Treatment of Hypoxic-Ischemic Encephalopathy in Newborns

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Opinion statement

Hypoxic-ischemic (HI) brain injury is the most common cause of encephalopathy and seizures in term newborn infants. There is no single, valid test for birth asphyxia leading to HI brain injury, and thus this disorder is often poorly characterized, and the timing and etiology of the injury can be difficult to ascertain. Optimal management of HI brain injury involves prompt resuscitation, careful supportive care including prevention of hyperthermia and hypoglycemia, and treatment of clinical and frequent or prolonged subclinical seizures. Recent evidence suggests that therapeutic hypothermia by selective head or whole-body cooling administered within 6 hours of birth reduces the incidence of death or moderate/severe disability at 12 to 22 months. Hypothermia is a promising new therapy that physicians should consider within the context of a registry or study. Optimal seizure treatment remains controversial because the most widely used drug, phenobarbital, has limited efficacy, and the value of monitoring and treating subclinical seizures is uncertain. There is compelling need for well-designed clinical trials to address treatment of ongoing brain injury in the setting of hypoxia-ischemia and seizures. Emerging evidence from preclinical studies suggests that future therapy for HI brain injury and neonatal encephalopathy will combine novel neuroprotective and anti-seizure agents. Pilot clinical trials of newer anticonvulsants are ongoing and will provide critical information for care of neonatal seizures.

Introduction

Neonatal encephalopathy due to perinatal hypoxic-ischemic (HI) brain injury is a significant cause of infant mortality and morbidity. In spite of improvements to obstetric and neonatal care, the incidence of HI encephalopathy (HIE) remains approximately 2 to 4 per 1000 live-term births. Although mild injuries leave little or no sequelae, more severe insults may result in cerebral palsy, mental retardation, epilepsy, and visual deficits.

Neonatal encephalopathy is a heterogeneous condition. There are no practical, valid markers of birth asphyxia in term neonates. Therefore, a diagnosis of HIE in an encephalopathic newborn involves evaluating the clinical history and biomarkers for evidence of preceding insult (as indicated by markers of fetal distress such as fetal heart rate abnormality, low Apgar scores, and cord blood acidosis). The differential diagnosis includes other causes of encephalopathy such as metabolic disturbance, intracranial hemorrhage, acute ischemic stroke, cerebral sinovenous thrombosis, intracranial infection, and drug exposure.

HI brain injury can result in encephalopathy, hypotonia, and brainstem dysfunction including impaired feeding and need for respiratory support. Seizures are common and typically occur within the first 24 hours of life. An easy scoring system adapted from the Sarnat stages of encephalopathy can be used to characterize the severity of injury and follow the progress of the newborn with encephalopathy (Table 1) [1]. Systemic HI injury

Table 1. Encephalopathy score for neonates*

Sign	Score 0	Score 1
Feeding	Normal	NPO, gavage or gastrostomy feeds, impaired oral feeding
Alertness	Alert	Irritable, poorly responsive, or comatose
Tone	Normal	Hypotonia or hypertonia
Respiratory status	Normal	Respiratory distress (need for CPAP or mechanical ventilation)
Reflexes	Normal	Hyperreflexia, hyporeflexia, or absent reflexes
Seizure	None	Suspected or confirmed clinical seizure

*Children are scored (0–6) daily for the first 3 days of life. Both first day of life and maximal encephalopathy score are predictive of neurodevelopmental outcome.
CPAP—continuous positive airway pressure; NPO—nothing by mouth.
(*Adapted from* Miller et al. [1].)

may lead to an increase in liver enzymes and creatinine, low urine output, and, in severe cases, cardiac dysfunction. However, multiple organ involvement is not necessary for the diagnosis of HIE.

The most common cause of seizures in term infants is neonatal encephalopathy due to HI brain injury. Seizures in this setting are associated with increased risk of neurodevelopmental disability and death. Evidence from animal models suggests that seizures themselves exacerbate neuronal injury through release of excitatory neurotransmitters, and, in the case of clinical seizures, fluctuations in brain oxygenation and perfusion [2–4]. Seizures may also worsen secondary neuronal injury by increasing cerebral metabolic demand, and seizures in human infants with HI brain injury are associated with increased lactate/choline on magnetic resonance spectroscopy [4]. The seizures are usually multifocal and often subclinical (electrographic) only. A diagnosis of stroke from arterial or venous thrombosis should be considered in cases in which the seizures are persistently focal. Serial or continuous electroencephalogram evaluation is useful in detecting seizures and helping to identify infants who will have a poor neurodevelopmental outcome. Markedly abnormal background pattern or inactive recording persisting beyond the first 8 to 24 hours of life indicates a poor prognosis [5,6]. Cerebral function monitoring is now being used worldwide to record a filtered, compressed, amplitude-integrated electroencephalogram (aEEG) from a small number of channels (usually one or two) in infants with suspected HI injury. The advantages of aEEG are its immediate availability, ease of application, and interpretation by bedside nursing staff and physicians. The evolution of the aEEG background pattern over the first hours to days of life is also helpful in predicting prognosis, with better outcome in infants who develop a normal background sooner [7•].

Neuroimaging is helpful in assessing cause of encephalopathy and, if injury is present, in determining the severity, timing, and mechanism [8••]. MRI, especially with diffusion-weighted imaging and spectroscopy, is the technique of choice. Magnetic resonance spectroscopy lactate peak may be present as soon as the first day of life; however, the full extent of HI injury is rarely evident this early. Conventional T1- and T2-weighted images typically show abnormalities between 2 to 3 (T1) and 6 to 7 days (T2) after the injury. Injury on diffusion-weighted images is maximal at 4 days after the injury [9], which makes this an optimal time to image an encephalopathic infant. Acute, profound injury, such as that seen with placental abruption or cord rupture, affects predominantly deep gray matter, including thalami (ventrolateral nucleus), basal ganglia (especially posterior putamen), and sometimes the hippocampi, rolandic cortex, and cerebellum [10]. Parasagittal or watershed injury follows prolonged partial asphyxia and involves cerebral convexities bilaterally in the zones of watershed between the anterior, middle, and posterior cerebral arteries [11]. Focal cortical injuries are seen in approximately 5% of infants with neonatal encephalopathy and are risk factors for HI injury [12]. Magnetic resonance angiography and venography should be performed in the case of stroke to identify the involved vessels. Thalamic hemorrhage in a term neonate is most often due to deep venous thrombosis [13]. In general, the pattern of injury seen on MRI correlates with outcome. The central pattern involving the deep gray nuclei is seen more often in children with severe encephalopathy, seizures, and worse neurodevelopmental outcome [14]. Abnormal signal intensity in the posterior limb of the internal capsule has high sensitivity and specificity for abnormal neurodevelopmental outcome [15], but this sign is typically not present until the third day after the injury [9]. Low N-acetylaspartate and high lactate concentrations in the basal ganglia are associated with poor neurodevelopmental outcome [16]. In centers where MRI is not available, CT performed with appropriate window and level settings for a neonate may show decreased attenuation in a parasagittal, deep grey nuclei, or combined pattern. Ultrasonography is important for rapid initial assessment of a sick neonate to identify hemorrhage or space-occupying lesions. However, CT (or preferably MRI) in the subacute phase should supplement ultrasonography to evaluate the full extent of injury. Echogenic

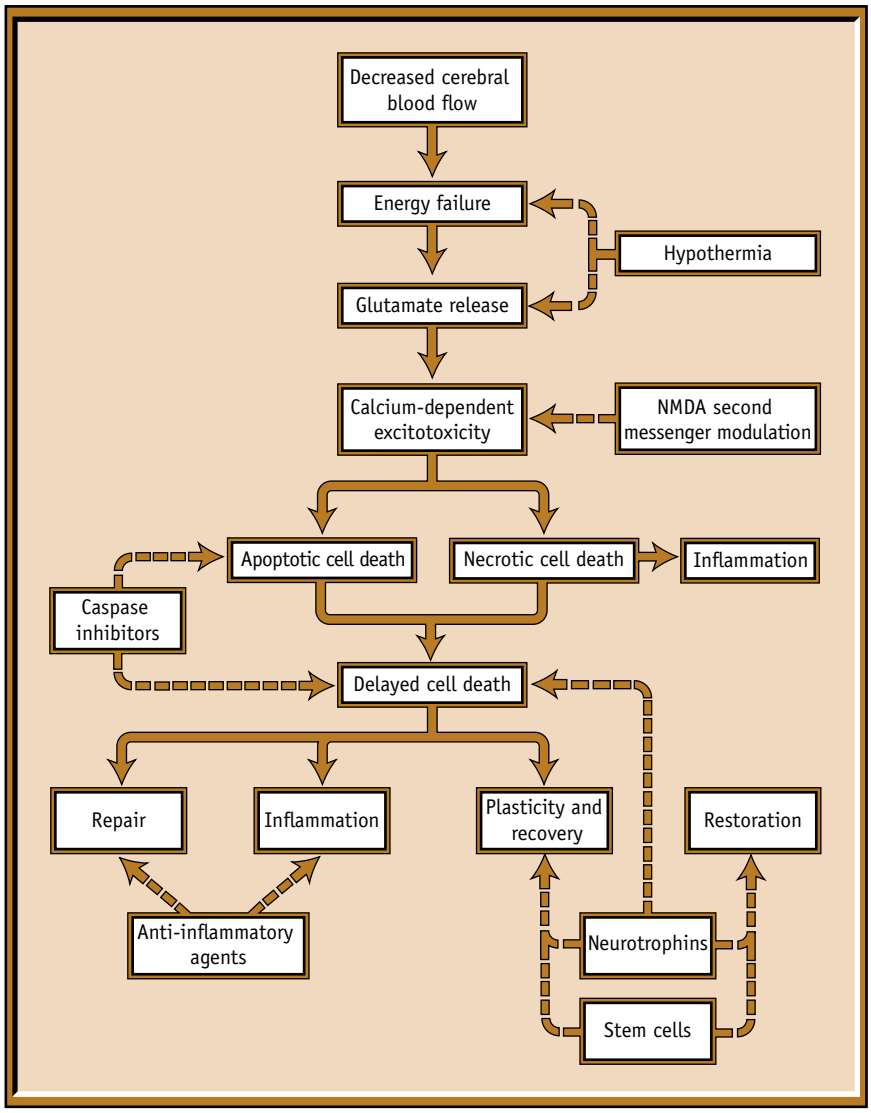

Figure 1. Neurotoxic cascade in hypoxia-ischemia. Impaired cerebral blood flow leads to energy failure, cell depolarization, and glutamate release. The initial insult may result in necrosis and apoptosis by calcium-dependent pathways. Injury, repair, and recovery evolve over days to months. Potential neuroprotective agents include excitatory amino acid antagonists, oxygen free-radical inhibitors, and scavengers, anti-inflammatories, and neurotrophic growth factors. NMDA—N-methyl-D-aspartate.

thalami seen on head ultrasound developing 3 to 4 days after injury represent a severe basal ganglia pattern of injury and predict poor prognosis [17].

HI brain injury is initiated by impaired cerebral blood flow due to disruption in placental perfusion and gas exchange and evolves over hours to days [18••,19••]. The acute injury leads to oxygen depletion and a shift to anaerobic metabolism, which results in depletion of high-energy phosphate reserves, accumulation of lactic acid, and failure of cell membrane homeostatic mechanisms (Fig. 1). The disruption in ion pumping leads to intracellular accumulation of sodium, calcium, and water, which depolarizes the cell and causes release of excitotoxic neurotransmitters, including glutamate. An increase in phospholipid turnover leads to accumulation of fatty acids, which undergo peroxidation. Calcium ion accumulation results in excessive production of the free radical nitric oxide. Depending on its duration and severity, the initial insult may lead to cell death by necrosis. After reperfusion, a more complex secondary phase of cell injury ensues. The result is a trigger of apoptotic pathways due to the accumulation of calcium, free radicals, nitric oxide, and inflammatory mediators. These secondary processes evolve over days to weeks and possibly months after the injury.

Ongoing investigation of the mechanisms of brain injury after hypoxia-ischemia is driving the search for novel neuroprotective agents and anti-seizure therapies. Candidate agents include oxygen free-radical inhibitors and scavengers, excitatory amino acid antagonists, anti-inflammatories, and growth factors. There is a strong need for well-designed clinical trials based on preclinical evidence to evaluate the efficacy of these agents in minimizing brain injury and maximizing neurodevelopmental outcome after HI insult.

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Treatment

Resuscitation and supportive care

Normothermia

- Encephalopathic infants should be kept normothermic, and iatrogenic hyperthermia should be avoided [20, Class I]. A secondary data analysis of the results from the CoolCap trial of selective head cooling showed that infants with pyrexia 38° C or more had a higher rate of unfavorable outcome (OR = 3.2; 95% CI = 1.2–8.4; $P = 0.03$) [20, Class I]. This recent study supports animal experiments and adult stroke data, which show worsening neuropathologic and functional neurologic outcome in subjects with hyperthermia/fever [21–23].

Normoglycemia

- Hypoglycemia may augment brain injury in the setting of hypoxia-ischemia; therefore, serum glucose should be maintained within the normal range [24, Class II]. In a retrospective cohort study of 185 term infants with umbilical arterial pH less than 7, the children with hypoglycemia (blood glucose ≤ 40 mg/dL) had an increased risk of short-term abnormal neurologic outcome including death or moderate to severe encephalopathy (OR = 6.3; 95% CI = 2.6–15.3). It is unclear from this study if early identification and treatment of hypoglycemia would have resulted in better outcome; however, the results are consistent with the known effect of hypoglycemia on animal models of brain injury [25].

Permissive mild hypercapnia

- Infants should be adequately ventilated, and low arterial carbon dioxide tension should be avoided (Class III). Studies using immature rats (human equivalent 32–34 weeks gestational age) suggest that normocapnic animals sustain less HI injury than hypocapnic animals and that mild hypercapnia is protective [26].

Adequate cerebral perfusion

- Blood pressure should be carefully monitored and maintained within the optimal range for gestational age to avoid cerebral ischemia or overperfusion (Class III).

Room air versus 100% oxygen

- A Cochrane Collaboration review of all randomized and quasi-randomized trials of room air versus 100% oxygen for resuscitation found that there was insufficient evidence to recommend use of either method [27, Class I]. The meta-analysis showed a reduction in mortality (RR = 0.71; 95% CI = 0.54–0.94) with room air; however, the number of studies was small, and methodologic limitations, including back-up use of 100% oxygen in more than 25% of infants randomized to room air, make interpretation of these results difficult.

Resuscitation training

- A cohort observational study [28, Class II] of obstetric emergency training in term, cephalic singleton infants born at Southmead Hospital (Bristol, UK) between 1998 and 2003 suggested that there is an associa-

tion between training in obstetric emergencies and a reduced incidence of 5-minute Apgar score of 6 or less and HIE.

Fluid management

- Recommendations for judicious fluid restriction to minimize cerebral edema in infants with HIE are based on extrapolation from older children and adults [29, Class III]. A recent Cochrane Collaboration review found that there were no randomized trials assessing the use of fluid restriction for perinatal HI injury.

Electrolyte balance

- Serum electrolytes, including sodium, calcium, and magnesium, should be monitored and maintained within the normal range (Class III).

Hypothermia

- Mild to moderate systemic or isolated head hypothermia (33–34° C) applied within 6 hours of an acute asphyxial event in term newborns reduces 12- to 22-month neurodevelopmental disability [30••,31,32••,33••, Class I].
- Three multicenter, randomized controlled trials evaluated the safety and efficacy of hypothermia (Table 2) [30••,31,32••,33••, Class I]. Eicher et al. [30••,31, Class I] randomized 65 term infants with one clinical sign and two neurologic findings of HIE to moderate systemic hypothermia (33° C) versus standard care. Treatment was initiated within 6 hours of birth and lasted 48 hours. The combined outcome of death or severe motor score at 12 months was lower in the hypothermia group (52%) than in the control group (84%; RR = 0.62; 95% CI = 0.41–0.92; P = 0.02). Shankaran et al. [33••, Class I] randomized 208 term infants with abnormal umbilical-cord blood gas and encephalopathy or seizures to treatment with systemic hypothermia (33.5°C) versus standard care. Hypothermia was initiated within 6 hours and maintained for 72 hours. Death or moderate to severe disability at 18 to 22 months of age was lower in the hypothermia group (44%) as compared with the control group (62%; RR = 0.72, 95% CI = 0.54–0.95; P = 0.01). Gluckman et al. [32••, Class I] randomized 234 term infants with severe neonatal encephalopathy and abnormal aEEG to selective head cooling for 72 hours within 6 hours of birth, versus standard care. The primary outcome was death or severe disability at 18 months. Unadjusted logistic regression analysis favored hypothermia treatment (OR = 0.61), although the result did not reach statistical significance (95% CI = 0.34–1.09; P = 0.1). Subgroup analysis showed that the group with moderate encephalopathy (as determined by aEEG) drove the favorable outcome. Predetermined subgroup logistic regression analysis of the 172 patients with moderate aEEG changes favored the hypothermia group, with an OR of 0.42 (95% CI = 0.22–0.80; P = 0.009).
- All three trials noted reversible cardiovascular effects, including bradycardia and hypotension requiring vasopressors. Eicher et al. [31, Class I] also reported higher prothrombin times and lower platelet counts, with more children in the treatment group requiring plasma and platelet transfusion.
- Evidence from animal studies suggests that hypothermia acts to prolong the latent phase before secondary energy failure, that the duration of

Table 2. Randomized, controlled clinical trials of hypothermia in term infants with hypoxic-ischemic birth injury and neonatal encephalopathy

Study	Study years	Patients enrolled (treated/control)	Severity of encephalopathy, *n* (%)	Treatment	Primary outcome	RR/OR (95% CI)
Eicher et al. [30••, Class I]	1998–2001	32/33	Sarnat stage: III = 50 (81); II = 10 (16); I = 2 (3)	Systemic hypothermia with target rectal temperature ± 33° ± 0.5° C for 48 hours	Death or severe disability (BSID PDI < 70) at 12 months	RR = 0.62 (0.41– 0.92)
Gluckman et al. [32••, Class I]	1999–2002	116/118	aEEG background abnormality: moderate or seizures = 155 (68); severe = 74 (32)	Head cooling with target rectal temperature 34–35° C for 72 hours	Death or severe disability (BSID MDI < 70, GMF level 3–5, or bilateral cortical visual impairment) at 18 months	Moderately abnormal aEEG: OR = 0.47 (0.26–0.87); severely abnormal aEEG: OR = 1.8 (0.49–6.4)
Shankaran et al. [33••, Class I]	2000–2003	102/106	Encephalopathy severity: moderate = 135 (65); severe = 72 (45)	Systemic hypothermia with target esophageal temperature ± 33.5° C for 72 hours	Death or moderate/severe disability (BSID MDI ≤ 84 and GMF ≥ level 2 or hearing loss, seizure disorder) at 18–22 months	RR = 0.72 (0.54–0.95)

aEEG—amplitude-integrated electroencephalogram; BSID—Bayley Scales of Infant Development; GMF—Gross Motor Function Classification System; MDI—Mental Development Index; PDI—Psychomotor Development Index.

this latent phase depends on the severity of injury, and that the optimal cooling temperature may depend on brain region [34–36]. The optimal degree, timing, and duration of hypothermia have not been determined in humans. Trials currently underway may help to clarify the best cooling technique and temperature, the safest and most effective duration, and the most appropriate target population for the intervention.

Seizure therapy

- Expert opinion supports treating clinical and electrographic seizures in infants with HIE [37•, Class III], although there is no good evidence regarding the relative benefit and harm of the anticonvulsants currently used to treat seizures in neonates.
- Phenobarbital is widely used as the first anticonvulsant (Class III), although more than 50% of infants continue to have clinical and/or electrographic seizures after an initial loading dose [38]. Lorazepam and midazolam may be used as an alternative to or in addition to phenobarbital in refractory cases (Class III). In North America, phenytoin (or, preferably, fosphenytoin) is commonly used in refractory cases, although erratic pharmacokinetics and drug interactions make dosing a challenge. Lidocaine is widely used for refractory neonatal seizures in Europe. Although infants with HIE remain at higher risk for future epilepsy, treatment for acute symptomatic seizures is rarely necessary beyond 5 to 7 days of life (Class III).
- A randomized, controlled trial of phenytoin versus phenobarbital for term infants with seizures found no difference in seizure cessation between these medications (RR = 0.97; 95% CI = 0.54–1.72; $P = 0.91$) [38, Class I].
- In a *Cochrane* review, Evans and Levene [39, Class I] concluded that there is no good evidence that prophylactic use of anticonvulsants reduces the risk of mortality or severe neurodevelopmental disability in the setting of HI brain injury. A more recent randomized trial of prophylactic phenobarbital in 45 term infants with neonatal encephalopathy showed reduced incidence of clinical seizures in the intervention group [40]. However, the study was limited by the absence of placebo control, clinical (rather than electrographic) detection of seizures, and failure to blind the clinicians detecting the seizures.

Pharmacologic treatment

Lorazepam

Standard dosage	0.05–0.1 mg/kg intravenously.
Contraindications	Inability to provide cardiorespiratory support, hypersensitivity.
Main drug interactions	None applicable to acute therapy.
Main side effects	Respiratory depression, depressed level of consciousness, and hypotension.
Special points	May cause myoclonus in very-low-birth-weight infants.

Midazolam

Standard dosage	Bolus 0.15–0.2 mg/kg intravenously, followed by continuous infusion (1 µg/kg/minute) increasing by 0.5–1 µg/kg/minute every 2 minutes until favorable response or a maximum of 18 µg/kg/minute [41].
Contraindications	Inability to provide cardiorespiratory support, hypersensitivity.
Main drug interactions	None applicable to acute therapy.
Main side effects	Respiratory depression, depressed level of consciousness, and hypotension.

Phenobarbital

Standard dosage	Bolus 20 mg/kg intravenously, repeated once as needed; daily dosing 5 mg/kg/day (target level 40–60 μg/mL).
Contraindications	Hypersensitivity, porphyria, severe liver dysfunction, and inability to provide cardiorespiratory support.
Main drug interactions	Multiple interactions with other drugs metabolized by the liver.
Main side effects	Respiratory depression, depressed level of consciousness, hypotension, and hypotonia. Idiosyncratic skin rash, hepatotoxicity, and blood dyscrasia.
Special points	Prolonged half-life in first week of life (43–217 hours) limits need for weaning phenobarbital in the case of short-term therapy.

Phenytoin and fosphenytoin

Standard dosage	Bolus 20 mg/kg intravenously; daily dosing 5 mg/kg/day (target level 10–20 μg/mL).
Contraindications	Hypersensitivity.
Main drug interactions	Multiple interactions with other drugs metabolized by the liver.
Main side effects	Infusion site reaction and arrhythmia with intravenous phenytoin. Idiosyncratic skin rash, hepatotoxicity, and blood dyscrasia.
Special points	Fosphenytoin is a water-soluble phenytoin prodrug that has fewer cardiovascular, central nervous system, and local cutaneous side effects than phenytoin. Due to saturable metabolism, small increases in phenytoin dose may produce disproportionate increase in concentration. Significant variability and changes in pharmacokinetics over the first weeks of life may lead to inconsistent drug levels.

Physical/speech therapy and exercise

- A multidisciplinary team should follow infants who survive HI brain injury. Physical, occupational, and speech therapists should be available to provide neurodevelopmental intervention as needed (Class III).

Emerging therapies

- Animal studies and early clinical trials suggest that novel neuroprotective agents such as oxygen free-radical inhibitors and scavengers, excitatory amino acid antagonists, anti-inflammatories, and growth factors may minimize neuronal damage and improve neurodevelopmental outcome after HI brain injury.
- Allopurinol reduces free-radical formation by inhibiting xanthine oxidase and scavenging the hydroxyl free radical. Animal models using piglets and rats have shown that treatment with allopurinol can improve energy status and brain injury after hypoxia-ischemia [19••]. Two small, randomized controlled trials of allopurinol versus placebo given to term infants with HI brain injury within 2 to 4 hours of birth found decreased levels of serum and cerebrospinal fluid nitric oxide but no significant improvement in early morbidity or mortality or neurodevelopmental outcome at 12 months of age [42,43].
- Deferoxamine is an iron-chelating agent that also inhibits prolyl hydroxylases responsible for degradation of hypoxia-inducible factor 1α (HIF-1α). The neuroprotective effect seen in cell culture in vivo rodent models may be due to reduced iron-mediated free-radical formation and stabilization of HIF-1α [44].
- Although erythropoietin is best known for its hematopoietic effects, neurons, glia, and endothelial cells also produce this cytokine and express

its receptors [45]. The potential neuroprotective effects of erythropoietin include decreased glutamate toxicity, induction of anti-apoptotic factors, reduced inflammation, decreased nitric oxide–mediated injury, and direct antioxidant effects. This cytokine has shown preclinical efficacy in more than 40 animal and cell culture models of HI brain injury, including improvement in functional outcome and preservation of hemispheric volume in an infant rat model of stroke [45,46]. An added benefit of erythropoietin is that it is already widely used in the clinical setting, including in infants for anemia of prematurity, albeit at lower doses than those required for neuroprotection.

- Magnesium antagonizes neuronal influx of calcium at the N-methyl-D-aspartate (NMDA)–activated channel. The use of magnesium for neuroprotection in animal models of HI brain injury has produced conflicting results [19••]. A randomized but nonblinded trial in term infants with birth asphyxia showed that postnatal administration of magnesium is safe and may improve short-term neurologic outcome [47].
- Topiramate is a broad-spectrum antiepileptic medication with several mechanisms of action, including use-dependent blockade of voltage-activated sodium channels, enhancement of γ-aminobutyric acid–mediated chloride flux, attenuation of glutamate-mediated calcium influx via antagonism at the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid–kainate receptor, attenuation of high-voltage-activated calcium channels, and weak inhibition of carbonic anhydrase. Neonatal rodent models using topiramate show that it is effective in suppressing seizures induced by hypoxia-ischemia and that it acts to extend the therapeutic window of hypothermia, making it an attractive candidate for human trials of neuroprotection in HIE [48,49].
- Xenon is a noble gas with favorable anesthetic, pharmacokinetic, cardiovascular, and safety properties [50]. Xenon is an NMDA antagonist and may protect neurons in multiple ways, including anti-apoptosis and reduction of calcium-mediated injury. Xenon is not used routinely for general anesthesia because of its high cost.

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