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The Role of the Neurointensive Care Nursery for Neonatal Encephalopathy

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KEYWORDS

• Neurocritical care • Infant • Critical care • Therapeutic hypothermia
• Neonatal seizures • Cerebral palsy • Neonatal encephalopathy
• Hypoxic-ischemic encephalopathy

KEY POINTS

- In neonatal neurocritical "brain-focused" care units, all bedside providers maintain constant awareness of the neurologic complications of critical illnesses, and the impact of management on the developing brain.
- Neonatal encephalopathy is the commonest condition treated by a neonatal neurocritical care service.
- A neurocritical care approach may mitigate adverse outcomes among neonates with HIE by preventing secondary brain injury, rapid recognition and treatment of neurologic complications, consistent management using guidelines and protocols, and use of optimized teams at dedicated referral centers.

INTRODUCTION

Neonatal encephalopathy due to intrapartum events is estimated to occur in 1 to 2 per 1000 live births in high-income countries.[1] Outcomes following neonatal encephalopathy due to birth asphyxia include death and neurologic disabilities, such as cerebral palsy, epilepsy, and cognitive impairment.

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Neonatal neurocritical care has emerged over the past decade as a subspecialty that involves a culture change toward a "brain-focused" approach with all bedside providers (physicians, nurses, respiratory technologists, and trainees) maintaining constant awareness of the potential neurologic complications of critical illnesses, as well as the impact of management on the developing or injured brain. Several important advances have prompted this culture change, including increased survival from critical illness, as well as the advent of digital neurophysiology monitoring and safe, high-resolution MRI. Conditions cared for in a neurocritical care unit include neonatal encephalopathy (and hypoxic-ischemic encephalopathy [HIE]), seizures, intracranial hemorrhage, ischemic stroke, and intracranial infection, among others. A neurocritical care approach to monitoring, diagnosis, and treatment of neurologic conditions has been shown to improve outcomes among adults.[2,3] In neonates, a neurocritical care approach may mitigate adverse outcomes among neonates with HIE by preventing secondary brain injury; rapid recognition and treatment of neurologic complications, like seizures; early identification of HIE mimics, like neonatal-onset epileptic encephalopathies; consistent management using guidelines and protocols; and use of optimized teams at dedicated referral centers, although long-term outcome studies are needed to show the benefits of this management.

Neonatal encephalopathy is the commonest condition treated by a neurocritical care service.[4,5] Neonates with HIE require rapid implementation of neuroprotection with hypothermia, have high rates of multiorgan failure, and neurologic signs and symptoms, such as encephalopathy, seizures, and brain injury. Therefore, this condition lends itself to the neurocritical care approach. In principle, a neurointensive care nursery (NICN) can lessen adverse outcomes as a result of prevention of secondary brain injury through attention to basic physiology, earlier recognition and treatment of neurologic complications, such as seizures, consistent management using guidelines and protocols, and use of optimized teams at dedicated referral centers, as discussed later in this article.[6] Moreover, the NICN can also serve as an ideal platform for research. Early diagnosis will allow interventions during critical neuroplasticity windows,[7–9] high-intensity therapies,[10] and patient stratification for novel interventions. For example, recent early phase safety studies have evaluated hypothermia combined with administration of potential biological (eg, erythropoietin[11,12]), inhaled (eg, Xenon[13]) and cell-based (eg, cord blood stem cells[14]) therapeutics.

Establishing a Neurointensive Care Nursery

The neurocritical care approach involves a culture shift for the entire neonatal intensive care unit (NICU) toward brain-focused care, such that providers at every level are continually aware of the potential neurologic complications of critical illnesses and the impact of their management strategies on the developing brain. From the time of birth through patient discharge, the neonatal neurocritical care team serves to prevent secondary injury, implement neuroprotective strategies, including therapeutic hypothermia, manage neurologic complications, optimize developmental care, and establish outpatient developmental services and high-risk follow-up.

To establish an NICN, a leadership team (with representatives from neonatology, neurology, and nursing) must work together to establish a program for the following core functions of the unit:

- Training and education for all providers, including physicians, nurses, nurse practitioners, and respiratory therapists

- Local guidelines for management of neonatal encephalopathy (including resuscitation, implementation, and maintenance of hypothermia and use of extracorporeal membrane oxygenation), as well as neurologic monitoring and treatment of complications, including use of electroencephalogram (EEG) amplitude–integrated EEG (aEEG), seizure treatment, and brain imaging using MRI
- Ensuring adequate resources, equipment, and training for brain monitoring, imaging, and application of hypothermia
- Community outreach and education to foster timely referrals

Current NICNs are closed units, with the neonatologist acting as the physician of record and the neurologist acting as a consultant with an active role in decision-making and communication with the family. The NICN itself may have a dedicated or specific area within the NICU, or else operate "virtually" with a team that can operate at any bedside.

Role of the neonatologist

The neonatologist typically acts as the physician of record and identifies neonates who are eligible for hypothermia and consultation by the NICN team. Neonatologists will perform the initial resuscitation and manage the patient with close attention to physiologic homeostasis with a focus on cardiopulmonary support, maintaining normal electrolyte and glucose levels, and temperature control to minimize secondary brain injury (**Table 1**).

Role of the neurologist

The neurologist takes an early active role from the time of the initial presentation of neurologic signs or symptoms. For neonates with encephalopathy due to birth asphyxia, the neurologist is notified at the time of referral or admission. At most centers, the neonatologist makes the decision of whether or not to initiate cooling therapy, conferring with the neurologist as needed. The neurologist then serves to document a detailed neurologic examination, as well as guide the initial investigation and management decisions, including rapid implementation of hypothermia (if not initiated at the referral center or during transport). The neurologist will often consider other causes of neonatal encephalopathy, such as congenital brain anomalies, intracranial infection

Table 1
Preventing secondary brain injury

Parameter	Approach
Temperature	• Avoid hyperthermia (associated with worse outcomes in term neonates with encephalopathy[16])
Ventilation/ oxygenation	• Maintain normocarbia/permissive mild hypercapnia • Avoid hypoxemia including transfer to extracorporeal membrane oxygenation if needed in cases of severe persistent pulmonary hypertension • Avoid rapid shifts in carbon dioxide tension • Both hypocarbia and hypercarbia can impact cerebral blood flow
Blood pressure	• Maintain normal blood pressure to support cerebral blood flow • Cerebral autoregulation may be impaired[17]
Glucose	• Maintain normoglycemia • Hypoglycemia is associated with both de novo brain injury and worse outcome in the setting of existing brain injury[18–20]

or hemorrhage, inborn errors of metabolism, neonatal-onset epilepsy, and other genetic conditions, and plan additional investigations accordingly.

At the time of admission, the neurologist serves to coordinate with the neurophysiology service for application and interpretation of EEG, and urgent cranial imaging if needed (eg, suspicion for hemorrhage). Along with the neonatologist, the neurologist manages the patient and communicates with the family during the period of critical illness. The neurologist is key in providing guidance for seizure therapy and coordinating with the neuroradiologist to ensure appropriate imaging protocols. Finally, the neurologist perspective is especially important when discussing prognosis and neurologic follow-up with the family, and the neurologist assists with planning outpatient services, such as physical and occupational therapy or Early Start program, especially if the child is expected to have a long-term disabling neurologic condition.

Role of the specialized neurointensive bedside neonatal intensive care unit nurse

The bedside nurse has a vital role in the NICN program.[15] Didactic and hands-on education to care for neonates with neurologic conditions distinguishes the specialized neurologic nurse from the general NICU nursing pool. The nurse learns to recognize neurologic signs and symptoms, as well as interpret the aEEG so the physician can be alerted at the first sign of clinical or electrographic seizure, or worsening of encephalopathy. The bedside nurse can help to optimize care by quickly setting up the cooling blanket and EEG/aEEG machine, which allows for faster treatment. In addition, nurses learn to adhere to management guidelines and anticipate next steps in care, safely transport critically ill neonates to the MR scanner, and communicate effectively with families.

Preventing Secondary Injury

Perinatal asphyxia puts the neonate at risk for end-organ failure, which can lead to cardiopulmonary instability, inadequate brain perfusion, and hypoglycemia. Hypotension, hypoxemia, hypocarbia, hyperthermia, and hypo/hyperglycemia can exacerbate brain injury and so these parameters must be carefully monitored and actively managed by all members of the neurocritical care team from the time of birth (see **Table 1**).

Implementing Therapeutic Hypothermia

Neonatal encephalopathy is the most common condition managed by a neurocritical care service, and therapeutic hypothermia is among the most common treatments.[5,21] Several randomized controlled trials have shown that treatment with hypothermia leads to lower rates of death or disability at 18 to 24 months of age (Relative risk (RR) 0.75, 95% confidence interval 0.68–0.83), and the benefit appears to be sustained through school age.[22–24]

Treatment of neonatal encephalopathy in the setting of a specialized NICN can offer the following benefits:

1. Quicker onset of cooling by an experienced team
2. Rapid, around-the-clock detection and treatment of seizures
3. High-quality brain imaging
4. Counseling for parents by experienced physicians and nurses
5. Timely and accurate diagnosis of conditions that can mimic HIE, such as neonatal-onset epilepsies, inborn errors of metabolism, and congenital central and peripheral nervous system disorders

Screening tools, such as the hypothermia toolkit by the California Perinatal Quality Care Collaborative can help outlying centers to quickly identify neonates who may benefit from hypothermia (**Fig. 1**).[25] Both animal and human studies show that early

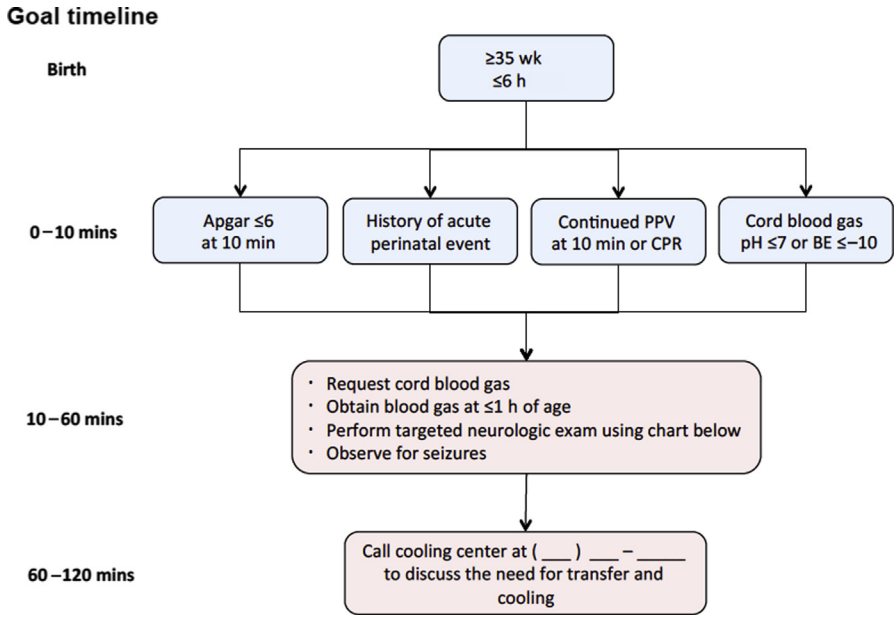

Fig. 1. Screening criteria for evaluation of risk for neonatal encephalopathy. BE, base excess; CPR, cardiopulmonary resuscitation; PPV, positive pressure ventilation.

initiation of therapy is associated with improved outcomes, and so rapid implementation of hypothermia is critical.[26–28] Implementation of hypothermia at the referral center or by the transport team is safe. Use of a portable servo-controlled cooling device on transport provides more stable temperature management with a higher percentage of temperatures within the target range as compared with neonates who are passively cooled.[29]

Guidelines and protocols that are site specific and endorsed by neonatology, neurology, and nursing can help to standardize the approach to implementation of therapeutic hypothermia (**Table 2**).

Managing Neurologic Complications

Although recent reports suggest that the burden of seizures among neonates undergoing hypothermia is lower than for neonates who are not cooled, the risk remains approximately 50%.[30–32] Neonates with encephalopathy due to perinatal asphyxia should receive neurophysiology monitoring using continuous, video EEG and/or a simplified montage aEEG monitoring for bedside use. Continuous neurophysiology monitoring is important to evaluate dynamic change in background brain activity and degree of encephalopathy, as well as seizures. Clinical indicators such as resuscitation parameters and degree of encephalopathy do not appear to be associated with risk of seizures. An abnormal initial EEG background (ie, excessively discontinuous, burst suppression, depressed and undifferentiated, or extremely low voltage) is associated with greater than 60% seizure risk. Neonates with a normal initial EEG background have the lowest risk of seizures (~10%).[30] The EEG and aEEG recordings also provide important prognostic information that can be used to start counseling parents regarding risk of disability and goals of care. Early normal or mildly abnormal

Table 2
Guidelines for therapeutic hypothermia

Guideline	Examples of Guideline Contents
Therapeutic hypothermia	• Inclusion/exclusion criteria • Resuscitation and transport procedures • Temperature monitoring and management • Cardiopulmonary support • Use of extracorporeal membrane oxygenation • Sedation • Laboratory/blood work • Hydration/nutrition • Brain monitoring • Imaging • Skin care
Seizures	• Monitoring modality and duration • First, second, and third-line antiseizure agents
Imaging	• Timing • Sequences • Safe transport • Use of magnetic resonance–compatible equipment

EEG/aEEG is reassuring for a good prognosis, whereas an early severely abnormal EEG/aEEG (eg, burst suppression, depressed and undifferentiated, extremely low voltage, or status epilepticus at the onset of recording) is associated with a poor prognosis and brain injury if it persists beyond 24 to 36 hours of life.[33,34]

aEEG and full-montage EEG can be recorded by using the same system. The aEEG can be displayed at the bedside for the neurocritical care team and the full-montage EEG sent to remote servers for access in the neurophysiology laboratory or personal device. The limited montage of the aEEG can be easily applied at the time of admission so that the bedside nurse and neonatology team can quickly assess the degree of encephalopathy and for the presence of seizures. The full-montage EEG is applied as soon as a technician is available. The aEEG is then available as a screening tool for the bedside neurocritical care team and yet the EEG is available to the neurophysiologist as the gold standard to confirm presence or absence of seizures and detect seizures that are not visible on the aEEG recording.[35]

Neonates undergoing hypothermia are at high risk for brain injury. MRI is an important tool to assess the location and severity of injury, and to rule out other causes of encephalopathy (eg, dysgenesis).[36,37] Furthermore, moderate-severe injury on MRI is associated with a high risk of death or disability.[38] The neurocritical care team should be prepared to safely take a critically ill neonate to the MRI scanner. Resources for safe transport include MRI-compatible incubators, ventilators, and cardiopulmonary monitoring equipment, as well as skilled staff who have completed training and mock codes in the MRI suite. The optimal timing of MRI may depend on the resources of the neurocritical care team. Because the appearance of the injury evolves over time, neonates at a given center should be imaged within a standard time frame. Imaging neonates just after cooling has ended (day 4–6) offers several advantages:

1. Lower need for sedation, as the neonate often remains encephalopathic
2. Serves as a good turning point between the neurocritical care phase of the admission and convalescence
3. MRI can be performed before discharge home

At some centers, the second week of life is the preferred timing for imaging, as there are rare reports that the brain injury can evolve over this time period. To mitigate issues related to timing of imaging, it is our practice to repeat imaging in a neonate whose early scan is normal but who remains encephalopathic after the first 5 to 7 days after birth or if the results of ancillary testing are discordant (ie, very abnormal neurologic examination or EEG results and/or difficulty establishing feeding and with a normal MRI).

Palliative Care

Unfortunately, therapeutic hypothermia does not prevent death or developmental disabilities in all patients with neonatal encephalopathy due to birth asphyxia; approximately 50% have adverse outcome.[39] When a neonate has multiorgan failure that is not compatible with life, and/or is expected to develop severe and permanent developmental disabilities, the neurocritical care team may wish to discuss the option of transition to a palliative approach. Using information from the neurologic examination, EEG and aEEG, and MRI, an experienced team can predict those children who are likely to suffer severe disabilities, and counsel the family accordingly.[40] The entire neurocritical care team, including the neonatologist, neurologist, and bedside nurse must work together to provide a consistent message to the family and provide compassionate supportive care.

Compassion fatigue and burn out are common among bedside providers who frequently care for children with adverse outcomes. All members of the team should be given the option to request a different patient assignment in case of ethical concerns or compassion fatigue. An important aspect of the NICN is to provide specialized neurologic nurses with adequate breaks, psychological support, and a safe space to debrief difficult cases, as well as updates on children with good outcomes.

Optimizing Developmental Care

Once the neonate with encephalopathy has recovered from the critical illness, the focus of the neurocritical care team should turn toward achieving oral feeds and optimizing developmental outcomes. Inpatient services include consultation with physical and occupational therapists, as well as lactation consultants. Neonates with neurologic disorders may need assistance with state regulation, positioning, and oral feeding readiness and preparation, as well as optimizing tone, strength, and ability to take in external stimuli. The family also should learn about developmentally appropriate exercises (eg, upright positioning, tummy time, language exposure, and early exposure to fine motor tasks). Enriched environments can provide the intensive, repetitive, task-specific interventions that are needed for improved outcomes.[7,8,41,42]

Outpatient Developmental Services and Neurologic Care

Survivors of neonatal encephalopathy due to perinatal asphyxia are at high risk for long-term disabilities, including cerebral palsy, epilepsy, and intellectual disabilities. A neonatal neurointensive care program should make provisions for outpatient care by a neurologist and/or high-risk infant program. The American Academy of Pediatrics recommends that longitudinal neurodevelopmental outcome be monitored in all neonates who undergo hypothermia.[43] Although practically speaking, this means follow-up until 18 to 24 months of age, this is inadequate to capture major learning milestones. Consideration of follow-up through age 6 is

encouraged to better evaluate the ultimate impact of neonatal neurointensive care interventions.

SUMMARY/DISCUSSION

Neonates with encephalopathy are often critically ill with multiorgan failure. They are at high risk for brain injury and seizures, which can lead to death or long-term disabilities. A NICN can optimally support neonates by providing brain-focused care from the time of resuscitation through discharge home. Members of the neurocritical care team include a neonatologist, neurologist, and specialized bedside nurse. Guidelines and protocols can help to standardize care and optimize therapies. Early recognition and treatment of neurologic complications, such as seizures, as well as prevention of secondary brain injury through attention to basic physiology can minimize brain injury. Finally, experienced teams at dedicated referral centers provide the specialized care that children and parents need, which includes close follow-up to address late-emerging issues.

Best practices

What is the current practice?

Therapeutic hypothermia is standard of care for neonates with encephalopathy due to perinatal asphyxia who would have fulfilled inclusion and exclusion criteria for the clinical trials.

Best Practice/Guideline/Care Path Objective(s)

Neonates with encephalopathy should be quickly identified and transferred to a center with experience in management of multiorgan failure, neurologic complications, and therapeutic hypothermia.

What changes in current practice are likely to improve outcomes?

1. Careful attention to basic physiology, including temperature regulation, glucose homeostasis, oxygenation, and blood pressure support to prevent secondary injury;
2. Use of protocols and/or guidelines;
3. Early recognition and treatment of neurologic complications;
4. Management by an experienced, multidisciplinary neurocritical care team in a dedicated referral unit.

Major Recommendations

- Establish an experienced team of neonatologists, neurologists, and bedside nurses to manage neonates with encephalopathy due to perinatal asphyxia.
- Establish guidelines to manage implementation of therapeutic hypothermia, brain monitoring, seizure treatment, and brain imaging.

Summary Statement

A NICN can optimally support neonates with encephalopathy due to birth asphyxia by providing brain-focused care from the time of resuscitation through discharge home.

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