Updates in Treatment of Hypoxic-Ischemic Encephalopathy

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KEYWORDS

• Brain • Encephalopathy • Neonate • Neuroprotection • Neurorestoration

KEY POINTS

- Hypoxic-ischemic encephalopathy (HIE) remains one of the leading causes of nervous system disabilities around the world.
- Therapeutic hypothermia (TH) is the current standard of care treatment for HIE.
- Up to 29% of neonates with HIE treated with TH still experience adverse neurodevelopmental outcomes.
- Treatments for HIE targeting neuroprotection and/or neurorestoration are under investigation.
- Attentive daily management of the multiorgan failure during the first days of life is essential.

INTRODUCTION

Birth asphyxia and the resulting hypoxic-ischemic encephalopathy (HIE) in neonates cause significant mortality and long-term morbidities. HIE is a subtype of neonatal encephalopathy (NE), characterized by a hypoxic-ischemic (HI) sentinel event around the time of birth and/or the development of the typical pattern of HI brain injury.[1] Currently, the standard treatment for neonates with HIE is therapeutic hypothermia (TH), which has improved outcomes in neonates with moderate and severe HIE. However, this treatment has several limitations: a sentinel event is not always clearly identified, and thus, clinical criteria for treatment are not met (eg, delays in diagnosis exceeding the optimal time limit for initiating TH); many hospitals around the world lack the resources to provide TH safely and reliably; and up to 29% of treated neonates still

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Abbreviations	
aEEG	Amplitude-integrated electroencephalogram
cEEG	Continuous video electroencephalogram
EEG	Electroencephalogram
EPO	Erythropoietin
HI	Hypoxic-ischemic
HIE	Hypoxic-ischemic encephalopathy
HRV	Heart-rate variability
IV	Intravenous
MSC	Mesenchymal stem cell
NAA	*N*-acetylaspartate
NMDA	*N*-methyl-D-aspartate
NE	Neonatal encephalopathy
NSC	Neural stem cell
RCT	Randomized controlled trial
TH	Therapeutic hypothermia
UCBC	Umbilical cord blood cell

develop disabilities despite TH.[2,3] Therefore, there is an important need for alternative treatment options for HIE.

In this review, the authors review the initial assessment of neonates when faced with a clinical suspicion of HIE, the current management practices for HIE, as well as the outcomes of the affected children.

EVALUATION AND ASSESSMENT

NE is an altered level of consciousness, seizures, hypotonia, and altered reflexes in a neonate.[2] Although determining the cause of NE is not always straightforward, HIE is one of the most frequent causes.[4] The presentation of neonates with NE may thus vary,[5] because the origin of the NE may differ and/or the HI event may have occurred at a different time during the peripartum or intrapartum period. A low or variable level of consciousness, reduced spontaneous movements, seizures, low Apgar scores, or resuscitation at birth should prompt timely and thorough evaluation by neonatal health care providers.[6] Following resuscitation and stabilization, determination of eligibility for TH should be initiated as soon as possible within the first 6 hours of life. The initial evaluation should also investigate the cause of the NE, even though a clear cause is not always identified. Maternal history, obstetric history, and intrapartum events are relevant to collect to determine if an HI event is at cause for the NE.[1]

Clinical and Biochemical Assessments

All neonates born at or after 36 weeks with a history of a sentinel HI event, a need for significant resuscitation at birth, acidemia from the cord or on a postnatal gas within the first hour of life, and/or a 10-minute Apgar score of 5 or less should be assessed for TH eligibility assessment (**Fig. 1**).[7] Sentinel events may include a variety of events, such as maternal (eg, uterine rupture), fetal (eg, fetal heart rate abnormalities), and/or placenta issues (eg, placenta abruptio).[2] Inclusion criteria for TH may vary slightly by location, but typically include evidence of fetal and/or neonatal distress associated with moderate to severe encephalopathy.[8] If a neonate meets the TH clinical criteria, but is born in a facility that does not provide this treatment, the health care providers should immediately communicate with and facilitate transfer to a center equipped to offer TH for the optimal management of these neonates.[9,10] If deemed appropriate, cooling can be started on transport for outborn neonates with servo-control devices

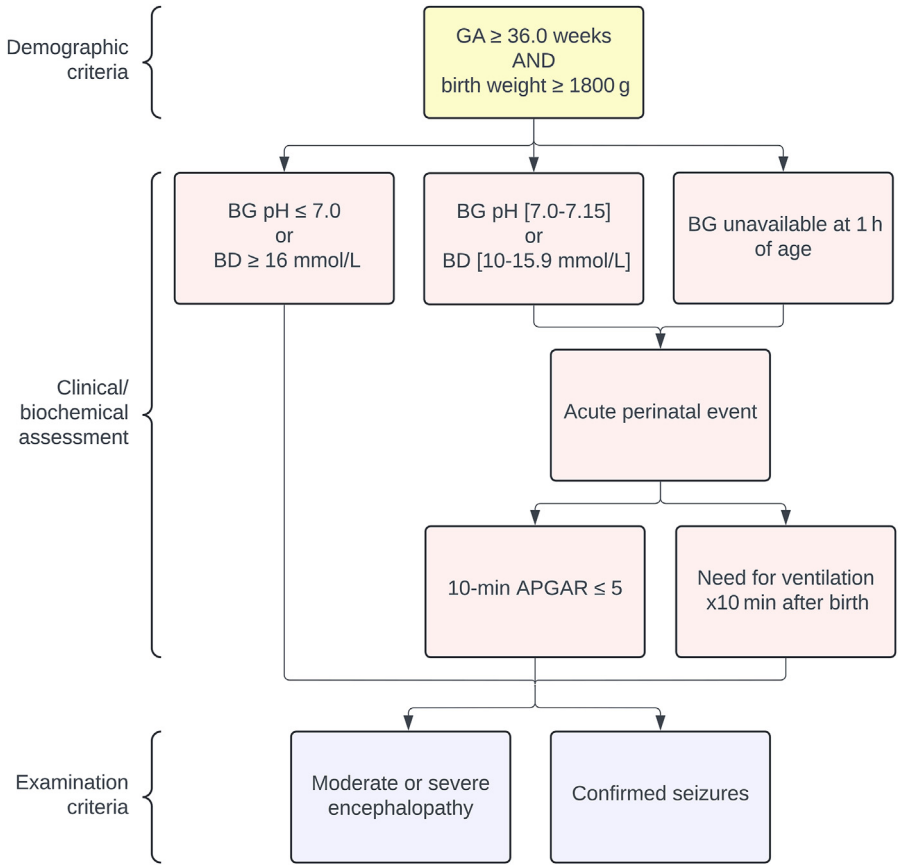

Fig. 1. Algorithm for quick assessment of eligibility for TH.[5,56] BD, base deficit; BG, blood gas; GA, gestational age.

or with closely monitored passive cooling, because it decreases the time-to-target temperature and improves outcomes.[11]

In addition to the brain, multiple organs may be affected by the NE/HIE and need to be monitored and supported until recovery. Affected neonates should be continuously monitored in terms of heart rate, respiratory rate, oxygen saturation, blood pressure, and temperature during the first days of life. Lactates levels may reflect the severity of the initial event, the hemodynamics, and/or ongoing organ injuries (brain, impaired glucose metabolism, and so forth).[12] Cardiac troponin I and creatine-kinase levels may more specifically reflect the hemodynamics.[13] Creatinine values are important indicators of acute kidney injury.[14,15] Glucose imbalance may worsen injury.[16] Other issues important to monitor are electrolytes abnormalities, coagulation, and liver function tests.[5,7]

Furthermore, histopathologic examination of the placenta is recommended to highlight features that could have predisposed the neonates to NE/HIE and contributed to associated brain injury.[17,18]

Neurologic Assessment

After resuscitation and stabilization, the neonates meeting TH clinical/biochemical criteria should be evaluated through a standardized neurologic examination within

the first hours of life.[5] The most used scoring systems to determine the level of NE include the modified Sarnat score[5] and the Thompson score.[19–22] The modified Sarnat is based on the Sarnat scoring system, which has been modified over the years to enhance its application in clinical trials.[23] It is the score that has been the mostly widely used in TH trials.[24–28] This scoring system requires categorization of encephalopathy according to level of consciousness, spontaneous activity, posture, muscle tone, primitive reflexes, and autonomic reflexes[29]; neonates with 3 or more findings in the stage of moderate to severe encephalopathy fulfill the neurologic criteria for TH.[30] Alternatively, the Thompson score proposes a numeric score to describe the severity of encephalopathy. The severity of encephalopathy may vary during the first hours of life, so repeated examination should be performed within the first 6 hours of life if a neonate meets the TH clinical/biochemical criteria on the initial evaluation, but not the neurologic assessment criteria.[7]

Electrophysiologic Assessment

Neonatal seizures are a common feature of NE/HIE. To optimize seizure detection and management, early monitoring using continuous video electroencephalogram (cEEG) or amplitude-integrated electroencephalogram (aEEG) is warranted.[7,31] Confirmed seizures are an additional inclusion criteria for TH.[32]

Neuroimaging

Neuroimaging studies are used to diagnose pattern and extent of brain injury and to discuss prognosis with parents.[4] MRI remains the modality of choice in this context, even if a point-of-care head ultrasound may be considered on the first day of life to rule out major intracranial hemorrhage. A brain MRI is typically obtained after rewarming for diagnosis and prognosis; it may be repeated around day 10 of life to assess the full extent of injury, especially if the initial neuroimaging findings are inconsistent with the clinical status.[2,4,33] An MRI may also safely be performed during TH without treatment interruption[34,35] and already demonstrates extent of injury by day 2 of life[36,37]; this may be useful especially when withdrawal of care is contemplated or for research purposes.[36,37]

Anatomic T1- and T2-sequences are used to detect ischemia and hemorrhage; changes may be subtle within the first days of life and become more evident by the second week of life. Diffusion-weighted imaging allows early detection of edema and thus contributes to diagnosis of injury within the first days of life. Magnetic resonance spectroscopy is also commonly used in the context of NE/HIE to assess metabolic changes occurring after HI injury[4]; lactates and *N*-acetylaspartate (NAA) are the most reported metabolites.[4,38]

MANAGEMENT

Management of neonates with NE/HIE is complex and should be personalized according to the illness severity during the first days of life.[7,39] It includes supportive treatments and TH if indicated.

Daily Management

Daily management of neonates with NE/HIE should be first supportive with the target goal to re-establish homeostasis of the different body organs/systems.[7] Ongoing cardiac dysfunction, acute kidney injury, electrolyte imbalances, impaired gas exchange, and such, may all contribute to worsening of brain injury and thus subsequent adverse neurodevelopmental outcomes.[39–42] **Table 1** highlights the clinical features of HIE, the

Table 1
System-based monitoring and management[6,15,17,70–73]

System	Clinical Features	Monitoring/Investigations	Management Considerations
Neurologic	Abnormal neurologic examination Seizures	aEEG/cEEG NIRS MRI	IV phenobarbital is first-line ASM, should be used for EEG-confirmed seizures Avoid systematic prescription of ASM at discharge
Respiratory	Hypoxemia Hypocapnia Respiratory acidosis	Cord blood gas Arterial blood gas CXR	Extubate when stable to limit hypocapnia Use pH-stat for temperature-corrected blood-gas values interpretation[7] Use lowest F_iO_2 effective to achieve P_aO_2 (50–70) mm Hg and $SpO_2 \geq 92\%$
Cardiovascular	Hypotension Shock Arrythmias Heart failure Ischemia	Blood gas Echocardiography Cardiac troponin Lactates	Correct hypotension; adjust treatment according to clinical pictures and lactates[7] Sinus bradycardia is acceptable if adequate cardiac output Consider ECMO if severe pulmonary hypertension
Metabolic	Hypoglycemia/hyperglycemia Hypocalcemia Hypomagnesemia Metabolic acidosis Hyponatremia	Blood glucose Calcium Lactates Electrolytes	Start with 10% IV dextrose, customize as needed aiming for ≥2.6 mmol/L, avoid hyperglycemia Customize IV fluids to meet electrolyte requirements
Renal	Acute tubular necrosis Oliguria Polyuria Hematuria	Urea Creatinine Fluid balance (body weight, urine output, fluid intake)	Start with 60–70 mL/kg/d of IV fluid with customized electrolytes and glucose Avoid systematic fluid restriction[7] If oliguria, management based on cause of oliguria
Hematologic	Elevated nucleated RBCs Thrombocytopenia Bleeding, DIC Thrombosis Anemia	CBC Coagulation profile	Transfuse platelets if needed Transfuse FFP if needed Transfuse cryoprecipitate if needed Give supplemental vitamin K if needed Transfuse PRBC if needed
Gastrointestinal	Feeding intolerance GI bleeding Necrotizing enterocolitis	LFTs	NPO during TH, but possible benefit of introduction of enteral breast milk if stable[7]

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Table 1
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System	Clinical Features	Monitoring/Investigations	Management Considerations
Infectious	Sepsis	CBC Blood culture	Initiate empiric antibiotics until sepsis is excluded
Temperature	Hypothermia/hyperthermia	Esophageal or rectal temperature	Start TH as soon as possible within the first 6 h of life Avoid hyperthermia
Skin	Subcutaneous fat necrosis	Regular skin examination	Frequent repositioning of neonates on cooling during TH Hyperhydration and diuretic treatment for SFN Monitor for hypercalcemia
Comfort & sedation	Discomfort Shivering		Promote nonpharmacologic approaches (holding, parental presence) Consider low-dose morphine

Abbreviations: ASM, antiseizure medication; CBC, complete blood count; CXR, chest X ray; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; $F_{I}O_2$, fraction of inspired oxygen; GI, gastrointestinal; LFTs, liver function tests; NIRS, near-infrared spectroscopy; NPO, nil per os; $P_{a}O_2$, partial pressure of oxygen in arterial blood; PRBC, packed red blood cells; RBCs, red blood cells; SFN, subcutaneous fat necrosis; Spo_2, peripheral capillary oxygen saturation.

monitoring methods, and the management considerations, classified by body organ/system. Variations in the management of neonates with HIE have been demonstrated across neonatal intensive care units (NICUs) and may explain variations in outcomes, such as death and/or brain injury.[21,43,44] Further research in a large international cohort of neonates with HIE is needed to test optimal care practice bundle.[7]

Health care providers should promote shared decision making with parents. Frequent transparent and consistent communication, including discussion of upcoming events, as well as interpretation of prognostic markers, is helpful to families. Parents may be referred to social workers, psychologists, and peer-support groups to help them navigate this event. Parents should be encouraged to get involved in the daily care of their neonate and hold their baby, even during TH.[7] This may contribute to promoting bonding, improving comfort, and decreasing stress for the neonate and the family.[45]

Therapeutic Hypothermia

Whole-body TH consists of decreasing core temperature to 33.5°C for 72 hours, followed by slow rewarming to normothermia.[27,46–49] It reduces the risk of death and severe disability when initiated within 6 hours of birth in neonates meeting TH inclusion criteria, with these benefits lasting into childhood.[50–53]

Upon HI injury, the lack of metabolic substrates to the brain leads to primary energy failure, which includes increased lactate production, excitotoxicity, cerebral edema, microvascular damage, and cell death.[54] After successful resuscitation, the brain enters a latent phase. About 6 to 8 hours later, secondary energy failure occurs with a burst of oxidative damage, inflammation, and cell death. This is thought to be due to failure to adapt to the aerobic condition following reperfusion.[55] Starting after the secondary energy failure and lasting weeks to months after, the tertiary phase takes place, with increased seizure susceptibility, persistent inflammation, and impaired connectivity and maturation.[54]

As a neuroprotective therapy, TH targets the latent phase.[56] TH prevents the injury caused by the secondary energy failure by decreasing metabolic demand, excitotoxicity, and cerebral edema, along with preventing apoptosis and stabilizing the blood-brain barrier.[55] TH should thus be initiated as soon as possible within the first 6 hours of life to maximize its chances to prevent secondary energy failure and injury.[55,56]

Whole-body cooling is usually preferred over selective head cooling, because none of the 2 methods has proven to be significantly better,[27,57] but whole-body cooling is less labor-intensive and less costly.[56] Deeper or longer cooling is not recommended.[58] Although no randomized controlled trial (RCT) has formally evaluated the rate of rewarming, neonates are typically rewarmed at a rate of 0.5°C per hour.[59] TH has been associated with systemic complications, such as sinus bradycardia, thrombocytopenia, and coagulopathy, but these issues can be monitored and managed.[60]

In the original TH trials, only the neonates with moderate to severe NE/HIE were selected.[27,46–49] However, over time, practices have deviated to include neonates with mild NE and/or to start cooling beyond 6 hours of life.[61,62] Mild HIE has also been associated with a risk of cognitive and motor impairments,[63,64] and some retrospective studies have suggested possible benefit of TH for mild HIE in reducing the incidence of MRI brain injury, and improving cognitive composite scores.[61,62,65,66] However, a recent RCT suggested that TH did not reduce brain MRI biomarkers in neonates with mild HIE.[67] Additional RCTs are ongoing in neonates with mild HIE to formally test safety and efficacy of TH. The only published RCT about late (ie, beyond 6 hours of life) cooling did not demonstrate significant benefits.[58]

Another area of uncertainty is whether TH is safe and efficient in late preterm neonates. Two TH RCTs used 35.0 weeks of gestational age as the lowest boundary of the demographic inclusion criteria and demonstrated the benefit of TH; however, the number of neonates born between 35.0 weeks and 35.6 weeks in both studies was small.[47,68] Although some retrospective studies suggest that the use of TH for the treatment of HIE in preterm (34.0–35.6 weeks of gestational age) neonates is safe and feasible,[69] a formal RCT is ongoing to test its safety and efficacy. Until then, the decision to cool late preterm neonates should be based on clinical judgment and shared decision making with families.[3]

Therapies Under Investigation

Although TH may *prevent* the development of brain injuries in some neonates with HIE by avoiding the secondary energy failure after birth asphyxia, it is often not successful,[28,46,48,70–73] because up to 30% of the neonates with HIE treated with TH still develop brain injury and thus significant neurodevelopmental impairments.[27,74] Also, it remains debated if TH is efficient in low- and middle-income countries.[75] The search for further therapies is thus actively ongoing. **Table 2** presents a summary of the therapeutic interventions currently being investigated, classified by mechanisms of action. The authors differentiated neuroprotective therapies *preventing* the development of brain injuries and neurorestorative therapies *repairing* brain injuries. Here some of these potential therapies are discussed. For many of these therapies, optimal dosing and timing of treatment to give the therapy still need to be determined.

Neuroprotective therapies

Melatonin. In animal models of HIE, melatonin was neuroprotective as a monotherapy and as an adjunct therapy to TH with a potentiating effect.[76] In preclinical models, effect was optimal when administered in the hours after the initial event.[77] Dosage varied between 10 and 20 mg/kg with a first dose right after injury, and repeat doses usually at 24 and 48 hours after injury, mostly through intraperitoneal route.[78] So far, in human clinical trials, both the intravenous (IV) and the oral routes are being explored.[79] A few RCTs in human neonates have demonstrated encouraging results,[79,80] although sample sizes remained small.[81] Larger RCTs are needed to establish safety and efficacy of melatonin.

Allopurinol. Allopurinol is a xanthine oxidase inhibitor with antioxidative action.[82] In preclinical models, allopurinol was given as a single intraperitoneal injection 15 minutes after the HI event.[83] A phase III RCT is underway to evaluate outcome in neonates with HIE receiving allopurinol in addition to TH. In this trial, neonates are receiving a first dose of allopurinol intravenously less than 30 minutes after birth, and a second dose 12 hours later.[84]

Caffeine. Caffeine, which is already widely used in the NICU for apnea of prematurity, has been suggested as an adjuvant to TH.[85] Preclinical studies have suggested improved functional outcomes when combined with TH.[86] In studies in rodents, caffeine was given intraperitoneally or enterally.[86] It appeared to reduce moderate to severe brain damage only when given directly after the HI injury, but not 6, 12, or 24 hours later.[87] In a phase I trial in human neonates, a loading dose of 20 mg/kg of caffeine citrate was given intravenously, with up to 2 subsequent doses of 5 mg/kg at 24-hour intervals,[88] without significant adverse event.[88]

Magnesium sulfate. Magnesium sulfate therapy may modulate the *N*-methyl-D-aspartate (NMDA) receptors and, through this mechanism, reduce excitotoxicity.[89] In preclinical models, it has been used both prenatally and postnatally for

Table 2
Novel therapeutic agents by mechanism of action (by alphabetical order)[55,78,81,82,84,86,88,90,97,102,107,111,126,143–145]

	Neuroprotective					
Therapies	**Antiexcitatory**	**Antiapoptotic**	**Anti-inflammatory**	**Antioxidative**	**Neurorestorative**	**Route, Dosing, and Schedule**
Allopurinol			✓	✓		Pre: IP, 135 mg/kg immediately post-HI RCT: IV, 20 mg/kg post-HI (30 min after birth) + 10 mg/kg H12 if TH
Azithromycin			✓			Pre: IV or IV, 1.5–150 mg/kg 15 min–4 h post-HI or 2 h post-HI + H24 + H48
Caffeine			✓			Pre: IP or PO, 5–20 mg/kg immediately post-HI RCT: IV, 20 mg/kg post-HI (before 24 h of life) + 5 mg/kg q24h ×2 doses
Erythropoietin	✓	✓	✓	✓	✓	Pre: IV, 5000 U/kg 3 h post-HI + 833.3 U/kg/h × 69 h or 1000 U/kg immediately post-HI + H24 + D7 RCT: IV, 1000 U/kg post-HI (before 26 h of life) + D2 + D3 + D4 + D7
$MgSO_4$	✓	✓	✓	✓		Pre: IP, SC, or IV, 100–1000 mg/kg immediately post-HI RCT: IV 250 mg/kg within 6 h post-HI + H24 + H48
Melatonin	✓	✓	✓	✓		Pre: IP, 10–20 mg/kg immediately post-HI + H24 + H48 or 0.5 mg/kg/h infusion × 2 h or 10–15 mg/kg immediately post-HI RCT: PO or IV, single dose on admission or q2h ×8 doses or daily ×3–5 d

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Table 2
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	Neuroprotective					
Therapies	**Antiexcitatory**	**Antiapoptotic**	**Anti-inflammatory**	**Antioxidative**	**Neurorestorative**	**Route, Dosing, and Schedule**
Sildenafil		✓	✓		✓	Pre: IP immediately post-HI or PO 12 h post-HI RCT: PO 2–3 mg/kg q12h × 7 d starting D2/3
Stem cells		✓	✓		✓	Variable, usually single dose
TH	✓	✓	✓			33.5°C × 72 h started within 6 h
Topiramate	✓					Pre: IP 20–100 mg/kg immediately post-HI + H2 or PO 50 mg/kg immediately post-HI + H2 + q12h × 5 d RCT: PO 5 mg/kg post-HI (at TH initiation) + 3 mg/kg/d × 5 d
Xenon	✓	✓				Pre: Inhaled 50% Xe × 3 h immediately or up to 2 h post-HI RCT: Inhaled 30% Xe × 24 h immediately post-HI

Abbreviations: D, day postinsult; H, hours postinsult; IP, intraperitoneal; $MgSO_4$, magnesium sulfate; PO, oral administration; Pre, preclinical studies; SC, subcutaneous; Xe, xenon.

neuroprotection. For postnatal administration, rodents received a single dose between 100 and 1000 mg/kg by subcutaneous or intraperitoneal route, whereas large animals received 160 to 400 mg/kg IV.[90] In a clinical trial in 134 neonates testing magnesium sulfate as an adjunct to TH, the neonates received either 250 mg/kg of magnesium sulfate IV within 6 hours of birth, with 2 subsequent doses at 24-hour intervals, in addition to TH, or TH only; magnesium sulfate therapy in addition to TH did not significantly reduce neonatal mortality and neurodevelopmental outcome at 1 year of age.[91] Another clinical trial with a sample size of 200 neonates followed the same regimen of administration of magnesium sulfate as monotherapy and suggested that it improved mortality and short-term outcome defined as early discharge and oral feeding.[92] However, a systematic review and meta-analysis, including 20 RCTs and a total of 1485 infants, found that, when used alone, magnesium sulfate did not significantly reduce death or abnormal neurologic examination at NICU discharge.[93]

Topiramate. Topiramate is an antiseizure medication used for treating neonatal seizures, with potential neuroprotective properties, primarily through antiexcitatory mechanisms. In preclinical models, monotherapy reduced brain injury,[55,94] when administered in rodents as 2 intraperitoneal injections (20–100 mg/kg), immediately after and 2 hours after the HI event, or by oral route (50 mg/kg) immediately after the HI event, 2 hours after, and at 12-hour intervals for 5 days.[95] All formulations were neuroprotective, but starting treatment 2 hours after HI was not protective.[95] An RCT with 110 neonates with HIE, who received either topiramate at an initial dose of 5 mg/kg and maintenance dose of 3 mg/kg/d for 5 days orally in addition to TH or a placebo, showed a trend toward less mortality and seizures, but the difference was not significant; no improvement was seen on MRI brain injuries.[96]

Xenon. Xenon is a noble gas, which acts as a noncompetitive antagonist of the NMDA subtype of the glutamate receptor and decreases excitotoxicity and apoptosis.[97] Preclinical studies have shown that xenon attenuated brain damage and improved neurobehavioral function.[97] Although xenon acted synergistically with TH, it was most effective as monotherapy.[97] An RCT in 92 neonates with HIE demonstrated that administration of xenon was safe and feasible, but did not demonstrate improvements in MRI markers of brain injury,[98] and did not report long-term neurodevelopmental outcome.[99]

Azithromycin. Azithromycin is an antibiotic with anti-inflammatory properties.[100] In rodent models of HIE, azithromycin administered intraperitoneally with a 3-dose regimen beginning 2 hours post-HI (45.0 mg/kg), and repeated at 24 hours and 48 hours (22.5 mg/kg), was most effective at improving sensorimotor function and reducing the extent of brain damage, although single-dose protocols still displayed neuroprotection, with efficacy depending on dose and time to treatment.[100] In lambs, IV azithromycin treatment allowed earlier extubation, improved ability to feed and activity assessed in the first week of life.[101] Research in preclinical models of HIE is ongoing to look into the efficacy and safety of azithromycin combined with TH.[102] No RCTs have yet investigated the safety or efficacy of azithromycin in the context of neonatal HIE; its previous use in neonates has been associated with QT prolongation.[102]

Neurorestorative agents

Most of these neurorestorative therapies aimed at repairing brain injuries may also have neuroprotective properties.

Erythropoietin. Erythropoietin (EPO) was proposed as another potential therapy for neonatal HIE after it displayed neuroprotective and neurorestorative effects in

preclinical models.[103] It acts in the brain by decreasing neuronal death and promoting neurogenesis and angiogenesis.[103] In preclinical studies in a lamb model of HIE, who received a loading dose of 5000 units/kg of recombinant EPO IV, followed by continuous infusion of 833.3 unit/kg/h for 72 hours, with or without TH, neuroprotection was observed from both TH and EPO individually.[104,105] However, EPO had limited additional benefits when given in combination with TH.[104,105] After phase I and phase II trials demonstrated the safety of EPO for neonates with HIE,[106–108] a larger phase III RCT in 500 neonates with HIE did not demonstrate significant benefit regarding the combined death and neurodevelopmental outcome at 22 to 36 months of age.[109] Additional trials testing this therapy are ongoing.[110] Darbepoetin, a longer-acting form of EPO, is also being tested in neonates with HIE.[111,112] The timing and the dose of EPO may be crucial factors to obtain its full effects.

Stem cells. Stem cells therapies have been widely investigated in the last years. In the context of HIE, most promising sources include umbilical cord blood cells (UCBCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs).[113] UCBCs could be used for autologous transplantation and may thus have low immunogenic potential. Various sources of stem cells have been tested in rodents, such as UCBCs, umbilical cord tissue-derived MSCs, placenta-derived MSCs, endothelial progenitor cells, or bone-marrow MSCs; they were given intraperitoneally, intravenously, intrathecally, or via the intraventricular route, and the time of treatment varied between 3 hours post-HI and 3 weeks post-HI, with some studies using a single dose, whereas others using repeated doses.[114,115] In preclinical models, UCBCs promoted neurogenesis, differentiation, and maturation of NSC and angiogenesis, in addition to having antiapoptotic and anti-inflammatory effects.[113] Clonally expanded immortalized MSCs from adult bone marrow grafts have been delivered intranasally in a rodent model of neonatal HIE, producing a stronger anti-inflammatory effect and inducing neural regeneration,[114] reducing HI-induced cognitive deficits in adolescence.[114] Phase I trials in neonates with HIE have deemed the administration of autologous UCBCs to be safe and feasible.[113,116,117] Additional studies are needed to determine the optimal type of stem cells, and the best timing and method of delivery in the context of neonatal HIE.

Interestingly, a recent RCT evaluating cord milking in 1730 neonates demonstrated that it reduced the rate of moderate to severe HIE and the need for TH.[118] This result widely contrasted with the practice of avoiding delayed cord clamping in nonvigorous term and near-term neonates. It led to a change in the Neonatal Resuscitation Program recommendation on cord handling, and now the option of cord milking in nonvigorous term and near-term neonates is included.[119]

Sildenafil. Sildenafil is a phosphodiesterase type 5 inhibitor, already used in neonates for the treatment of pulmonary hypertension. It has been found to prevent neuronal death, enhance neurogenesis and synaptic plasticity, and improve motor outcomes in preclinical models of HIE.[120–122] In these models, sildenafil was administered either intraperitoneally immediately after HI[123,124] or enterally with a delay after HI.[121,122] Moreover, it appeared to have a synergistic effect in reducing neuroinflammation when administered along with TH.[125] A phase I RCT demonstrated the feasibility and safety of administering sildenafil along with TH in a limited number of neonates with HIE.[126] Further trials are needed to assess efficacy.

Outcomes. In neonates with HIE, TH has improved survival without major neurologic disabilities at 18 months,[27,53,60,127] and this beneficial effect persisted at least until 6 to 7 years of age.[53] However, worldwide, HIE remains the second leading cause of

nervous system disability-adjusted life-years, a time-based measure combining years of life lost owing to premature mortality and years of healthy life lost owing to disability.[128] More than one million infants still die annually from birth asphyxia and the resulting neonatal HIE, especially those with severe HIE[5,129]; one in 4 HIE survivors still develop significant neurodevelopmental sequelae.[53,130,131] Children who survive neonatal HIE are at risk for major disabilities, including cerebral palsy (especially spastic quadriplegia and dyskinetic subtypes), cognitive delay, epilepsy, hearing loss, and blindness, depending on the associated brain injury.[2,5] Among children without major disabilities, many will demonstrate cognitive, educational, and behavioral issues affecting their school-readiness.[53,132] Sequential neurodevelopmental follow-ups through childhood are essential for early detection of neurodevelopmental disabilities and interventions in these children.[66]

Predictors of Outcome

MRI

Neuroimaging is a sensitive prognostic tool for HIE.[4] Basal-ganglia-thalamus injury pattern, watershed injury pattern, and near-total injury pattern are the most frequently observed patterns in neonates with HIE.[4] Different scoring systems have been developed to standardize the description of brain injury and have been shown to successfully predict adverse outcomes at 18 to 24 months[4,133] and potentially up to 6 to 7 years of age.[4,133] Neonates without brain injury on MRI are unlikely to develop substantive motor of cognitive deficits.[53,133] In addition, decreased NAA and increased lactate-to-NAA ratio measured in the thalamus by magnetic resonance spectroscopy (MRS) have been shown to be a highly sensitive and specific marker for predicting adverse outcomes at 2 years.[4] Further MRI biomarkers may need to be developed to test efficacy of neurorestorative therapies.

Amplitude-integrated electroencephalogram/electroencephalogram

Electrophysiology is useful to guide clinical management and for prognostication. Although single recordings may have low specificity and sensitivity, serial electroencephalograms (EEGs) or continuous EEG have better prognostic value. The severity of EEG abnormalities is correlated with the severity of neurologic insult and can help identify neonates who are at risk of adverse outcomes.[134] A cohort study found that selected features of aEEG (eg, continuity, background) at 6 and 24 hours of life were significantly correlated with early clinical outcome.[135]

Other biomarkers

Recent studies have suggested serum lactates in the first 6 hours of life or on the fourth day of life as an independent predictor of adverse outcomes in neonates with HIE treated with TH.[136] Measurement of heart-rate variability (HRV) via continuous recordings of electrocardiogram has also been shown to consistently predict the neuroimaging and neurodevelopmental outcomes of these neonates, with a higher HRV being associated with more favorable outcomes.[137,138] Blood biomarkers, such as serum tau protein,[139] S100B,[140] neuron-specific enolase,[141] and neutrophil-to-lymphocyte ratio,[142] have been studied to predict the severity of HIE and neurodevelopmental outcomes; however, validation studies in a larger sample is necessary before these markers can be used in clinical practice.[139,141,142]

SUMMARY

In conclusion, although TH has significantly improved short- and long-term outcomes of neonates with HIE, birth asphyxia remains a significant cause of mortality and long-

term neurodevelopmental disabilities in children around the world. The limitations of TH underscore the need for alternative treatment approaches. Ongoing research into novel therapeutic agents, particularly those with neurorestorative properties, holds promise for improving outcomes of neonates with HIE, especially those ineligible or nonresponsive to TH.

Best Practices

What is the current practice for hypoxic-ischemic encephalopathy (HIE)?

Therapeutic hypothermia (TH) is the current standard of care treatment for HIE.

Best Practice/Guideline/Care Path Objective(s)

To provide controlled TH to prevent further brain injury, and to re-establish homeostasis of the different body organs/systems to prevent further brain injury.

What changes in current practice are likely to improve outcomes?

Variations in the management of neonates with HIE have been demonstrated across NICUs and may explain variations in outcomes, such as death and/or brain injury. Further research in large international cohort of neonates with HIE is needed to test optimal care practice bundle.

Is there a Clinical Algorithm?

See **Fig. 1**

Pearls/Pitfalls at the point-of-care

See **Table 1**

Major Recommendations

Daily management of neonates with NE/HIE should be first supportive with the target goal to re-establish homeostasis of the different body organs/systems. Ongoing cardiac dysfunction, acute kidney injury, electrolytes imbalance, impaired gas exchange, and similar may all contribute to worsening brain injury and thus subsequent adverse neurodevelopmental outcomes. Health care providers should promote shared decision making with parents. Parents should be encouraged to get involved in the daily care of their neonate and hold their baby, even during TH.

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