Hypoxic-ischemic encephalopathy (HIE) is a major cause of neurologic disabilities in term neonates despite the recent widespread use of hypothermia therapy. The incidence of HIE ranges from 1 to 8 per 1000 live births in developed countries, and is as high as 26 per 1000 live births in underdeveloped countries. Although the advent of therapeutic hypothermia offers neuroprotection, the improvement in outcomes has been modest. Therefore, new synergistic therapies are needed to improve outcomes. This review is intended for the clinician and briefly examines the pathophysiology of HIE in the context of clinical care (more extensive reviews on this topic are found in Johnston et al). This review examines practical clinical information, such as diagnostic considerations, and emphasizes evidence-based practices for neonates with HIE (eTable 1 in the Supplement summarizes pertinent publications from the past 5 years in each of these categories). The review examines 75 articles (of the 102 selected for critical review), with an emphasis on articles published between January 1, 2004, and December 21, 2014.

### Pathophysiology

Clinicians must understand the pathophysiology of injury during hypoxia-ischemia (HI) to manage this critical illness in neonates appropriately because the injury evolves over the course of days and possibly weeks (Figure 1). Furthermore, a bedside clinician who understands the pathophysiology of HIE will understand the mechanism of action of the various emerging neuroprotective agents.

Adequate cerebral blood flow delivers oxygen and glucose to the fetal brain. This blood flow helps the fetal brain maintain homeostasis and meet cellular energy demands. A variety of conditions decrease placental perfusion or disrupt the delivery of oxygen and glucose in the umbilical cord, including placental abruption, prolapse of the umbilical cord, and uterine rupture. The hypoxia eventually leads to a decrease in fetal cardiac output, which reduces cerebral blood flow. If the decrease in cerebral blood flow is moderate, the cerebral arteries shunt blood flow from the anterior circulation to the poste-
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Clinical deterioration in neonates with moderate to severe injury. Seizure activity characterizes this secondary phase, which leads to cell death and secondary energy failure with near-complete failure of mitochondrial activity. This secondary phase, which leads to cell death and clinical deterioration in neonates with moderate to severe injury. Secondary energy failure with nearly complete failure of mitochondrial activity characterizes this secondary phase, which leads to cell death and clinical deterioration in neonates with moderate to severe injury. Seizures typically occur in the secondary phase. A tertiary phase occurs during the months after the acute insult and involves late cell death, remodeling of the injured brain, and astrogliosis.

Figure 1. Schematic Overview of the Pathophysiological Features of Hypoxic-Ischemic Encephalopathy

Biomarkers

In neonates with HIE, monitoring and evaluation, outcome prediction, and response to the hypothermia treatment are measured with a combination of a neurologic examination, MRI, and electroencephalography (EEG). However, unstable neonates may not tolerate transport for an MRI of the brain or the length of the MRI scanning time. Moreover, hypothermia therapy may depress the amplitude-integrated EEG (aEEG) and thus limit the early predictive ability of aEEG. Improvement in aEEG tracings may be delayed until the patient undergoes rewarming and is no longer sedated. Serum biomarkers may enable clinicians to stratify neonates with HIE undergoing hypothermia into the following 3 groups based on biomarker levels: (1) responders to hypothermia alone with good neurodevelopmental prognosis, (2) nonresponders to hypothermia at high risk for surviving with neurologic injury and/or neurodevelopmental deficits who then may be candidates for other clinical interventions, and (3) neonates who will die. Biomarkers, such as ubiquitin carboxyl-terminal esterase L1 (UCH-L1) and glial fibrillary acidic protein (GFAP), have demonstrated predictive capabilities in several studies (eTable 2 in the Supplement). Combining biomarkers with scoring systems may improve the sensitivity and specificity of diagnosis.

Diagnosis Considerations

A bedside test is not available for an accurate diagnosis of HIE in a neonate. Physicians diagnose HIE based on the presence of a neurologic dysfunction in the form of neonatal encephalopathy. Hallmarks of neonatal encephalopathy are depression of the level of consciousness, often with respiratory depression, abnormality of muscle tone and power, disturbances of cranial nerve function, and seizures. Evidence of low Apgar scores and metabolic acidosis (in arterial cord oxygen or newborn blood oxygen levels) must accompany the neurologic dysfunction. Metabolic acidosis strongly suggests HI injury. Concomitant injury to other organs, such as the liver (elevated transaminase level), the kidneys (elevated creatinine level), and/or the heart (elevated creatine kinase-MB fraction and troponin T levels), provides further evidence of HI injury. In addition, the pattern of injury on magnetic resonance imaging (MRI) of the brain may further confirm HIE.

Neonates with suspected HIE are classified according to the Sarnat staging system, which evaluates the level of consciousness, muscle tone, tendon reflexes, complex reflexes, and autonomic function. The Sarnat stage classifies neonatal HIE into the following 3 categories: stage I (mild), stage II (moderate), and stage III (severe). Entry criteria for therapeutic hypothermia include a modified version of the Sarnat staging system.

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Hypoxic-Ischemic Encephalopathy

Placental Abnormalities
Only a small fraction of patients with HIE (15%-29%) have a documented sentinel event, such as a placental abruption, uterine rupture, cord prolapse, or shoulder dystocia. In neonates without a sentinel event, placental analysis can provide valuable information regarding the cause and timing of the adverse events in utero. For example, placenta with decreased maturation of the terminal villi are associated with injury to the white matter/watershed areas and basal ganglia. Immature placental villi increase the distance between the maternal and fetal blood with a net effect of reduced oxygen diffusion to the fetus or fetal hypoxia. Placentas with reduced weight can represent an adverse intrauterine environment owing to decreased uteroplacental perfusion.

Neuroimaging
Brain MRI is the preferred imaging choice in neonates with HIE and is a useful tool to predict long-term outcomes (eTable 3 in the Supplement). In the first week after birth, diffusion-weighted MRI of the brain may assist physicians in making management decisions for patients undergoing ventilator support. Diffusion-weighted imaging refers to MRI that is sensitive to water molecule diffusion. However, diffusion-weighted imaging obtained during the first hours after the injury may underestimate the final extent of injury. The sensitivity and specificity of this technique can be improved by quantification of the apparent diffusion coefficient, which is performed by voxelwise analysis of the information contained within diffusion-weighted imaging. After moderate or severe HIE, abnormal signal intensity is commonly detected in the basal ganglia and thalami, corticospinal tract, white matter, and cortex. Neonates with a history of a sentinel event are likely to sustain basal ganglia and thalamic lesions. These lesions are usually accompanied by abnormalities in the appearance of the intervening posterior limb of the internal capsule.

Abnormalities in the MRI of the brain correlate with outcomes. Lower apparent diffusion coefficient values in the basal ganglia during the first 7 days after HIE predict adverse neurologic outcomes. Injuries to the posterior limb of the internal capsule and basal ganglia are associated with motor deficits. Injury to the posterior limb of the internal capsule combined with diffuse basal ganglia injury and a peripheral (ie, hemispheric gray and white matter) abnormality are associated with death, hearing and visual impairments, and severe cerebral palsy. Recently, the TOBY (Total Body Hyperthermia for Neonatal Encephalopathy) trial demonstrated that hypothermia does not influence the ability of MRI to predict neurodevelopmental outcomes.

Magnetic resonance spectroscopy allows for in vivo quantitative analysis of brain metabolites and therefore may serve as an early biomarker for brain injury. Findings on MRI without spectroscopy could be normal for as long as 24 hours after an acute HI event (eg, abruption), but magnetic resonance spectroscopy or diffusion-weighted imaging detects early acute events. When clinicians add magnetic resonance spectroscopy to standard MRI, scanning time increases by only 6 to 7 minutes and may improve the predictive value of the scan. An elevated ratio of lactate to N-acetyl aspartate in the basal ganglia can predict long-term neurologic impairments and can be seen in the first 48 hours of life.

The clinician should be cautious when predicting outcomes in neonates with HIE who have normal findings or minor degrees of brain injury on MRI. As many as 26% of neonates with HIE who underwent hypothermia and had normal MRI findings experienced abnormal neurodevelopmental outcomes.

Treatment

Systemic Support
Systemic support remains the foundation of care for neonates with HIE. The goal of systemic support is to restore adequate cerebral blood flow, which ensures delivery of the metabolic substrates oxygen and glucose to prevent secondary brain injury (an overview of recommendations is available in the eFigure in the Supplement). Secondary injury may occur because of other organ impairment. For example, cardiac injury may result in decreased cardiac output and hypotension, which further decrease cerebral blood flow. Persistent pulmonary hypertension of the newborn may worsen hypoxia. Although systemic support is the foundation of therapy, evidence-based optimal practice parameters are scarce. Researchers have not validated most of the parameters with long-term follow-up of the patients. We herein present a summary of a system-based approach to supportive care of neonates with HIE.

Respiratory System
Infants with an HI insult have metabolic changes that lead to less carbon dioxide (CO₂) production. Respiratory compensation for the initial severe metabolic acidosis may lower CO₂ levels. In addition, hypothermia may reduce CO₂ production. Patients with HIE need less ventilator support to obtain a desirable CO₂ level. Hypocapnia is harmful in patients with HIE because it decreases cerebral perfusion and oxygen release from hemoglobin. Hypocapnia is associated with death and poor neurodevelopmental outcomes.

Hyperoxia can have a detrimental effect on neonates with HIE because it increases oxidative stress and free radical production, especially during the reperfusion phase. Furthermore, hyperoxia is associated with death and poor long-term outcomes in neonates with HIE. Infants with a history of respiratory depression at birth and resultant HIE often undergo vigorous resuscitation at birth. As a result, hyperoxia and hypocapnia may exist after resuscitation, leading to worse outcomes. Therefore, normal oxygenation and normocapnia after newborn resuscitation may prevent secondary injury (Paco₂, 40-55 mm Hg; Paco₂, 50-100 mm Hg).

Cardiovascular System
Blood pressure must remain in a safe range to avoid hypotension, which can produce a secondary ischemic injury. The ideal mean arterial blood pressure (MAP) for term infants with HIE has not been established. Because infants operate within a narrow blood pressure range and because HI impairs cerebral autoregulation, experts recommend that MAP be maintained within the critical range of 40 to 60 mm Hg unless the hemodynamics suggest a more optimal MAP. Organ-specific regional oximetry may indicate the optimal MAP for individual patients, helping to individualize care. The use of echocardiography in patients with HIE is useful because the treatment of low pressure is different in infants with poor cardiac function vs neonates with normal function. Patients with HIE, good

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cardiac function, and low blood pressure may require more volume, especially if clinical or historic evidence of hypovolemia (ie, severe anemia, placental abruption, or cord compression) is found. However, the unwarranted use of fluid therapy may exacerbate cerebral edema.28

In patients with cardiac dysfunction, minimal evidence exists regarding the ideal method to augment MAP for infants with HIE. A 2002 Cochrane systematic review29 did not find conclusive evidence regarding the use of dopamine for the prevention of morbidity and mortality in patients with HIE. Furthermore, dopamine may not be the ideal first-line agent for infants with evidence of pulmonary hypertension and HIE because dopamine increases systemic and pulmonary vascular resistance.30 Dobutamine can reduce afterload and therefore decrease the ratio of systemic to pulmonary vascular resistance.31 Epinephrine at low to moderate doses increases the cardiac index with no effects on the ratio of systemic to pulmonary arterial pressures. In infants with HIE and pulmonary hypertension with cardiac dysfunction, epinephrine may be the optimal choice for blood pressure augmentation.30 In patients with HIE and pulmonary hypertension, milrinone lactate may be advantageous because milrinone increases myocardial contractility and acts as a systemic and pulmonary vasodilator.32

Antiseizure Medications

Consensus has not been reached regarding the best medication for treating seizures in patients with HIE. Clinicians frequently use phenobarbital, but only 27% of seizures are controlled. Recently, topiramate has emerged as a potential neonatal antiseizure medication. Topiramate modulates 2-(aminomethyl)phenylacetic acid, kainate, and y-amino butyric acid-activated ion channels and voltage-activated sodium and chloride channels. Animal models and 1 human pilot clinical trial37 showed that topiramate worked synergistically with hypothermia, but its efficacy in neonates is unknown. Levetiracetam is also a promising antiseizure medication that decreases excitotoxicity and does not induce neuronal apoptosis, but researchers have not yet evaluated its efficacy in large clinical trials.

Hypothermia

Therapeutic hypothermia is considered the standard of care for neonates with HIE; the treatment uses mild hypothermia in the range of 33.5°C to 35.0°C. Several large multicenter trials demonstrated that the therapy is safe and efficacious (eTable 4 in the Supplement).38-40 A recent meta-analysis reviewed outcomes of 7 hypothermia trials, including 1214 neonates who were randomized to hypothermia or systemic supportive care.41 Therapeutic hypothermia reduced the risk for death or major neurodevelopmental disabilities at 18 months of age in neonates with moderate and severe HIE.41

At present, the 2 types of treatment used include whole-body hypothermia and selective head cooling. Although the 2 cooling methods are equally effective, clinicians predominantly use whole-body cooling owing to its reduced cost and ease of use. Meta-analysis41 did not show a difference in the reduction of long-term neurologic impairments between the 2 methods.

Recently, 2 of the original large multicenter hypothermia trials published follow-up data on their original cohort of patients at school age.42,43 The CoolCap Trial Group42 performed neurodevelopmental assessments on 46% of the original cohort and demonstrated a correlation between the neurodevelopmental assessments at 18 to 22 months of age with the functional outcomes at 7 to 8 years of age. The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network whole-body hypothermia trial43 demonstrated a significant reduction in death, death or severe disability, and death or cerebral palsy at 6 to 7 years of age. The trial also demonstrated a strong trend in the primary outcome of death or IQ score of less than 70.43

Because little variability was evident in the therapeutic hypothermia trials, the optimal timing for the initiation of hypothermia, the depth and duration of hypothermia, and the safety of hypothermia for late preterm neonates are uncertain. These uncertainties are being addressed in ongoing trials that examine the efficacy of initiation of hypothermia at 6 to 24 hours of age,44,46 longer durations of hypothermia (120 hours) and a lower temperature of hypothermia (32°C),45 and whether neonates with HIE and a gestational age of 33 to 35 weeks benefit from hypothermia.46

Recent data showed that the time to initiate hypothermia correlated with outcomes. Neonates undergoing earlier cooling therapy (within 180 minutes of birth) had better outcomes compared with those who underwent the therapy later (180-360 minutes after birth).47 The results have stimulated interest in transporting neonates with active hypothermia.48-50

Emerging Therapies

Although the pathophysiological features of HIE are complex, the multiple steps leading to cellular damage provide many opportunities for therapeutic intervention. A search is currently under way to identify other agents that may be synergistic with therapeutic hypothermia. Potential agents include xenon, erythropoietin, melatonin, and stem cell therapy. A brief discussion of these agents follows. These agents, along with other potential therapies, are
During hypoxic-ischemic encephalopathy, an excessive amount of the excitatory amino acid glutamate is released from the presynaptic terminal. This excess glutamate leads to overstimulation of the glutamate receptors (2-(aminomethyl)phenylacetic acid [AMPA], kainite [KA], and N-methyl-D-aspartate [NMDA]) located on the postsynaptic neuron and leads to excitotoxicity. Overstimulation of the KA and AMPA receptors causes sodium ($Na^+$) and chloride to enter the cell, which increases cell osmolality. Overstimulation of the NMDA receptor triggers the influx of calcium ($Ca^{2+}$). The 3 aberrant cellular processes lead to apoptosis and necrosis. The various neuroprotective agents are illustrated at the points where they interfere with the pathophysiological cascade. Solid arrows represent the pathophysiological cascade that is unleashed as a result of HI injury; dashed arrows, interruption of the cascade by the various neuroprotective agents (circled numbers). As in Figure 1, the orange boxes represent excitotoxicity; blue boxes, oxidative stress; yellow box, cell death; and dark blue box, HI. NO indicates nitric oxide; 1, magnesium; 2, xenon; 3, erythropoietin; 4, stem cells; 5, N-acetylcysteine; 6, melatonin; 7, antioxidants; 8, allopurinol sodium; 9, BH$_4$ (tetrahydrobiopterin); and 10, hydrogen sulfide.

Erythropoietin is a naturally occurring glycoprotein frequently used to stimulate erythropoiesis and is a safe and efficacious treatment for anemia of prematurity. Erythropoietin is locally produced in the central nervous system and is found in elevated levels in the cord blood of infants who have perinatal asphyxia. Erythropoietin has many possible mechanisms for neuroprotection. It provides neuroprotection against apoptosis and has an anti-inflammatory effect when bound to erythropoietin receptors on astrocytes and microglial cells. Erythropoietin prevents nitric oxide–induced death of neurons and protects neurons from the toxic effects of glutamate. Erythropoietin is neurotrophic and affects neurogenesis, differentiation, and repair after injury. In the study by Zhu et al, patients with moderate or severe HIE were randomized to receive erythropoietin or supportive care without hypothermia therapy. Erythropoietin was administered within 48 hours of birth at a dose of 300 U/kg or 500 U/kg every other day for 2 weeks. At 18 months of age, the erythropoietin group had reduced rates of death and moderate or severe disability. The outcome was the same when the 300- and 500-U/kg doses were compared. Researchers saw these improvements only in patients with moderate, not severe, HIE. Recently, a phase 1 pharmacokinetic study combined erythropoietin with hypothermia and demonstrated that participants tolerated doses up to 1000 U/kg. This dose produced plasma concentrations similar to those in animal models of HI injury that are neuroprotective.

The pineal gland produces melatonin, a naturally occurring substance used for regulating the circadian rhythm. Melatonin has many other effects that may benefit infants with HI injury. Melatonin serves as a free radical scavenger of the hydroxyl radical, oxygen, and hydrogen peroxide. In addition, melatonin decreases inflammatory cytokine levels and stimulates antioxidant enzymes, such as glutathione.
thione peroxidase and reductase, glucose-6-phosphate dehydrogenase, and superoxide dismutase. In a cohort study of newborns with asphyxia, melatonin (10 mg by mouth given every 2 hours for 8 doses) reduced malondialdehyde and nitrate/nitrite levels compared with placebo. These reduced levels demonstrated a decrease in lipid peroxidation and nitric oxide production.

Stem cell therapy may be a good adjunctive therapy because of its potential for benefit through several different mechanisms. Stem cell transplant may increase levels of brain trophic factors and antiapoptotic factors, decrease inflammation, preserve endogenous tissue, and support replacement of damaged cells. A recent pilot study showed better outcomes with the combination of hypothermia plus autologous umbilical cord blood vs hypothermia alone. Validation of the efficacy of stem cell therapy will require a bigger sample size and protocols that standardize the source of cells, doses, and method of delivery.

Conclusions

Great strides in the care of neonates with HIE have been made. The advent of therapeutic hypothermia has armed the bedside clinician with a therapy that helps reduce the long-term neurologic impairments in 1 of 8 treated neonates. However, the fields of neonatology and neonatal neurology should continue to search for neuroprotective strategies and long-term optimization of infant neuroplasticity.

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