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Neurocritical Care for Neonates

Hannah C. Glass, MDCM, MAS [1,*]
Sonia L. Bonifacio, MD [2]
Thomas Shimotake, MD [2]
Donna M. Ferriero, MD [1,*]

Address
*,[1]Departments of Neurology & Pediatrics, University of California San Francisco, Box 0663 521 Parnassus Avenue, C-215, San Francisco, CA 94143-0663, USA
Email: Hannah.Glass@ucsf.edu
Email: ferrierod@neuropeds.ucsf.edu
Email: Hannah.Glass@ucsf.edu
[2]Department of Pediatrics, University of California San Francisco, Box 0734 533 Parnassus Ave, UC Hall u503, San Francisco, CA 94143-0734, USA
Email: bonifacios@peds.ucsf.edu
Email: shimotake@peds.ucsf.edu

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Opinion statement

Neurocritical care is an emerging subspecialty that combines expertise in neurology, critical care medicine, neuroradiology, and neurosurgery. Increasing evidence from the adult literature suggests that specialized neurocritical care can lead to improved outcomes following acute brain injury. Critically ill neonates with neurologic conditions may also benefit from specialized neurocritical care. Adherence to guidelines and managing patients in intensive care nurseries with dedicated, multidisciplinary neurocritical care personnel may optimize outcomes. This goal may be achieved by more quickly recognizing neurologic impairment, preventing secondary brain injury by maintaining basic physiologic functions, and rapidly implementing therapies. Nurseries that care for neonates with suspected acute brain injury should be prepared to adequately support multiorgan involvement, monitor the brain to detect seizures, evaluate for brain injury using MRI, and follow development through school age.

Introduction

Up to 25% of patients in a tertiary-level intensive care nursery setting may have neurologic conditions [1]. Typical presentations include neonatal encephalopathy and seizures but may also include asymptomatic acute brain injury discovered on routine imaging, as well as recognition of high risk for brain injury or developmental anomalies (Table 1). Advances in neonatal medicine have lead to improved survival for critically ill neonates, but this population remains at very high risk for adverse neurodevelopmental outcome, with high rates of cerebral palsy, cognitive disability, and epilepsy among survivors of preterm birth, neonatal seizures, and congenital heart defects [2]. Neonatal neurocritical care has developed in response to shifting goals of neonatal intensive care from cardiopulmonary support to optimization of neurodevelopmental outcomes.

Neurocritical care is a relatively new subspecialty. In 2002, the Neurocritical Care Society was established with the mission “to improve outcomes for patients

Table 1. Populations that may benefit from specialized neonatal neurocritical care

Acute acquired brain injury
Hypoxic-ischemic encephalopathy
Ischemic perinatal stroke (arterial or venous)
Intracranial parenchymal hemorrhage or high-grade intraventricular hemorrhage
Meningoencephalitis
Inborn error of metabolism
High risk for acquired brain injury
Neonatal encephalopathy
Extreme prematurity (<28 weeks gestation at birth)
Hydrocephalus
Need for extracorporeal life support (ECLS)
Congenital heart defect
Postnatal cardiopulmonary arrest
Central nervous system vascular malformation
Symptomatic hypoglycemia
Developmental anomalies
Brain malformation
Microcephaly
Dysmorphic neonate
Multiple congenital anomalies
Neonatal seizures

with life-threatening neurological illnesses." Since 2007, the Accreditation Council for Graduate Medical Education (ACGME) has administered certification examinations to physicians who complete an accredited program. Neurocritical care for adults encompasses a broad range of serious neurologic conditions including intracranial hemorrhage, stroke, status epilepticus, central nervous system infection, and traumatic brain injury. There is no accredited training for pediatric neurocritical care, and there are few published protocols to guide management for children and neonates.

The developing brain differs enormously from its adult counterpart, but several important diagnostic and therapeutic constructs translate from the adult world to the emerging field of neonatal neurocritical care [3]:

- Early recognition and treatment of neurologic conditions can lead to improved outcomes.
- Attention to basic physiology, including temperature regulation, glucose homeostasis, oxygenation, and blood pressure support can help prevent secondary injury.
- A protocol-driven approach can achieve lower mortality and higher rates of favorable outcomes.
- Specialized, multidisciplinary neurocritical care teams in dedicated referral units can reduce mortality and improve resource utilization.

Though neonatal neurocritical care is not yet well established as a subspecialty, several programs in the United States and abroad are emerging as centers of excellence, including some centers with dedicated, multidisciplinary personnel trained to care for newborns with neurologic conditions. Further, these centers have the capacity to monitor and image the newborn brain and are able to provide advanced multiorgan life support and surgical procedures. As in adult settings, many centers have developed institutional guidelines for transport of neonates at risk for brain injury and for implementation of time-sensitive protocols.

Key principles of neurocritical care in the nursery include resuscitation and supportive care designed to minimize secondary brain injury, early identification of neonates who have suffered brain injury or are at risk for brain injury, anticipation of complications through frequent clinical examination and multimodal monitoring, as well as imaging for diagnostic and prognostic purposes (Fig. 1).

At our center, the neurocritical care team consists of a bedside nurse who is specially trained in neurology,

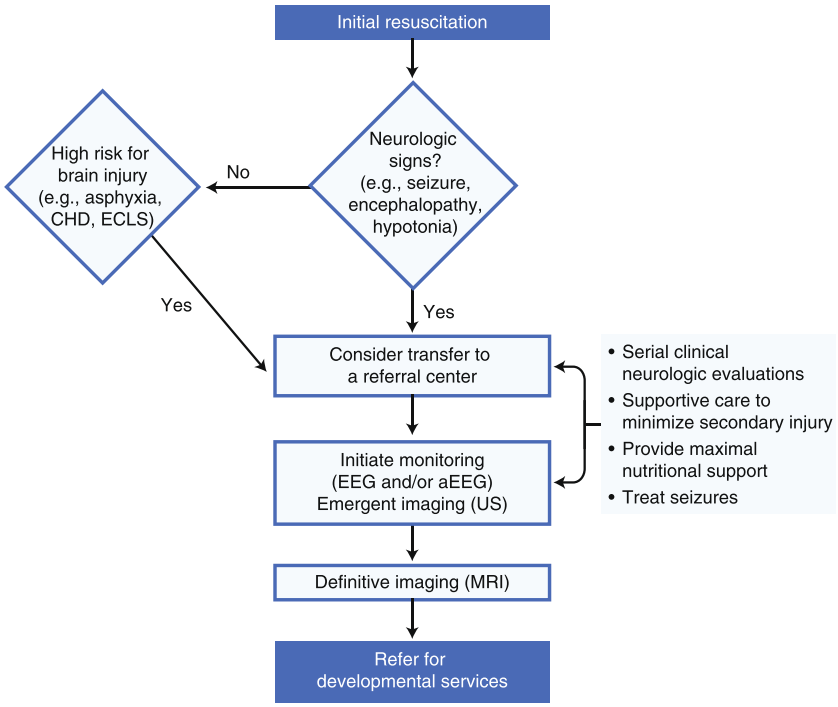

Figure 1. Approach to neonatal neurocritical assessment and therapy. *aEEG* amplitude-integrated electroencephalogram; *CHD* congenital heart disease; *ECLS* extracorporeal life support; *EEG* electroencephalogram; *US* ultrasound.

a neonatologist, and a neurologist (Table 2). Transport physicians and nurses are also trained to recognize and manage neurologic conditions.

This review describes an approach to critically ill newborns with neurologic conditions, including guidelines for management (where available) or evidence-based best practices, and it demonstrates how an organized, educated, and experienced neurocritical care team may improve outcomes. The preterm and term neonate are considered separately where appropriate. We conclude with a discussion of emerging therapies and future directions in the field of neonatal neurocritical care.

Treatment

Resuscitation and supportive care

- The initial period of neurologic compromise is often around the time of delivery. The first consideration in optimizing support for the developing brain is with newborn resuscitation and initiation of supportive care. The concept of the "golden hour"—borrowed from trauma and emergency medicine—has been translated to neonatal resuscitation. It refers to a period during which prompt and appropriate medical treatment, as well as transfer to a center where definitive care can be provided, will be most likely to prevent death or permanent disability.
- Initial resuscitation may be at a center without capacity for neurocritical care, and the decision to transport a neonate with possible brain injury often hinges on a neurologic evaluation conducted by telephone. Providing referring hospitals with local management guidelines and creat-

Table 2. The neonatal neurocritical care team: members and their roles

Team member	Role	Co-management
Bedside nurse	Triage patient and equipment Initial clinical assessment Apply specialized equipment (e.g., cooling blanket, aEEG)	
Neonatologist	Stabilize patient Pay careful attention to physiology Perform advanced support: blood pressure, ventilation, ECLS	• Apply standardized guidelines • Perform neurologic examination • Determine eligibility for neuroprotection & research studies • Plan investigations
Neurologist	Provide differential diagnosis Coordinate application and interpretation of video-EEG Manage seizures Interpret MRI Determine mechanism of injury Determine prognosis	• Interpret aEEG • Communicate with family, anticipate needs

aEEG amplitude-integrated EEG; *ECLS* extracorporeal life support; *EEG* electroencephalography

ing education programs for referring physicians—including training to recognize candidates for therapeutic hypothermia as well as early signs of neurologic compromise such as encephalopathy or seizures—can help to optimize care in the first hours. Neurologic conditions often occur in the context of multiorgan failure. Roughly 25% of asphyxiated neonates treated with cooling require inhaled nitric oxide or, less commonly, support with extracorporeal membrane oxygenation (ECMO) [4]. These newborns benefit from transfer to a center that can provide both neurologic care and maximal support for organ systems. A training curriculum for transport teams and bedside nurses can help ensure ongoing optimization of care, early recognition of clinical seizures, and allocation of appropriate resources once the neonate arrives at the referral center.

Resuscitation

- The principles of resuscitation and supportive care for preterm and term newborns are similar. Resuscitation should follow guidelines published by the International Liaison Committee on Resuscitation (ILCOR) or the Neonatal Resuscitation Program (NRP) [5••]. The ILCOR guidelines address initial resuscitation, but several of the principles also pertain to ongoing care and should be applied for all children with identified brain injury or risk of brain injury, as they are of particular importance in preventing secondary brain injury.
- *Oxygenation and ventilation:* Support respiratory functions but avoid hyperoxia and hyperventilation. Hyperoxia increases the risk of oxygen toxicity during reperfusion, tissue damage from oxidative stress, and cerebral pro-inflammatory responses. Thus, room air should be

used when possible, and then blended air and oxygen used judiciously as guided by pulse oximetry and blood gases [5••, Class III]. Asphyxiated neonates often develop a compensatory respiratory alkalosis that may become more pronounced as metabolism and CO_2 production are reduced with cooling. Hypocapnia disrupts cerebral autoregulation and blood flow, so it should be avoided [6].

Supportive care

Circulatory support

Support normal hemodynamics for adequate brain perfusion. In the setting of acidosis, if hypovolemia is likely (pale skin, weak pulses, poor perfusion), then volume replacement therapy (e.g., normal saline or blood) should be provided first. Care should be taken with the rate of administration in premature infants, as rapid infusions of large volumes have been associated with intraventricular hemorrhage (IVH) [5••, 7, 8••].

Temperature control

Maintain normothermia [9, Class II]. Hyperthermia can exacerbate underlying brain injury in animal models and is independently associated with an increased risk of adverse outcome in human newborns [9, 10]. Temperature should be actively managed and maintained within the normal range in any neonate with suspected brain injury.

Glucose management

Maintain normoglycemia [11, Class III]. There is no evidence-based consensus regarding what constitutes clinically relevant hypoglycemia. However, low plasma glucose can cause *de novo* brain injury or can worsen existing tissue damage, so blood glucose should be monitored closely and managed aggressively, especially in children with underlying brain injury or symptomatic hypoglycemia [11].

Interventional procedures: neuroprotection

- Once the neonate has been resuscitated and appropriate supportive measures applied, the child should be evaluated for eligibility for neuroprotective strategies. Evidence and strategies differ for the preterm and term populations, and are discussed separately.

Neuroprotection of preterm neonates

Caffeine citrate/methylxanthine therapy: Caffeine therapy, commonly used in preterm infants to prevent apnea, was found in a large randomized trial of very low birth weight infants to have a neuroprotective effect, with decreased rates of cerebral palsy (4.4% vs 7.3%; adjusted OR, 0.58; 95% CI, 0.39–0.97; P=0.009) and cognitive delay (33.8% vs 38.3%; adjusted OR, 0.81; 95% CI, 0.66–0.99; P=0.04) [12, Class II]. The regimen in this trial consisted of a loading dose of 20 mg/kg and a maintenance dose of 5 mg/kg per day, with a median age of 3 days at the onset of therapy.

Neuroprotection of term neonates

Therapeutic hypothermia for hypoxic-ischemic encephalopathy: In term infants with perinatal asphyxia and hypoxic-ischemic encephalopathy (HIE), there is sufficient evidence to recommend mild hypothermia therapy (whole-body or selective head cooling) to reduce the risk of death and impairments at 18 to 22 months (RR, 0.81; 95% CI, 0.71–0.93; $P=0.002$; number needed to treat=9) [13••, Class I]. ILCOR recommends that hypothermia with a goal temperature of 33.5°C±0.5°C be initiated within 6 hours after birth in newborns with evolving moderate to severe HIE, that institutions follow inclusion/exclusion criteria and protocols that are similar to those used for the randomized controlled trials, and that all infants be followed up longitudinally [5••].
Successful implementation of a therapeutic hypothermia program requires careful preparation and a multidisciplinary approach [14]. Rapid initiation of therapeutic hypothermia results in better outcomes in animals and humans [15, 16, Class II]. Cooling on transport is safe and feasible and results in earlier time to therapeutic temperature than initiation of cooling at the referral center [17]. The main risk is overcooling, which can be avoided with close core temperature monitoring and anticipatory guidelines [18].

Monitoring and seizure management

Monitoring electrocortical function

- Neonates with encephalopathy, acute brain injury, suspected seizures, or high risk for seizures should be monitored to assess severity of injury and degree of recovery, as well as how the brain is tolerating intensive care interventions (Table 1). There is increasing evidence that ICU populations of all ages have a high frequency of clinically silent seizures, and brain monitoring throughout the period of critical illness is increasingly utilized [19]. Clinical detection of neonatal seizures is not reliable, even among experienced health care providers [20•]. Furthermore, seizures without clinical correlates are frequent, especially after the administration of anticonvulsant medications [21].
- Acute symptomatic neonatal seizures commonly self-resolve within 48 to 72 hours of onset. Initiation of monitoring should commence as soon as possible after the first witnessed spell or recognition that the patient is at high risk for seizures. Continuous monitoring should continue until 3 to 4 typical clinical spells have been captured or until the neonate has been without EEG seizures for at least 24 hours.

Video-EEG

Conventional video-electroencephalogram (video-EEG) using the International System 10–20 montage adapted for neonates is the gold standard for detecting seizures and monitoring the overall background level of maturation and/or encephalopathy [22, Class III].

EEG trending

Amplitude-integrated EEG (aEEG) is a simplified method of presenting EEG output on a compressed time scale [23]. Although it is easy for the

bedside neonatology team to apply and interpret, aEEG is less accurate than video-EEG for detecting seizures that are brief, low-voltage, or focal [24, Class II]. Other EEG trending modalities such as color density spectral array (CDSA) and envelope trend appear to have seizure identification rates similar to those of aEEG [25, 26].

Bedside teams may quickly apply and interpret aEEG while concurrent video-EEG is recorded and analyzed remotely. This model of seizure co-management may allow for quicker detection while minimizing treatment of nonseizure artifact or nonseizure clinical spells, especially if there is good communication between the neonatology and neurology providers.

EEG background

EEG and aEEG background can be helpful to predict prognosis in many settings, including neonatal seizures, HIE, and preterm birth, and should be considered as part of multimodal prognostic evaluation [27–29, Class IV].

Seizure therapy

- Based on animal evidence that seizures may harm the developing brain and are associated with high burden of brain injury [30•, 31], expert opinion supports treating clinical and electrographic seizures with the aim of abolishing electrographic seizures as quickly as possible [22, Class III]. Rapid seizure treatment using a standardized protocol results in lower burden of electrographic seizures [31, 32]. However, there is no evidence to suggest that treating seizures improves outcome. In addition, several medications currently used to treat seizures in neonates are known to cause neuronal apoptosis in animal models, though the effect on the developing human brain is not known [33].
- Phenobarbital is often the first-line agent; seizures are controlled in roughly half of patients using a single loading dose [34, 35]. In North America, phenytoin (or preferably, fosphenytoin) is often used in refractory cases. Midazolam infusion may be used as an alternative or add-on agent in refractory cases [36]. Lidocaine is used for refractory neonatal seizures in Europe [37]. There are early data from case series that suggest safety and possible efficacy of intravenous levetiracetam, for which off-label use is increasing [38].
- Acute symptomatic neonatal seizures typically abate within days and have a low risk of early recurrence, and so early withdrawal of medications is often warranted [39, Class III]. Children who are discharged home on seizure therapy should be reassessed with consideration of discontinuing medications within 3 months, given the potential negative effects of ongoing therapy [2, Class III].

Monitoring brain tissue oxygenation

- Multimodal techniques for monitoring of brain oxygenation and metabolism have proven useful to guide management and prognosis in adult patients with brain injury, and they are in early use in neonates [40].

- Optical near infrared spectroscopy (NIRS) is a noninvasive method for long-term trending of brain tissue oxygenation. The tissue oxygenation index (TOI) and regional cerebral oxygen saturation ($rScO_2$) are measurements that reflect the saturation of oxygen in veins (70%–80%), arteries (20%–25%), and capillaries (5%). NIRS is increasingly being adopted to guide management of blood pressure in the setting of absent autoregulation, and patent ductus arteriosus closure in preterm neonates, as well as to help establish prognosis in term neonates with HIE [41, Class IV].

Neuroimaging

- The two main functions of imaging of neonates with neurologic conditions are to facilitate diagnosis (for both congenital and acquired conditions) and to help determine prognosis [42••]. A critically ill newborn can be safely imaged, but transport and observation during the procedure are best performed by a well-prepared team. This section discusses the most commonly used imaging modalities—ultrasound, MRI, and CT scanning—and reviews considerations for urgent versus definitive imaging of preterm and term neonates.
- Ultrasound is commonly the initial diagnostic modality because it is readily performed at the bedside at most centers. It should be performed urgently for newborns with suspected neurosurgical conditions (e.g., posterior fossa bleed or hydrocephalus), or when more definitive imaging by MRI will be delayed [2, Class IV].
- CT scans require a higher dose of radiation in neonates to achieve resolution similar to that in older populations. Prior guidelines have recommended CT in the case of suspected intracranial hemorrhage [43], but many experts contend that although estimated individual risks from radiation exposure are small, CT scanning should be avoided in newborns, especially if MRI is available [44, Class IV].
- MRI is the most sensitive imaging modality to interrogate the white and gray matter; it is helpful to clarify diagnosis and aid in determining prognosis [43, 45••, Class II]. For both preterm and term neonates, MRI requires a specialized team and equipment, with training for transport, MR safety, sequence acquisition, and interpretation [46]. MR-compatible incubators are commercially available and can be equipped with an MR-compatible ventilator and monitors to measure heart rate, blood pressure, temperature, and oxygen saturation. Although scans can be accomplished without sedation by feeding and using a papoose device, in our experience, 25% to 30% of patients require sedation [47]. Dedicated neonatal imaging coils increase the signal-to-noise ratio, which improves image quality and acquisition time [46]. T1, T2, diffusion-weighted imaging (DWI), and MR spectroscopy are the core sequences for evaluating neonates with encephalopathy or seizures. Together, these allow for eval-

uation of white matter and gray matter integrity, identification of acute or subacute ischemia and hemorrhage, and assessment of tissue metabolites. Susceptibility-weighted imaging (SWI) is helpful for detecting blood products and can be useful when evaluating hemorrhage, vascular malformations, and venous sinus thrombosis [48]. Imaging sequences must be adapted to account for the higher water content in the neonatal brain [49]. Standard commercial adult protocols used for adult stroke or seizure evaluation are inadequate.

Neuroimaging in preterm neonates

Routine screening

According to guidelines developed in 2002, preterm neonates (<30 weeks gestation) should have ultrasound performed at 7 to 14 days of life and once again at 36 to 40 weeks postmenstrual age [43, Class III]. Some studies and guidelines recommend earlier and more frequent ultrasound imaging, especially to monitor for posthemorrhagic hydrocephalus and cyst formation in the setting of large IVH [43, 50, 51, Class III]. Ultrasound can detect important and common intracranial pathologies such as IVH, periventricular hemorrhagic infarct, white matter echolucencies, ventriculomegaly, large cerebellar hemorrhages, and cystic white matter injury.

Although injury shown by ultrasound is a strong risk factor for cerebral palsy, MRI is more sensitive and specific than ultrasound for detecting subtle pathologies associated with cognitive impairment, including focal, noncystic white matter injury, diffuse white matter injury, and small cerebellar hemorrhages [52–59]. Based on increasing evidence that MRI may be more accurate than ultrasound for determining outcome, some have recommend imaging all children born at less than 28 weeks gestation [60, Class IV]), but routine use of MRI for all preterm neonates remains controversial.

The appropriate timing for MR imaging in the preterm newborn is not well defined. In the early neonatal period, white matter injury is best detected as focal, noncystic, hyperintense areas on T1-weighted MRI scans. These lesions normally stabilize or improve on follow-up scans obtained at term-equivalent age, and volume loss or signal changes are findings seen among near-term infants [61–63].

Imaging of intraventricular hemorrhage and periventricular hemorrhagic infarct

The intraventricular hemorrhage grading system was initially created for ultrasound, and studies comparing ultrasound and MRI show that germinal matrix hemorrhage, IVH, and periventricular hemorrhagic infarct are accurately detected using ultrasound [59].

In the setting of suspected unilateral parenchymal hemorrhage, MRI is useful to evaluate for abnormal signal intensity in the ipsilateral posterior limb of the internal capsule (PLIC), which is associated with hemiplegia [64].

Imaging of preterm neonates with seizures

In preterm neonates with clinical or electrographic seizures, MRI should be performed to determine etiology and better delineate tissue abnormalities [65, Class IV].

Neuroimaging in term neonates

Imaging of neonatal encephalopathy

According to the 2002 guidelines, conventional T1-weighted and T2-weighted MRI and DWI should be performed for diagnostic evaluation and to help determine prognosis in the setting of neonatal encephalopathy at 2 to 8 days of life [43, Class III]. Pseudonormalization of diffusion values occurs at 7 to 10 days after an insult, and early conventional imaging may be normal, so centers able to perform DWI should image between day 3 and day 6 [66, Class IV]. Some experts recommend later imaging, at 1 to 2 weeks of age [49]. Consistency within a center is key, so that providers can become accustomed to the appearance of injury at a given time point.

A high ratio of lactate to N-acetylaspartate in the basal ganglia, detected using single-voxel proton magnetic resonance spectroscopy (MRS), has emerged as a quantitative MR biomarker for prediction of neurodevelopmental outcome after neonatal encephalopathy; experts recommend adding spectroscopy to conventional imaging protocols [67•, Class III]. Pattern and degree of injury on MRI at both early and later time points is highly predictive of neurodevelopmental outcome, including in newborns treated with therapeutic hypothermia [68•, 69].

Imaging in neonates with seizures

For nonencephalopathic term neonates with seizures, MRI with DWI and vascular imaging (MR angiogram and MR venogram) should be performed within 24 to 72 hours of presentation to evaluate for hemorrhagic or ischemic stroke [70, Class IV]. In the case of venous clot, repeat imaging is indicated to evaluate for extension of the clot, with consideration of initiating anticoagulant therapy [71, Class III].

Imaging of neonates at high risk

MRI should be considered for other high-risk conditions listed in Table 1 [45••, 72, 73, Class IV].

Other investigations

- Placental pathology should be requested for neonates with encephalopathy, to help determine the timing and mechanism of injury [74–76, Class III].

Diet and nutrition

- Cumulative nutrient deficits are common in neonates with brain injury and may contribute to poor somatic and brain growth [77].

The risk of adverse outcomes in critically ill premature neonates appears to be mediated by nutritional intake during the first week of life [78]. Failure to thrive in the first postnatal year may result from energy and protein deficits accumulated during the period of neonatal intensive care, and poor postnatal growth in preterm neonates is an independent factor for adverse outcome [79].

Nutrition for preterm neonates

- Early, aggressive parenteral and enteral nutritional support is associated with a reduction in mortality and short-term morbidities, and improvement in growth and neurodevelopmental outcome [78, Class III]. Protein and energy enrichment of enteral feeds during the neonatal period is associated with better somatic and head growth and may affect long-term neurodevelopmental outcome [80•, 81, 82, Class II].

Nutrition for term neonates

- A diet high in energy and protein may help to offset cumulative nutritional deficits in patients with HIE [83, Class II]. A study of asphyxiated neonates randomized to either a diet with high energy and protein (120% recommended average intake) or a normal diet was terminated early after initial analysis showed significant improvements in all growth parameters (occipitofrontal head circumference, weight, and corticospinal tract axonal diameter) at 12 months [83].
- Some centers initiate nonnutritive feedings during the cooling period in neonates treated with therapeutic hypothermia [84, Class IV].

Follow-up and early-intervention programs

- Centers that manage high-risk neonates should have a follow-up mechanism to monitor children for emerging delays or disability and to refer them to specialists as needed [5••, Class IV].
- Neonates that are evaluated by a neurocritical care service should be routinely referred to an early-intervention program [85, Class I]. Most children will be eligible for free or low-cost evaluation and rehabilitation services from state-run programs for infants and toddlers with disabilities. Animal studies have shown that environmental enrichment enhances cerebral plasticity and reorganization of cortical maps and also improves functional outcomes; these studies provide a good theoretical basis for early-intervention programs for at-risk infants [86]. A recent Cochrane analysis concluded that early-intervention programs may positively influence cognitive outcomes in the preterm population [86]. Another study found that a preventive home-care program may improve behavioral outcomes and reduce anxiety and depression for primary caregivers [87].

Emerging therapies and future directions

- Future directions include improved brain monitoring, novel neuroprotection agents and seizure treatment strategies, and use of advanced MR biomarkers for predicting outcome.

Improved brain monitoring

Integrated, multimodal brain-monitoring programs may include automated algorithms for seizure detection and management.

Neuroprotection strategies

Combination regimens that add to hypothermia (i.e., hypothermia plus a second agent), that improve outcome for those neonates identified outside the therapeutic window are being explored, along with therapies that are effective in conditions other than term HIE. Agents in the advanced phases of testing include erythropoietin, xenon, and melatonin.

Erythropoietin is a pleiotropic cytokine expressed in the developing brain that has antioxidant, anti-apoptotic, and neuroproliferative effects, as demonstrated in multiple animal models. Post-injury treatment protocols in neonate rodents have demonstrated short-term and long-term histologic and behavioral improvement. Two recent human trials suggest that in the setting of HIE, multiple doses of erythropoietin over several days can improve mortality and short-term outcomes. These encouraging data must be tested in large, randomized masked trials to establish proper dosing and safety [88, 89, Class II].

Xenon is a noble gas that acts through NMDA receptor blockade. It is neuroprotective alone and synergistic with hypothermia in animal models, and a human safety trial is under way [90, 91].

Melatonin is an endogenously produced indoleamine that is a potent free radical scavenger. Experimental evidence regarding the neuroprotective effects of melatonin against excitotoxic and hypoxic-ischemic brain lesions in immature animals provides support for considering melatonin as a candidate therapy for injury to the preterm brain [92].

Discovery of safe and effective *seizure therapies* is a high priority. Newer agents, including levetiracetam, bumetanide, and topiramate, are being tested for safety and pharmacokinetics, and randomized, controlled trials are planned.

New MR biomarkers

Quantitative magnetic resonance studies, including spectroscopy and tractography, have shown early promising associations with neurodevelopmental outcome. These measures may be useful as surrogate markers for intervention trials or for guiding discussions regarding prognosis.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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