CE 2.3 HOURS

# While Waiting

## *Early Recognition and Initial Management of Neonatal Hypoxic-Ischemic Encephalopathy*

Craig B. Sussman, MD; Michael D. Weiss, MD

**ABSTRACT**

Hypoxic-ischemic encephalopathy (HIE) occurring during the perinatal period is one of the primary causes of severe, long-term neurological deficits in children. Initial systemic supportive therapy remains a critical aspect of HIE management. In addition to support therapy, the widespread use of hypothermia has demonstrated a reduction in death and neurodevelopmental disability in infants with moderate to severe HIE. Neonates with HIE born outside of tertiary care centers must be rapidly identified as hypothermia candidates and have emergent transport arranged. While waiting for the transport team to arrive, these neonates often require intensive stabilization, including meticulous temperature management. This article examines the need for HIE outreach teaching programs, assists in the identification of a neonate for hypothermia therapy, and supplies evidence-based recommendations for the initial stabilization and care of neonates delivered at nontertiary care facilities. The guidelines and materials supplied represent the outreach model used by our regional hypothermia center and disseminated to the surrounding referral hospitals.

**Key Words:** birth asphyxia, hypoxic-ischemic encephalopathy, management, neonate, recognition

Hypoxic-ischemic encephalopathy (HIE) occurring during the perinatal period is one of the primary causes of severe, long-term neurological deficits in children. Hypoxic-ischemic enceph is the brain manifestation of systemic asphyxia, which occurs in approximately 2 to 4 per 1000 live births.[1] Most often, the neurological insult is an indirect consequence of myocardial dysfunction and results in loss of cerebral autoregulation.[2] This pathophysiological sequence results in destructive neuronal injury, with 20% to 50% of affected neonates expiring during the newborn period. Up to 25% of the survivors exhibit severe, permanent neuropsychological handicaps in the form of cerebral palsy, with or without associated mental retardation, learning disabilities, or epilepsy.[1]

Because normal physiology is significantly disrupted during the hypoxic-ischemic insult, homeostasis must be promptly regained and maintained postinjury. Until the advent of therapeutic hypothermia, systemic supportive management was the mainstay of therapy for HIE. Hypothermia, either via whole-body or selective head cooling methods, reduces death and neurodevelopmental disability in infants that have suffered from moderate to severe HIE.[3] Prompt initiation of hypothermia is critical and must occur within 6 hours of birth. Moreover, expert opinion indicates that cooling should be initiated as early as feasible, preferably within 2 hours of birth.[4] This critical window is easily achieved when infants are born in a tertiary care center with all the necessary cooling equipment and personnel. However, infants born at hospitals not able to provide this level of care require transport to a tertiary care center that offers hypothermia therapy.

Although hypothermia is currently the single most promising intervention for neonatal HIE, meticulous attention must be focused on all physiological

*Author Affiliations:* Department of Pediatrics, Division of Neonatology, University of Florida, Jacksonville (Dr Sussman); and Department of Pediatrics, Division of Neonatology, University of Florida, Gainesville (Dr Weiss).

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*Correspondence:* Craig B. Sussman, MD, Department of Pediatrics, Division of Neonatology, University of Florida, 655 W 8th St, Clinical Center, 3rd Floor, Box C3, Jacksonville, FL 32209 (cbsussman@gmail.com).



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parameters, including body temperature. This scrupulous attention is particularly important and often challenging in the first several hours postinjury. When an infant is born at a center not accustomed to caring for neonates with multiorgan systemic dysfunction, assistance is often sought from the regional tertiary NICU. In this article, we discuss the need for outreach teaching programs and provide examples of educational material that assist in managing these fragile and complex infants while waiting for transport to the nearest hypothermia center. Specifically, we focus on the recognition of HIE, determination of hypothermia candidacy, and initiation of passive hypothermia if indicated. We further outline evidence-based supportive management guidelines for the initial management and stabilization of neonates with HIE.

## RATIONALE FOR HIE OUTREACH PROGRAM

In 2010, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Hypothermia Workshop published a consensus statement on the current state-of-the-art treatment of HIE, specifically hypothermia. The panel disclosed the following major areas that require more attention: education of the medical staff to identify eligible neonates for hypothermia therapy, training of personnel for initiation of hypothermia, and an increase in outreach education to smaller community/rural referral centers.[5] No current, standardized outreach program exists to fill this educational void. Tertiary care hypothermia centers are the most likely candidates to do so by supplying their referral region with educational materials related to the recognition and initial management of neonates with HIE. Referral centers do not routinely provide neonatal intensive care and are often staffed by general pediatricians and physician extenders who may not be up-to-date on the latest neuroprotective strategies for HIE. For these reasons, referral centers should partner with their regional hypothermia center to obtain educational outreach lectures and construct focused management guidelines and transport protocols.

## EDUCATIONAL TOOLS

### Outreach Lectures

We provide outreach lectures for nurses, respiratory therapists, physicians, and extenders on the following topics: HIE overview, brief pathophysiology discussion, clinical recognition of HIE, early supportive management, and supportive evidence for hypothermia with details of how to safely initiate passive hypothermia before transport. For some medical centers, these lectures are placed on the facility's Web site for review, new-staff familiarization, or anyone unable to attend the live session. Because smaller centers may not encounter neonatal HIE frequently, we supply them with laminated, hard copies of pertinent materials, including a "Freeze Warning" (described hereafter and Figure 1) and an evidence-based, early-management algorithm to assist the clinician until the neonate is safely transported (Figure 2).

### Freeze Warning: Early Recognition of Potential Hypothermia Candidates

Early recognition of neonatal HIE is paramount to the success of treating such infants. Of importance, neonates who are hypothermia candidates must be cooled within 6 hours of the initial neurological insult.[4] Neonates with severe HIE are usually recognized as stuporous and flaccid, with poor or no respiratory effort early in their course. Because of these signs, neonates with severe HIE are identified early and considered hypothermia candidates without delay. However, neonates with mild to moderate HIE may have more subtle symptoms. Subsequently, a clinician's decision to use hypothermia therapy for these infants is frequently and unfortunately delayed. Therefore, we have created a "Freeze Warning" (Figure 1) that serves 3 important roles. First, the Freeze Warning assists the clinician in determining whether a neonate meets the hypothermia criteria. Second, we outline the steps to perform safe and effective passive hypothermia when indicated. Last, we provide the direct contact number to the nearest hypothermia center to hasten immediate transport.

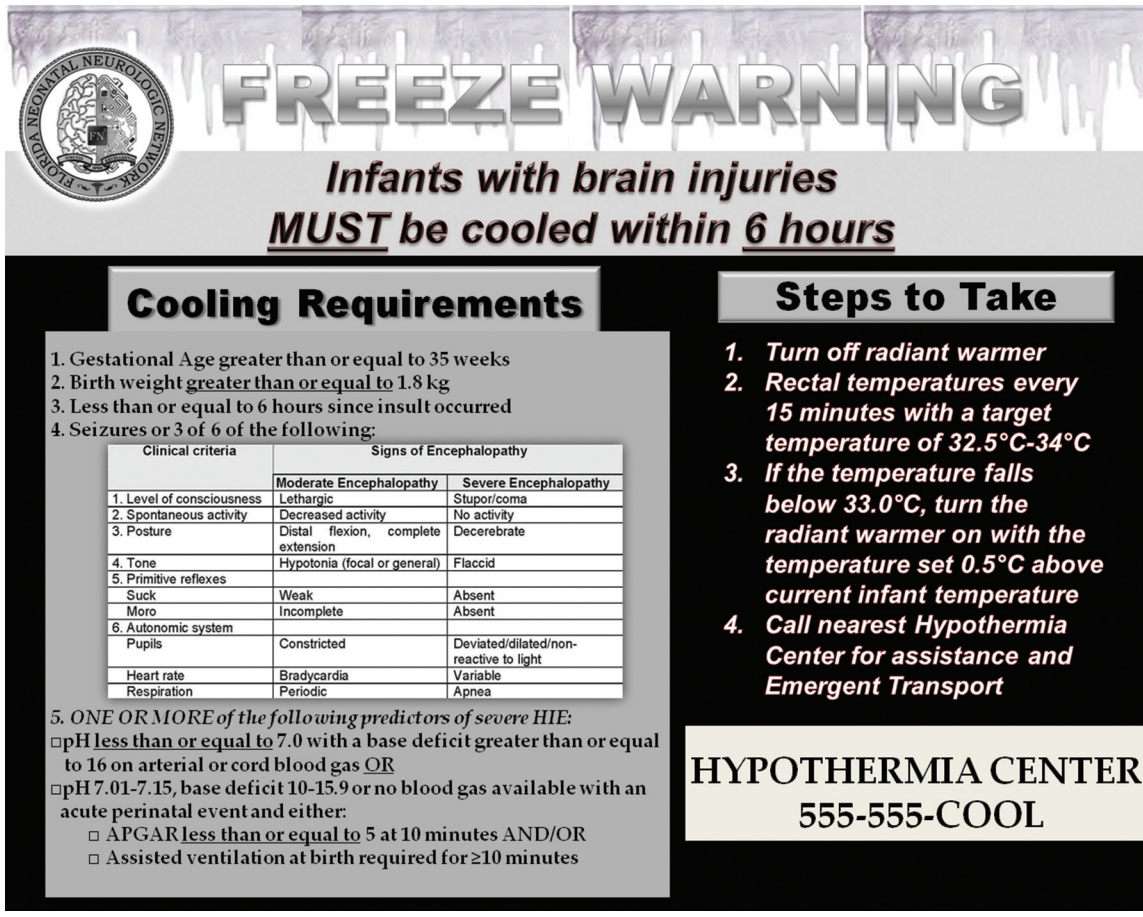
The Freeze Warning can be posted in the nursery or placed in an easy-to-access location for prompt review when necessary. Note that the hypothermia criteria documented in the Freeze Warning may vary from other centers or published literature. The criteria listed in this article are based on a consensus among hypothermia centers that encompass the Florida Neonatal Neurologic Network.

Although these guidelines are supplied, thorough communication between centers is the most important aspect of optimizing care before and during transport. The effortless capability to connect healthcare personnel via videoconferencing (ie, telemedicine) with handheld devices can improve the communication and management approach for HIE-affected infants. This technology allows the accepting physician to be visually involved in the neurological assessment, assist in determining hypothermia candidacy, and aid in clinical seizure detection and management.

## OPTIMIZING SUPPORTIVE MANAGEMENT: RESUSCITATION TO TRANSPORT

Most neonates with moderate to severe HIE have multiorgan system dysfunction that requires

FIGURE 1.




Freeze warning, which can be posted in the nursery or placed in an easy-to-access location for prompt review. It assists the clinician in determining whether a neonate meets the hypothermia criteria, outlines the steps to perform passive hypothermia, and provides the direct contact number to the nearest hypothermia center (*phone number shown in Figure 1 is factitious*).

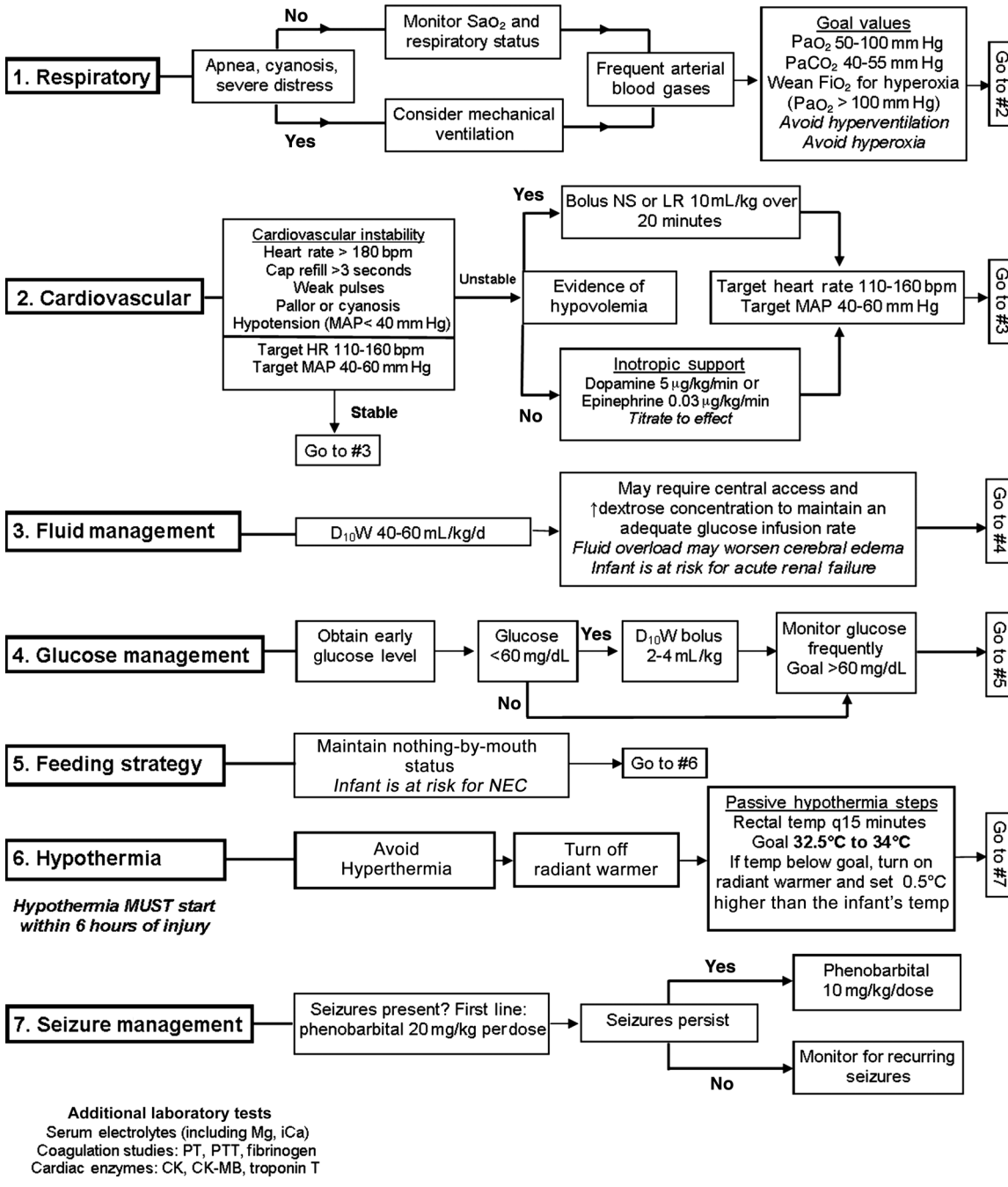
scrupulous monitoring and interventions.[2] For example, because of the impairment of cerebral autoregulation postinsult, the infant's blood pressure must be continuously monitored and tightly controlled to prevent ongoing injury.[6,7] In addition, studies have shown that hypoglycemia is detrimental to the already-injured brain.[8,9] Furthermore, clinicians must attentively manage the ventilator to ensure normal carbon dioxide levels are maintained and to avoid hyperoxia and free radical generation.[10,11] In the following sections, we will discuss evidence-based guidelines for initial supportive management of HIE at the referral center. In this early stage of management, the goals are to support all systems, restore homeostasis, and passively cool the neonate to minimize or prevent ongoing brain injury. The subsequent information is provided to the referring medical centers in the forms of a summary flow diagram (Figure 2) and outreach lectures.

## DELIVERY ROOM MANAGEMENT

All neonatal resuscitation measures should be consistent with the current *Neonatal Resuscitation Textbook*, 6th edition.[12] Current guidelines recommend the use of room air for the initial resuscitation of term infants.[12] Neonates resuscitated with room air have higher Apgar scores at 5 minutes and higher heart rates at 90 seconds of age and take their first breath 30 seconds earlier than those who receive 100% oxygen.[13]

For infants requiring extensive delivery room resuscitation, our institution recommends that once the heart rate is consistently greater than 100 beats per minute and the airway is secure, the neonatal team should consider turning off the radiant warmer, allowing passive cooling and avoiding hyperthermia. Core temperature must be monitored closely, as described in the "Passive Hypothermia" section hereafter.

FIGURE 2.




Initial supportive management for neonatal hypoxic-ischemic encephalopathy (≥35-week gestational age).

[a]Continue to assess steps 1 to 7 until transport.

[b]If, suspected sepsis, consider ampicillin and cefotaxime.

Adopted from the Florida Neonatal Neurologic Network Consensus on Supportive Management for Neonatal HIE (Sussman and Weiss, 2012).

Abbreviations: bpm, beats per minute; CK, creatine kinase; CK-MB, creatine kinase-MB; $D_{10}W$, 10% dextrose solution; $FiO_2$, fractional inspired oxygen; HR, heart rate; LR, lactated ringer's; MAP, mean arterial pressure; NEC, necrotizing enterocolitis; NPO, nil per os; NS, normal saline; $PaO_2$, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; PT, prothrombin time; PTT, partial thromboplastin time; $SaO_2$, oxygen saturation; temp, temperature.

Although definitions vary, *extensive resuscitation* may be defined as the need for chest compressions, epinephrine use, positive pressure ventilation for 10 minutes or more, and/or an Apgar score of 5 or less at 10 minutes. We recommend that any infant in the delivery room who requires extensive resuscitation measures be thoroughly evaluated for HIE and considered a hypothermia candidate until deemed that the hypothermia criteria are not fulfilled. Of significance, if the resuscitation is prolonged, *the infant should not become hyperthermic*, as pyrexia is associated with adverse neurodevelopmental outcomes.[14,15]

## RESPIRATORY MANAGEMENT

Neonates who suffer from perinatal depression and resultant HIE often undergo vigorous resuscitation at birth. Many of these neonates have respiratory depression, requiring intubation and mechanical ventilation. As a result, they may experience hyperoxia and hypocapnia early in their course. Hypocapnia is harmful in this population and leads to decreased cerebral perfusion and decreased oxygen release from hemoglobin.[16] Clinical evidence has demonstrated that hypocapnia is associated with death and poor neurodevelopmental outcome in infants afflicted with HIE.[11] Furthermore, hyperoxia leads to increased oxidative stress and free radical production, which is detrimental to infants with HIE.[17] Hyperoxia is especially toxic in the setting of reperfusion, and injury to fragile neuronal tissue can be exacerbated.[10,17] Most importantly, hyperoxia is associated with poor long-term outcomes postasphyxia and death.[11] We, therefore, recommend obtaining an early arterial blood gas in this population, with goal partial pressure of oxygen ($PaO_2$) values of 50 to 100 mm Hg and partial pressure of carbon dioxide ($PaCO_2$) values of 40 to 55 mm Hg. The clinician should adjust ventilator settings to obtain the aforementioned target values and frequently monitor blood gases.

Hypothermia affects blood gas parameters such as pH and $PaCO_2$. At lower temperatures, pH increases and $PaCO_2$ decreases.[18] For example, in a healthy neonate with a body temperature of 37°C, the pH should approach 7.4 with $PaCO_2$ values near 40 mm Hg and $PaO_2$ values near 90 mm Hg. However, an arterial blood gas obtained from the same neonate undergoing hypothermia with a core temperature of 33°C would likely reveal a pH of approximately 7.5, a $PaCO_2$ of 34 mm Hg and a $PaO_2$ of 61 mm Hg.[18] These values occur if the blood gas analyzer is unable to correct for body temperature. Most blood gas instruments contain a temperature-controlled sample chamber specified to be 37°C, referred to as the α-stat method. In this technique, uncorrected values are used to maintain the pH and $PaCO_2$ at the 37°C reference values. Alternatively, in the pH-stat method (also referred to as the temperature-corrected method), the measured pH is corrected to the actual body temperature of the patient. Currently, it is unclear whether the α-stat or pH-stat method should be used for the ventilator management of the asphyxiated neonates undergoing hypothermia.[18] We recommend investigating the sampling method used at each institution, being cognizant of the aforementioned alterations, and considering modified ventilator strategies to obtain target blood gas values.

## CARDIOVASCULAR MANAGEMENT

Systemic blood pressure must remain in a safe range after hypoxic-ischemic injury. The goal of blood pressure management includes avoiding hypotensive-associated cerebral ischemia while ensuring that the infant is not hypertensive, which may lead to intracerebral hemorrhage.[6,7] The ideal mean arterial pressure (MAP) for *term* infants with HIE has not been established. Since infants operate over a narrow blood pressure range and hypoxia-ischemia impairs cerebral autoregulation, MAP should be maintained within the critical margin of *40 to 60 mm Hg* unless the hemodynamics suggest a more optimal MAP.[2] If feasible, the clinician should place an invasive arterial catheter for continuous blood pressure monitoring and frequent blood sampling.

Minimal documentation exists regarding the ideal method to augment MAP for infants with HIE. If clinical or historical evidence of hypovolemia (ie, severe anemia, placental abruption, cord compression) exists, then volume expansion is likely indicated. However, the unwarranted use of fluids may exacerbate cerebral edema.[19] If evidence of hypovolemia is present, volume expansion should be considered in the form of normal saline or lactated Ringer's at 10 mL/kg infused intravenously over 15 to 20 minutes.

The optimal blood pressure agent to treat an infant with hypotension and HIE is unknown. No single agent has shown to be superior or to prevent morbidity and/or mortality.[20-22] Therefore, on the basis of expert opinion, we recommend initiating either dopamine (5 μg/kg/min) or low-dose epinephrine (0.3 μg/kg/min) and titrating to effect. We must emphasize that the treating clinician should select a blood pressure agent that supports the clinical needs of the individual neonate.

## INITIAL FLUID MANAGEMENT

To limit the consequences of HIE, experts recommend careful management of fluids to avoid fluid overload and, thus, to prevent cerebral edema. Although no exact literature exists, the most common practice is to administer intravenous $D_{10}W$

(10% dextrose solution) or $D_{10}W$ with amino acids upon admission. The suggested starting rate is 40 to 60 mL/kg/d. These recommendations for fluid restriction in neonates are based on the experience of restricting fluid intake in adults and older children.[23]

## GLUCOSE MANAGEMENT

Under normal conditions, the human brain relies almost entirely on glucose to provide substrate for metabolism. In newborn infants, cerebral glucose may be 70% of the total glucose consumption. Although the newborn brain can use other substrates, such as lactate or ketones, as an energy source, these alternate fuels usually have an unpredictable supply and may not compensate entirely for a decrease in glucose availability.[24]

During asphyxia, anaerobic glycolysis accelerates the use of glycogen stores. As a consequence, hepatic glycogen stores are depleted, and hepatic glucose production rapidly becomes insufficient to meet cerebral metabolic demands.[24] Also, perinatal asphyxia may be associated with hyperinsulinemia. Hyperinsulinemia may further impair hepatic glucose production and contribute to cerebral energy depletion by increasing the uptake of glucose by peripheral tissue.[24] Furthermore, for infants with hyperinsulinism, an operational blood glucose threshold of 60 mg/dL is appropriate for defining the lower limit of normal, as these neonates have very low levels of alternative energy such as ketones and lactate at low blood glucose concentrations.[25]

On the basis of human clinical observations, lower levels of serum glucose concentrations correlate with higher Sarnat scores, an advanced degree of clinical encephalopathy.[8] Furthermore, initial hypoglycemia (≤40 mg/dL) is an important risk factor for perinatal brain injury in depressed neonates.[9] On the basis of the aforementioned data, we recommend early (within 30 minutes of birth) screening for hypoglycemia in all infants with HIE. The target glucose range should be at least more than 40 mg/dL, with an ideal target of *60 to 70 mg/dL* or higher. If hypoglycemia is present, 2 to 4 mL/kg of $D_{10}W$ should be promptly administered intravenously. A follow-up glucose value should be obtained 10 to 20 minutes post-infusion. Because of the recommended low-maintenance fluid infusion discussed previously, if hypoglycemia is present, the infant may require central venous access to safely provide an increase in dextrose concentration while avoiding fluid overload. Of importance, animal models have shown hyperglycemia to be potentially detrimental in the setting of hypoxia-ischemia, and, thus, overaggressive administration of glucose should be avoided.[2]

## INFANTS WITH HIE SHOULD BE MADE NIL PER OS

Hypoxic-ischemic encephalopathy is a risk factor for necrotizing enterocolitis in term neonates. During this critical initial stabilization period, feeding is not recommended. Therefore, the infant should be placed on nothing-by-mouth status.[26] The early clinical stage of injury is an emotionally taxing experience for the parents of a child who has succumbed to HIE. When appropriate, a mother who is hospitalized at a referral center should be supplied with a hospital grade breast pump and encouraged to supply expressed breast milk for future feedings. Although evidence does not directly support the claim that breast milk is better than formula for improving the outcome of neonates with HIE, evidence has shown that breast milk may improve cognitive abilities in term neonates.[27] Furthermore, studies have demonstrated that breast milk feeding is associated with a lower incidence of necrotizing enterocolitis.[28]

## PASSIVE HYPOTHERMIA

As mentioned, prompt initiation of hypothermia is critical and must occur within 6 hours of injury. Moreover, expert opinion indicates that cooling should be initiated as early as feasible, preferably within 2 hours.[4] Passive cooling involves withholding any external heat sources and monitoring the neonate's temperature frequently. Maintaining the temperature within a target range is difficult, and infants often arrive to the tertiary NICU with temperatures outside of the target range. In addition, overcooling may increase serious adverse effects associated with hypothermia, such as arrhythmias, electrolyte abnormalities, thrombocytopenia, and coagulopathies.[29]

When passive cooling is applied before transport, we recommend using a reliable rectal temperature probe/thermometer and assessing the neonate's core temperature every 15 minutes until transported. The target rectal temperature should be between *32.5°C* and *34°C*. If the infant's temperature falls lower than 33°C, the radiant warmer should be turned on and set 0.5°C higher than the infant's current temperature. Then, continue to monitor the core temperature every 15 minutes to ensure it increases to within the target range. Each center must ensure their rectal thermometers accurately display temperatures within the target range, as some commercial thermometers do not register lower than a specific degree. Of note, the most accurate measurement technique is by inserting the rectal thermometer 2 to 3 cm into the rectum. If a center has the ability for continuous core temperature monitoring, either

rectal or esophageal, this technique may be substituted for the aforementioned intermittent (every 15 minute) measurements. These steps are outlined in the Freeze Warning (Figure 1).

Centers that may not be accustomed to caring for critical newborns and do not frequently use rectal temperature measurements may consider maintaining the axillary temperature between 33.5°C and 35°C. This approach may avoid unnecessary tissue injury from incorrect technique. Furthermore, the use of mild hypothermia in this setting will minimize systemic adverse effects while continuing to provide a degree of neuroprotection.

It is noteworthy that specialized neonatal transport teams are able to provide active hypothermia during transport via air and ground.[30] With this novel capability, the referral center's goal is to maintain the core temperature near the target range until transport arrives and active cooling can be initiated safely.

## SEIZURE MANAGEMENT

Hypoxic-ischemic encephalopathy is the primary cause of neonatal seizures. Despite the high incidence of seizures in this population of neonates, a Cochrane review did not find any benefit regarding morbidity and mortality with routine use of prophylactic antiepileptic medications.[31] However, studies indicate that infants with recurrent or persistent seizures (clinical or electrographic) may benefit from aggressive therapy.[32,33] The Food and Drug Administration has approved the antiepileptic medications phenobarbital and fosphenytoin or phenytoin for the management of neonatal seizures. Studies have not demonstrated a benefit of phenobarbital over phenytoin.[34] On the basis of the aforementioned and limited data, we recommend treating electrographic or clinical seizures with the institution's antiepileptic medication(s) of choice. Our current first-line antiepileptic is phenobarbital with a loading dose of 20 mg/kg/dose. After monitoring the patient for a response, if seizures continue, clinicians should consider reloading with phenobarbital 10 mg/kg/dose or introducing a second agent such as fosphenytoin or a benzodiazepine.

All antiepileptic medications should be administered intravenously. In addition, we recommended continuous electroencephalographic monitoring or amplitude-integrated electroencephalographic (aEEG) monitoring when treating suspected clinical seizures. However, this practice may not be feasible at the referral center.

Of importance, these first-line antiepileptic agents pose potential, detrimental effects to the developing brain. For instance, the antiepileptic medications mentioned previously, phenobarbital and fosphenytoin, may subject the immature brain to neuronal apoptosis.[35] Furthermore, phenobarbital administered to rat pups significantly decreases brain weight and reduces neuronal number.[36] Additional agents, such as topiramate and levetiracetam, are currently being evaluated and have promising antiepileptic and neuroprotective properties.[37] As studies progress, these medications may emerge as future, first-line therapy for neonatal seizures.

## SODIUM BICARBONATE USE FOR METABOLIC ACIDOSIS AND HIE

Intravenous sodium bicarbonate has been used to treat metabolic acidosis in the neonate under compromised circumstances such as HIE.[38] However, research has shown that sodium bicarbonate is not effective in reversing intracellular acidosis and may exacerbate the intracellular acidosis by increasing intracellular carbon dioxide concentrations.[39] Furthermore, a meta-analysis evaluated the efficacy of sodium bicarbonate used during resuscitation of infants at birth and found insufficient evidence from randomized controlled trials to determine whether sodium bicarbonate reduces morbidity and morbidity.[40] On the basis of the aforementioned data, we do not recommend the routine use of sodium bicarbonate to correct metabolic acidosis in neonatal HIE. Therefore, this therapy is not mentioned in our flow diagram (Figure 2).

## SEPSIS MANAGEMENT AND HIE

Neonates with HIE often present with severe clinical compromise. This clinical presentation may mimic or be complicated by severe septic shock. Furthermore, inflammation likely plays a role in the origin of neonatal brain injury. Neonates with evidence of chorioamnionitis and/or elevated levels of cytokines at birth have an increased likelihood of developing cerebral palsy in the future.[41,42] In the clinical arena, a neonate presenting with HIE is often placed on broad spectrum antibiotics until bacterial sepsis can be confidently excluded. To date, ampicillin and gentamicin remain the standard of care for neonatal empirical antimicrobial therapy.[43]

In this complex population of infants, renal dysfunction as a result of acute renal failure, cortical necrosis, and/or renal vascular thrombosis is frequently encountered.[44,45] Clinicians may need to consider an alternative medication to avoid the nephrotoxic effects of aminoglycosides.[45] Cefotaxime, a third-generation cephalosporin, provides similar antimicrobial coverage as gentamicin and has an acceptable safety profile in neonates while avoiding nephrotoxicity.[46] In addition to superior blood-brain barrier penetration, laboratory evidence supports cephalosporins as neuroprotective agents. However, the neuroprotective effect of cephalosporins has yet to be demonstrated in humans.[47,48]

Our current practice is to initiate ampicillin and cefotaxime in neonates with HIE and suspected sepsis. In an effort to minimize antibiotic resistance and adverse effects, these agents are discontinued when bacterial sepsis can be excluded.

The aforementioned supportive management recommendations have been summarized and organized into a flow diagram (Figure 2) and should be placed in an easily accessible location in the referral center's nursery for future use.

## CONCLUSION

Neonatal HIE is a complex medical condition that requires meticulous attention from the clinical team to provide optimal care. Because of the high morbidity and mortality associated with HIE, an organized management strategy with a systems-based approach in the first several hours postinjury is crucial to the infant's short- and long-term outcomes. In this article, we outlined our institutions' best practice approach to the initial stabilization and management of neonates with HIE and the dissemination of material to the outlying referral centers. Although we do not currently have measurable data to determine whether our outreach methods have been successful in improving overall care, we have provided detailed, evidence-based guidelines that were previously lacking. Our HIE patients' data are collected in a secure registry, and in the future, we intend to review data of all HIE infants born outside of tertiary care centers to determine the success of this program. We are optimistically expecting centers outside of our referral region to use these materials to optimize the initial care of neonatal HIE patients. In turn, this outreach strategy will help improve long-term neurodevelopmental outcomes.

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