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Interdisciplinary Approach to Neurocritical Care in the Intensive Care Nursery

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Neurocritical care is a multidisciplinary subspecialty that combines expertise in critical care medicine, neurology, and neurosurgery, and has led to improved outcomes in adults who have critical illnesses. Advances in resuscitation and critical care have led to high rates of survival among neonates with life-threatening conditions such as perinatal asphyxia, extreme prematurity, and congenital malformations. The sequelae of neurologic conditions arising in the neonatal period include lifelong disabilities such as cerebral palsy and epilepsy, as well as intellectual and behavioral disabilities. Centers of excellence have adapted the principles of neurocritical care to reflect the needs of the developing newborn brain, including early involvement of a neurologist for recognition and treatment of neurologic conditions, attention to physiology to help prevent secondary brain injury, a protocol-driven approach for common conditions like seizures and hypoxic-ischemic encephalopathy, and education of specialized teams that use brain monitoring and imaging to evaluate the effect of critical illness on brain function and development.

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Introduction

The advances in cardiopulmonary resuscitation and critical care during the 20th century have led to high rates of survival among neonates with life-threatening conditions such as perinatal asphyxia, extreme prematurity, and congenital malformations. However, in spite of these technological advances, neurologic complications of critical illness remain high, with up to 25% of patients at referral center intensive care nurseries having brain injury, seizures, or other neurologic conditions.^{1,2} The sequelae of neurologic conditions arising in the neonatal period include lifelong disabilities such as cerebral palsy and epilepsy, as well as intellectual and behavioral disabilities. The recent advances in digital monitoring of brain function, including simplified

trends like amplitude-integrated electroencephalogram (aEEG), as well as safe brain imaging using magnetic resonance (MR), allow physicians to evaluate the effect of critical illness on brain function and development. Patients who have both acute and subacute or chronic neurologic conditions may benefit from specialized neurocritical care (Table 1).

Neurocritical care is a multidisciplinary subspecialty that uses these advances to combine expertise in critical care medicine, neurology, neuroradiology, and neurosurgery, and has led to improved outcomes in adults who have critical illnesses.³ Centers of excellence in the United States and abroad have adapted the principles of neurocritical care (Table 2) to reflect the needs of the developing newborn brain.

At our center, the core neurocritical care team consists of a bedside nurse who is specially trained in neurology, a neonatologist, and a neurologist. This core comanagement team works together at the bedside to care for any neonate with suspected or confirmed neurologic signs or symptoms throughout the period of critical illness. The ancillary team members include pediatric neurosurgeons, neuroradiologists, and epileptologists. Before discharge, a neonatology specialist with expertise in developmental care and high-risk follow-up coordinates with the core team to help identify and care for children who are at risk for lifelong disability to implement services before hospital discharge.

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Table 1 Neonatal Neurocritical Care Populations

Acute acquired brain injury
Hypoxic-ischemic encephalopathy (HIE)
Arterial and venous ischemic stroke
Intracranial parenchymal hemorrhage
High-grade intraventricular hemorrhage
Meningoencephalitis
Inborn error of metabolism
Seizures
Acute symptomatic seizures
Neonatal onset epilepsies (benign and malignant)
High risk for acquired brain injury
Encephalopathy
Extremely low gestational age (<28-wk gestation at birth)
Hydrocephalus
Need for extracorporeal membrane oxygenation (ECMO)
Congenital heart malformations
Postnatal cardiopulmonary arrest
Vascular malformations of the central nervous system
Symptomatic hypoglycemia
Developmental anomalies
Brain malformation
Microcephaly
Dysmorphic neonate
Multiple congenital anomalies

Establishing a Neonatal Neurocritical Care Program

The development of a neonatal neurocritical care program entails more than including a neurologist in the day-to-day care of the patient. Use of brain monitoring devices, the application of neuroprotective therapies such as therapeutic hypothermia, and increased awareness of neurologic complications of critical illnesses result in a change in unit culture to one where the brain is considered as an important organ system that is affected by everyday management. Training and education of all care providers, including physicians, nurses, nurse practitioners, and respiratory therapists, among others, as well as identification of leaders in each care domain to provide consistent application of guidelines and protocols, facilitates culture change. These care providers learn to consider the neurologic system to be as important as the cardiorespiratory systems, which results in the provision of brain-focused care.

Within a given unit, a neonatal leader should be identified to work with nursing and neurology leaders to develop a

neonatal neurocritical care program. Together, this group develops neurology-specific guidelines and protocols. These guidelines and protocols (Table 3) are meant to standardize the approach to the neurologic evaluation and treatment and reduce practice variation that can occur in large units with high turnover of medical and nursing staff. A thorough review of the literature, and concepts from team-training science and quality improvement can facilitate the development and application of these guidelines and protocols.^{4,5}

The Role of the Neonatologist

The neonatologist plays a critical role in identifying patients at risk of brain injury, as well as those neonates with an acute or subacute neurologic condition, and in providing optimized resuscitation and supportive care to prevent secondary injuries. Neonatologists are primarily responsible for and are experts in resuscitation and supportive management of critically ill neonates. In the setting of a neurocritical care service, the neonatologist triages patients with acute vs subacute neurologic problems and consults the pediatric or neonatal neurologist to participate in the day-to-day care of patients with acute neurologic compromise.

With an increased awareness of neurologic complications of prematurity and the effect of critical illness on the developing brain,⁶ the neonatologist should be alert to neurologic compromise in these patients. When evaluating a neurologic sign or symptom, initial neonatal management includes the following: (1) close attention to the maintenance of physiological homeostasis with a focus on cardiorespiratory status, electrolytes, and glucose levels, and thermoregulation to help prevent secondary brain injury (Table 4); (2) early involvement of the pediatric or neonatal neurologist to help guide treatment and determine prognosis; and (3) initiation of brain monitoring to assess for seizures and degree of encephalopathy. As discussed later, the historical approach of neonatologists independently treating suspicious clinical events with anticonvulsants without the initiation of brain monitoring or EEG confirmation of seizures should no longer be the standard approach.

Resuscitation and Supportive Care

Since the initial period of neurologic compromise is often around the time of delivery, the first consideration when optimizing support for the developing brain is during newborn resuscitation and with initiation of supportive

Table 2 Principles of Neurocritical Care

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 brain 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

Adapted from Rincon and Mayer.³

Table 3 Guidelines and Protocols Developed by a Neonatal Neurocritical Care Program

Therapeutic hypothermia for treatment of hypoxic-ischemic encephalopathy
Patient selection criteria based on randomized, controlled trials
Passive cooling during transport
Brain monitoring guidelines
Seizure management guidelines
Brain imaging guidelines
Patient selection
Imaging without the use of sedation
Guidelines for stroke management

care. The “golden hour” after newborn delivery—a concept that is borrowed from trauma and emergency medicine—refers to the period during which prompt and appropriate supportive care, as well as transfer to a center where definitive care can be provided, will be most likely to prevent death or permanent disability.^{7,8}

Neuroprotection

Once the neonate has been resuscitated and the neonatologist has initiated supportive measures, neonates with encephalopathy or suspected brain injury must be evaluated for eligibility for neuroprotective strategies.

Therapeutic hypothermia is the standard of care for neonates with encephalopathy due to hypoxic-ischemia (HIE). According to a recent meta-analysis, therapeutic hypothermia, initiated within 6 hours of life, reduces risk of death and disability (risk ratio = 0.76, 95% CI: 0.69-0.84) and increases the rates of survival with normal neurologic function (risk ratio = 1.63, 95% CI: 1.36-1.95) at 18 months of age.⁹ Total body cooling and selective head cooling are equally effective; however, whole-body cooling

allows easier access to the head for video-EEG monitoring during the period of cooling and rewarming. Rapid initiation of therapeutic hypothermia is optimal since earlier initiation results in better outcomes.^{10,11} Cooling on transport is feasible and safe, and results in quicker time to therapeutic temperature than when initiated at the referral center.¹²

Although therapeutic hypothermia has significantly improved outcomes among neonates with HIE, the neuroprotective effect is incomplete, with death and severe disability rates at approximately 50% among those who received treatment in the clinical trials.⁹ Furthermore, many neonates do not qualify for therapeutic hypothermia, owing to identification outside the 6-hour window, prematurity, or brain injuries or encephalopathy or both due to causes other than HIE. There are several agents “in the pipeline” that are being evaluated for neuroprotection or use in combination with therapeutic hypothermia or both, including growth factors (eg, erythropoietin), antioxidants (eg, melatonin and allopurinol), antiexcitotoxic agents (eg, topiramate, levetiracetam, and magnesium sulfate), mast cell stabilizers (eg, disodium chromoglycate), as well as xenon and stem cells, among others.¹³⁻¹⁶

Education

Neonatologists, especially those in academic units, large quaternary care centers, and stand-alone children's hospitals play an important role in the education of both trainees and staff in their respective units, as well as in the education of physician and staff at referral centers. Education is needed to help staff at those smaller hospitals identify patients who may benefit from neurocritical care. Communication and education are critical to improve identification of patients with neurologic compromise that may require transfer to a higher-level of care. For example, patients with HIE due to perinatal asphyxia need to be identified and transferred quickly after birth, so that they may receive treatment with

Table 4 Supportive Care to Minimize Secondary Brain Injury

Temperature
Active normothermia for any neonate with suspected brain injury
Hyperthermia can exacerbate underlying brain injury and is associated with an increased risk of adverse outcome ^{59,60}
Glucose
Active maintenance of normal glucose for any neonate with suspected brain injury
Low plasma glucose can cause de novo brain injury, or worsen existing tissue damage ⁶¹
Oxygenation
Hyperoxia increases the risk of oxygen toxicity during reperfusion, tissue damage from oxidative stress, and cerebral proinflammatory responses
Room air should be used when possible, and then blended air and oxygen used judiciously as guided by pulse oximetry and blood gases ⁶²
Ventilation
Maintain normocapnea or mild hypercapnea
Hypocapnea disrupts cerebral autoregulation and blood flow and, therefore, should be avoided ⁶³
Blood pressure
Support normal hemodynamics for adequate brain perfusion

therapeutic hypothermia. The incidence of HIE is relatively high (1.5 per 1000 live births), but a small community hospital may only see 1 patient per year.¹⁷ Other relatively common, but sometimes underrecognized, conditions include neonatal seizures and stroke. The decision to transport a neonate with possible brain injury often centers on a neurologic evaluation conducted by telephone. The education programs for referring physicians should include training to recognize candidates for therapeutic hypothermia and early signs of neurologic compromise, as well as local management guidelines. Furthermore, neurologic conditions often occur in the context of multiorgan failure. Approximately 25% of neonates who are treated with therapeutic hypothermia have persistent pulmonary hypertension and require inhaled nitric oxide or, less commonly, extracorporeal membrane oxygenation support.¹⁸ These neonates may benefit from transfer to a center that can provide both neurologic care and maximal cardiopulmonary supportive care. A training curriculum for transport teams and bedside nurses, therefore, should include not only optimization of cardiopulmonary resuscitation and care, but also early recognition of clinical events that are suspicious for seizures, as well as allocation of appropriate resources once the neonate arrives at the referral center.

Specialized Nursing Care

The bedside nurse is often the first person to recognize infants who display signs and symptoms of brain injury. Specialized neonatal neurocritical care nurses that are trained to understand the clinical aspects of common neurologic illnesses can help to optimize care for neurologic patients in the intensive care nursery.^{19,20}

Specialized training through didactic sessions and hands-on learning help to prepare the bedside nurse to care for neonates with neurologic illnesses.²¹ Courses cover the fundamentals of neurologic care, including neurologic examination skills, neuroanatomy, hypothermia equipment and therapy, aEEG application and pattern recognition, seizure recognition, neurologic documentation, and palliative care.^{20,22,23}

With these tools in hand, the specialized neonatal neurocritical care nurse becomes an integral member of the interdisciplinary team.

The Role of the Neonatal Neurologist

Historically, the role of the pediatric neurologist in the nursery has been to provide brief consultation for children with neurologic conditions that are resistant to first-line therapies, for example, seizures that are resistant to phenobarbital, or patients with HIE that remain encephalopathic after the first several days of life. Increasingly, however, the neurologist is becoming involved early to help care for neonates at the time of initial presentation of neurologic signs or symptoms. The benefits of this early and more

prolonged involvement are multiple. First, the neurologic perspective often leads to additional etiologies considered on the differential diagnosis. Second, the neurologist is in a good position to coordinate with the neurophysiology service and EEG technicians (and in many centers, the same neurologist will also serve as neurophysiologist). The neurologist can help improve the speed of application and interpretation of EEG to diagnose or confirm seizures identified clinically or on aEEG, and aid in rapid, real-time treatment of seizures. Similarly, the neurologist is in frequent contact with the neuroradiology service and can assist with choosing the best imaging modality and sequences, as well as interpreting imaging findings. Finally, the neurologist perspective is important when discussing prognosis and follow-up with the family, especially if the child is expected to have a long-term disabling neurologic condition. These early discussions can help establish the relationship between the families and the neurology service.

Brain Monitoring and Seizure Management

Seizures are among the most common causes for neurologic consultation in the intensive care nursery¹ and are usually a sign of a serious neurologic condition. They are most often due to acute symptomatic causes, including treatable conditions such as hypoglycemia, infection, or electrolyte imbalance, as well as brain injuries due to focal or global hypoxia or hemorrhage. In addition, there are several well-described epilepsies with onset in the newborn period. The management of seizures in the intensive care nursery involves rapid and accurate identification of seizures with electrographic correlate, medical management to abolish electrographic seizures, and expedited stepwise evaluation for the cause of seizures.

Detection of seizures by clinical observation is, unfortunately, unreliable; distinguishing epileptic vs nonepileptic paroxysmal events that are detected at the bedside, even by the most experienced clinician, is accurate only approximately 50% of the time.²⁴ Furthermore, neonates often have seizures without clinical correlate, especially after administration of seizure medications or in the setting of severe brain injury.²⁵ Among neonates with HIE who are treated with hypothermia, only half of those with clinical events that are concerning for seizure go on to have electrographic seizures when monitored using prolonged, continuous video-EEG.²⁶

To address the limitations of clinical monitoring and brief intermittent monitoring, the American Clinical Neurophysiology Society provides guidelines for continuous neonatal brain monitoring. There are 3 main indications for monitoring: (1) differential diagnosis of abnormal paroxysmal events, (2) detection of electrographic seizures in selected high-risk populations, and (3) to judge the severity of an encephalopathy. High-risk populations include neonates with encephalopathy, brain injury, critical illness, and central nervous system infection.²⁷ Conventional video-EEG using the International

System 10-20 montage adapted for neonates is the gold standard for monitoring. Adapted montages and trending, for example, aEEG, which is widely used by neonatologists, can provide important information about background and be used for seizure detection, albeit with lower sensitivity and specificity than conventional video-EEG.²⁸ Monitoring should be initiated as soon as possible after the first witnessed paroxysmal event, determination of encephalopathy, or identification of other risk factors. EEG monitoring should continue until 3-4 typical clinical spells have been captured, or the neonate has been without EEG seizures for at least 24 hours.²⁷ At our center, the specialized bedside nurse quickly applies and, along with the bedside team, interprets the aEEG. Concurrent video-EEG is applied using the same machine and head set when the technician is available. The EEG is analyzed remotely, whereas the aEEG is displayed at the bedside. This model of seizure comanagement 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.

There are no widely accepted guidelines for medical treatment of seizures in neonates. A common approach is to treat clinically apparent events, with or without EEG confirmation, sometimes for up to 6 months.²⁹ This approach exposes neonates to potentially harmful medications like phenobarbital and fails to adequately treat electrographic events, by both overtreating paroxysmal events that are not seizures and undertreating seizures that have subtle or no clinical correlate. Expert opinion supports rapid treatment of electrographic seizures using an accepted institutional protocol to lower the burden of electrographic seizures.³⁰ Acute symptomatic neonatal seizures typically resolve within 48-72 hours of onset and have a low risk of early recurrence, and so most neonates can be safely discontinued from medications after resolution of acute symptomatic seizures,³¹ which decreases the duration of exposure to sedating and potentially harmful medications.

Phenobarbital is the most common first-line agent. Seizures are controlled in roughly half of patients using a single loading dose.³² Levetiracetam is increasingly used for refractory seizures.^{33,34} Although pharmacokinetic properties have been studied, and several studies report good safety and tolerability, the efficacy data for levetiracetam are very limited.^{35,36} Phenytoin (or, preferably, fosphenytoin) is another agent for refractory seizures that has similar efficacy as phenobarbital.³² Midazolam infusion is an alternative or add-on agent in refractory cases and status epilepticus.³⁷⁻³⁹ Lidocaine is used for refractory neonatal seizures, especially in Europe.^{40,41}

Neonates who have seizures without apparent cause or have refractory seizures must be evaluated for genetic epilepsies (eg, KCNQ2 epileptic encephalopathy), vitamin-responsive epilepsies, and inborn errors of metabolism.

Brain Imaging

Brain imaging for neonates with neurologic conditions is important to determine both diagnosis and prognosis.⁴²

Critically ill neonates can be safely imaged, optimally with MR imaging (MRI), which is the most sensitive imaging modality to visualize both the white and the gray matter.^{43,44} Ultrasound remains an important bedside tool that is performed urgently for newborns with suspected neurosurgical conditions (eg, intracranial bleed or hydrocephalus), or when more definitive imaging using MRI will be delayed.⁴⁵ We never use computed tomography for neonates, as it requires a relatively high dose of radiation to achieve adequate image resolution.⁴⁶ Core MRI sequences for neonates with encephalopathy include T1, T2, diffusion-weighted imaging, and MR spectroscopy, and must be adapted to account for the higher water content in the neonatal brain.⁴⁷ Susceptibility-weighted imaging is useful for detecting blood products, and vascular imaging (MR angiogram and MR venogram) can be useful when evaluating hemorrhage, vascular malformations, and venous sinus thrombosis.⁴⁸⁻⁵⁰

Developmental Care and the Follow-Up Specialist

For neonatal patients with brain injury, or those at high risk for disrupted brain development, both inpatient developmental care and long-term developmental screening and therapy are critical to optimize neurodevelopmental outcome. Several studies show that supportive care of critically ill infants' development in the intensive care nursery, such as through Newborn Individualized Developmental Care and Assessment Program or Wee Care, has benefits for the preterm population in both the short and the long term. For example, small randomized controlled trials have shown reduced ventilator days and length of hospital stay among children receiving a formal developmental care program, as well as improved parental satisfaction, and mental health and cognitive and language development of the infant.⁵¹⁻⁵³ However, randomized clinical trials and meta-analyses have not shown statistically significant benefits of developmental care programs.⁵⁴ Despite this, many units have adopted developmental care models as the standard of care owing to the many psychosocial benefits and the perception that ultimately, a connection between inpatient supportive care and longer-term outcome will be found to be significant.

Inpatient developmental care in the neurointensive care nursery consists of a multidisciplinary team of nurses, physicians, occupational and physical therapists, lactation experts, and developmental specialists who consider the individual environment and changing needs of each infant during their hospital course. Common issues include positioning and containment, oral feeding readiness and preparation, state regulation, and optimizing tone, strength, and ability to deal with environmental stimulation. Therapies are recommended and provided as needed, and the family is involved in all assessments and interventions.^{55,56}

After discharge, patients with brain injury or who are at risk for disrupted development require specialized follow-up with special focus on motor, cognitive, and behavioral

development. Many institutions provide developmental screening for their former preterm patients, but formalized screening for term infants with seizures or suspected brain injury is not yet commonplace within intensive care nursery follow-up programs. For example, in the state of California, the California Children's Services mandates that all infants cared for in intensive care nurseries who meet specific criteria be followed in high-risk infant follow-up program. The eligibility for California Children's Services has been expanded in recent years to include term infants at risk for chronic neurologic conditions. Within this program, it is mandated that at-risk patients receive neurologic and neuropsychological assessments. A nurse case manager who is familiar with risk factors for neurodevelopmental impairment identifies patients while still inpatient and enrolls them at the time of discharge. If deficits are detected during follow-up, patients are referred to early intervention services for physical, occupational, oral motor or speech, or developmental therapy. In addition, patients with documented brain injury or abnormal neurologic assessment in the nursery are referred to early intervention services upon discharge, and are followed up by a neonatal neurologist. Early intervention has been shown to improve both cognitive and motor outcomes based on the activation of the plasticity of the brain, which is known to vary with age, and therefore early recognition and referral is essential.^{57,58} Communication is key between the neonatal, follow-up clinic, and neurology staff to ensure that proper referrals are made at the time of discharge or at the time neurologic abnormalities are detected or confirmed after discharge to take best advantage of the plasticity window.

Collecting information from these follow-up visits is essential to tracking outcomes. The data generated are used to evaluate new management guidelines or clinical practices and to guide the family counseling and decision making in the nursery. Understanding center-specific outcomes helps ground prognosticating for families and making palliative care decisions. It is critical to educate nurses and medical providers about the management of these high-risk newborns and their outcomes.

Conclusions

Neonatal neurocritical care is a subspecialty that combines expertise in critical care medicine and neurology. A multi-disciplinary team that includes a specialized bedside nurse, a neonatologist, and a neurologist can work together to diagnose and prognosticate acquired neonatal injuries while minimizing secondary injury, and applying neuroprotective agents.

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