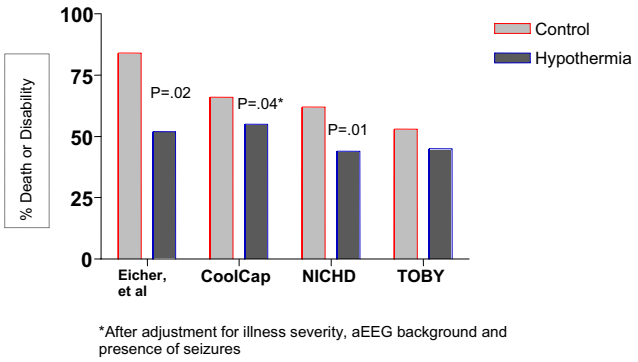

FIG 5. Primary outcome of death or survival with neurodevelopmental disability from the CoolCap, NICHD, and TOBY trials (18-22 months of age). (Color version of figure is available online.)

infant with hypoxic-ischemic encephalopathy. The CoolCap system was approved by the US Food and Drug Administration in 2007 for neuroprotective therapy in infants with perinatal asphyxia and moderate to severe encephalopathy. That same year, a meta-analysis (comprising 638 term infants with moderate/severe encephalopathy and evidence of intrapartum asphyxia) published by the Cochrane Collaboration reported statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability at 18 months of age in infants treated with hypothermia, with RR = 0.76 (95% CI 0.65-0.89) and a NNT of 7 infants.[146] Cooling also resulted in significant reduction in mortality, RR 0.74 (95% CI 0.58-0.94), and in neurodevelopmental disability in survivors, RR 0.68 (95% CI 0.51-0.92). Furthermore, a subgroup analysis of infants with severe encephalopathy (153 infants) demonstrated significant reduction in the death or major disability in survivors, RR 0.8 (95% CI 0.68-0.94), and NNT = 6, which was not found in any of the individual RCTs. Analysis of the pooled data in the Cochrane Review led to the conclusion that therapeutic hypothermia is beneficial in the treatment of hypoxic-ischemic encephalopathy and that cooling reduces mortality without increasing major disability in survivors. Other systematic reviews found the same benefit and recommended application of therapeutic hypothermia in clinical practice.[147-149] The most recent meta-analysis by Edwards et al,[150] which included the CoolCap, NICHD, and TOBY trials in their analysis, further demonstrated that moderate hypothermia is associated with a consistent reduction in death and neurological impairment at 18 months (RR 0.81, 95% CI 0.71-0.93, $P = 0.002$), with a NNT of 9. Hypothermia also increased survival with normal neurological function (RR 1.53, 95% CI 1.22-1.93, $P = 0.001$) as well as reduced the rates of severe disability in survivors ($P = 0.006$), cerebral palsy ($P = 0.004$), and MDI/PDI <70 ($P = 0.01$ and $P = 0.02$, respectively). This accumulated evidence has led to the incorporation of hypothermia into clinical practice in non-investigational settings. In October 2010, the AAP released a special report on Neonatal Resuscitation which included acknowledgement of the non-investigational status of this therapy for infants with moderate to severe hypoxic-ischemic encephalopathy.[84] They stated that "treatment should be consistent with the protocols used in the randomized control trials." Important questions remain, such as: Should hypothermia therapy be confined to larger NICUs (level 3-4) with specific availability of services? Is there a minimum number of infants that should be treated per year to maintain the outcomes expected with this therapy? If so, what is that number?

To ensure optimal care for infants with neonatal encephalopathy, registries of infants with perinatal asphyxial encephalopathy should be established to facilitate data collection and quality oversight regarding diagnosis, treatments, and outcome.

Other Potential Neuroprotective Therapies

Understanding the pathophysiology and evolution of brain injury in response to hypoxic-ischemic insult has provided a unique window of opportunity for assessment of neuroprotective treatment interventions. Single therapeutic agents or approaches may impact only one or two steps in the cascade of the complex neuronal injury process after hypoxic-ischemic injury. Currently, only hypothermia affects multiple processes in the events leading to neuronal injury after hypoxia-ischemia. However, many potential neuroprotective agents/interventions have been investigated targeting different pathways leading to neuronal cell death during the secondary phase of injury. These potential neuroprotective therapies can be grouped by the mechanism of action/effect as follows: agents that inhibit glutamate release, uptake, or blockade of glutamate receptors; blockade of free radical generation or removal; blockade of downstream effects and inhibitors of inflammatory effects.[11] This review describes some of the most promising interventions.

Magnesium

Magnesium inhibits glutamate-mediated excitotoxicity (NMDA receptor antagonist) and prevents neuronal influx of Ca^{2+}. In experimental animal models, the potential neuroprotective effect of magnesium has been conflicting.[151-154] A RCT by Ichiba et al,[155] in which 33 depressed term infants were recruited, 17 were pretreated with magnesium sulfate infusion (250 mg/kg for 3 days) within 24 hours of birth. Although a relatively small study, the results demonstrated a short-term neuroprotective benefit of magnesium as measured by enhanced survival with normal computed tomography, EEG, and oral feeding by 14 days of life in 12/17 compared with 5/16 untreated control infants ($P = 0.04$). A recent RCT used magnesium pretreatment of pregnant women (between 24 and 31 weeks of gestation) in labor conducted in 20 participating NICHD network sites.[156] A total of 2241 eligible women were randomly assigned in a double-blinded fashion to receive either IV magnesium sulfate (a loading dose of 6 g over 20-30 minutes, followed by a maintenance dose of 2 g/h) or placebo. The primary outcome was the composite of stillbirth or infant death by one year of age or moderate to severe cerebral palsy (assessed by 2 years of age). Although the results of the study did not reach a statistically significant reduction in the rate of the primary outcome (11.3% magnesium sulfate group vs 11.7% placebo group; $P = 0.8$), there was a significant reduction ($P = 0.03$) in the rate of children with moderate or severe cerebral palsy alone (1.9% vs 8.5%; RR 1.12; 95% CI 0.85-1.47). Further studies are necessary to assess the important role of magnesium as a therapy for the term infant with encephalopathy after perinatal hypoxic-ischemic insult.

Xenon

Xenon, a noble gas that rapidly reaches equilibrium in the brain when inhaled, exerts a neuroprotective effect via partial NMDA blockade. Xenon is an effective anesthetic approved for use in Europe and previously used in neonates. It has a very rapid onset and reversibility, with little to no metabolism by the body, and to date no reported or proven adverse hemodynamic side effects.[157] In the study by Hobbs et al, week-old rat pups were subjected to hypoxic-ischemic insult for 90 minutes and then assigned to four treatment groups: normothermia/hypothermia, xenon/no xenon.[158] Pups treated with xenon in combination with hypothermia demonstrated an additive neuroprotective effect after hypoxia-ischemia than either treatment alone. This benefit was sustained with complete restoration of long-term functional outcomes and significantly improved histopathology. Xenon is in the early stages as a potential therapeutic agent for the infant at risk for encephalopathy and may be a beneficial adjunct to hypothermia treatment in this population.

Erythropoietin

Erythropoietin derives its neuroprotective properties through inhibition of apoptosis, neuronal excitotoxicity, and inflammation. In experimental animal studies, erythropoietin has been shown to improve neurodevelopmental outcomes and reduce brain injury. A clinical trial by Zhu et al assessed neurological outcome after erythropoietin treatment within 48 hours of birth in term infants with neonatal encephalopathy.[159] Infants were randomly assigned to 3 treatment groups: those treated with 300 U/kg of erythropoietin, those with 500 U/kg of erythropoietin, and a third treated with placebo. Infants treated with erythropoietin displayed a significant reduction in composite outcome of death or disability assessed at 18 months of age (24.6% vs 43.8%; RR 0.62 95% CI 0.41-0.94; $P = 0.017$). The primary outcomes were not different between two erythropoietin doses. Furthermore, a subgroup analysis demonstrated that infants with moderate encephalopathy had the most benefit in protection from adverse neurological outcomes [6.4% vs 32.2%; RR 0.26 (95% CI 0.09-0.76); $P \leq 0.001$].

Currently, only hypothermia affects multiple processes in the events leading to neuronal injury after hypoxia-ischemia.

Free Radical Inhibitors

During hypoxic-ischemic insult, reduction in oxidative phosphorylation leads to an accumulation of adenosine and hypoxanthine, which is oxidated to xanthine leading to accumulation of superoxide radicals. Free radical inhibitors (eg, deferoxamine, allopurinol, and indometh-

acin) block specific reactions in the production of xanthines. In a small RCT, allopurinol demonstrated a significant reduction in circulating concentrations of free radicals, as well as a beneficial effect on cerebral perfusion and electrical brain activity in infants after perinatal asphyxia. No adverse toxic effects were identified.[160] As newborn infants are known to have a deficiency in antioxidant defenses, removal of free radicals in the immature brain after hypoxia-ischemia is an important neuroprotective intervention. Administration of free radical scavengers (eg, vitamin E, N-acetyl-cysteine) or antioxidant enzymes (eg, superoxide dismutase, catalase, glutathione peroxidase) may assist in removal of highly reactive radicals. Because of the large molecular size of the antioxidant enzymes, their action is restricted largely to the intravascular space. Thus, antioxidant enzyme mimetics, with their lower molecular weights, have better penetration across the blood–brain barrier.[11] Neuroprotection by administration of antioxidant enzymes seems to be more effective when given before a hypoxic-ischemic insult. Prophylactic administration of antioxidants during pregnancy has been investigated in animal models.[161] Supplementation of pomegranate juice (resveratol) to pregnant mice resulted in reduction of neuronal injury in pups subjected to hypoxia-ischemia. Last, the combination of systemic hypothermia (for two hours) and administration of N-acetylcysteine, 50 mg kg^{-1}, demonstrated a significant reduction in brain infarct volumes as well as an improvement in myelin expression and functional outcomes in neonatal rats after hypoxic-ischemic injury.[162]

While beyond the scope of this review, animal models of hypoxia-ischemia provide even more evidence of potentially effective neuroprotective therapies. However, animal models vary from the human infant in brain structure and development, leaving many challenges for the use of these therapies in the newborn infant. Future clinical studies in infants with neonatal encephalopathy are urgently needed: (1) to develop reliable means of identifying at risk infants during pregnancy so hypoxic ischemic encephalopathy can be prevented; (2) to target the multiple steps in the cascade leading to brain injury; (3) to determine the safety and efficacy of combining hypothermia therapy with other therapeutic strategies to further enhance neuroprotective effects; and (4) to establish safety profiles and optimal treatment regimens.

Conclusions

Currently, 12,000 infants are at risk for hypoxic-ischemic encephalopathy in the US annually. Hypothermia therapy with supportive care for the infant with neonatal encephalopathy has been demonstrated to significantly improve the neurologic outcome in full-term infants with moderate to severe encephalopathy. Evidence supports a neuroprotective effect of hypothermia therapy with a NNT of 6-9 infants to prevent 1 case of death or significant neurodevelopmental disability. It is important to note that hypothermia therapy is not associated with an increase in the number of survivors with greater neurodevelopmental disabilities. Many infants will still die or survive with significant disability despite hypothermia therapy. Thus, future research is needed for additional neuroprotective therapy in this vulnerable population. Based on the favorable results of a number of published clinical trials, hypothermia therapy is being implemented conservatively now in many neonatal intensive care units. However, many centers have chosen to delay implementation of hypothermia protocols or referral to a center performing hypothermia treatment pending the availability of longer term efficacy and safety data. As a result, many term infants with neonatal encephalopathy after perinatal hypoxia-ischemia are still not offered/referred for therapeutic hypothermia. Additionally, despite all therapies, the outcome for infants with severe encephalopathy remains poor overall, and further investigation is needed to identify improved supportive therapies and other treatment options. Identification of specific diagnostic predictors for patients likely to benefit from hypothermia treatment would allow for more targeted selection and likely enhanced outcomes. Hypothermia is a novel therapy that requires significant knowledge of the effects of cooling on all organ systems and its potential impact on medications or other interventions. Given the current state of knowledge, adherence to the eligibility criteria used in any of the large RCTs, such as initiation of treatment within the therapeutic window (before 6 hours of life) and duration of hypothermia for 72 hours with slow rewarming, is essential to provide the best care to critically

Evidence supports a neuroprotective effect of hypothermia therapy with a NNT of 6-9 infants to prevent 1 case of death or significant neurodevelopmental disability.

ill newborn infants with neonatal encephalopathy. Currently, data on initiation of hypothermia after 6 hours of life and inclusion of late preterm or near term infants are not available and until this safety and efficacy data are available it is strongly recommended to follow the current trial protocols. Because the incidence of neonatal encephalopathy because of perinatal asphyxia is low, to maximize the neuroprotective effect of hypothermia therapy and subsequent long-term outcome, this treatment should be confined to large NICUs with cooling centers where available clinical services (eg, neurology, epileptology, radiology), trained/experienced personnel, and neurodevelopmental follow-up programs are available. For referral NICUs or newborn nurseries it is important for care providers to develop connections with regional cooling centers, identify and refer eligible infants with perinatal asphyxia early, and initiate appropriate supportive care to avoid conditions that may worsen neurologic outcome (eg, hyperthermia, hypoglycemia, seizures).

It is important for pediatricians and other care providers who attend deliveries or care for infants in newborn nurseries to be able to recognize eligible infants with neonatal encephalopathy who may benefit from this neuroprotective treatment. Regardless of treatment received, infants with moderate to severe encephalopathy remain at high risk for neurodevelopmental disabilities and require close, long-term neurodevelopmental follow-up, with provision of early-intervention services and family support.

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