Title: The neurointensive nursery: concept, development, and insights gained

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Short Title: The neurointensive care nursery

Introduction

With the advent of therapeutic hypothermia for the treatment of hypoxic-ischemic encephalopathy, a new era of neuroprotection has begun for the care of the newborn with brain injury. Implementing such treatments requires a multi-disciplinary approach to "brain focused care." The Neurointensive Care Nursery (NICN) is a model of co-management of the at- risk newborn by a team comprising neurologists, neonatologists, and specialized nurses. Development of standardized protocols has optimized consistency of care and establishment of best practices. Central to treatment of these newborns is the availability of neuro-monitoring around the clock, including video EEG monitoring, aEEG monitoring, and state of the art MRI that provide a basis for rapid diagnosis and stratified treatment. Specialized nurses are critical to evaluate and properly triage newborns as a part of optimized care. Given progress in understanding evolution of brain injury, the impact of neonatal seizures, and the benefit of appropriate interventions, the NICN becomes indispensible in adopting new standards of care as well as a platform for research and further dissemination of knowledge. We envisage that the NICN of the future will incorporate novel technologies (e.g., whole genome diagnostics) and systems to capture long-term outcomes and demonstrate enduring benefit to patients.

Origins and Principles of Neonatal Neurocritical Care

Neurocritical care is an established subspecialty that combines expertise in neurology and critical care medicine. It is the intensive care provided for adults and children with severe neurological or neurosurgical conditions and combines specialized neurological monitoring and clinical expertise, as well as a culture shift for an intensive care unit (ICU) toward “brain-focused care.” Therefore, all providers are continually aware of the potential neurological complications of critical illnesses and how their management may be influencing the brain.[1-3] This culture shift can be achieved through education and development of specialized teams that work together using common management guidelines. In neonates, the team must pay particular attention to the impact of critical illnesses and management strategies on the *developing brain*, arguing for a comprehensive team approach that involves intensivists, developmental clinicians and even basic scientists.

The goal of neurocritical care is to minimize the impact of the initial insult or underlying condition through supportive and interventional clinical management to prevent ongoing or secondary brain injury, implement neuroprotective strategies and minimize adverse neurological outcomes after a primary insult such as traumatic brain injury, ischemic stroke, intracranial hemorrhage and global hypoxia.[1] The neurocritical care approach involves routine management of physiology (temperature, blood pressure, glycemia, among others), combined with intensive monitoring of brain activity through continuous electroencephalogram (EEG) and, in neonates, adapted monitors such as amplitude-integrated EEG (aEEG), monitoring intracranial pressure and autoregulation through invasive monitors in adults and children, as well as proxy measures such as near infrared spectroscopy (NIRS) and continuous invasive blood pressure monitoring in

neonates, as well as detailed brain imaging using MRI to determine diagnosis, extent of injury and prognosis.

Neurocritical care in adults has proven benefit[4,5] While there is less evidence in neonates, this vulnerable group should in principle also benefit from optimizations inherent in a focused neurocritical care approach, e.g., through recognition of neurological conditions, prevention of secondary brain injury, rapid identification and treatment of neurological complications such as seizures, consistent management using guidelines and protocols, careful consideration of gestational age and appropriate developmental care, the use of optimized teams at dedicated referral centers, and research. Specifically, a specialized neonatal neurocritical care service can offer the following brain care measures: rapid implementation of therapeutic hypothermia and other neuroprotective strategies by an experienced team, around-the-clock detection and standardized treatment of seizures with continuous brain monitoring, high quality brain MR imaging, and parent counseling by experienced physicians and nurses.

The neonatal neurocritical care approach starts at the time a neurological condition (or high risk for a neurological condition) is recognized and does not end until the family has been appropriately counseled about diagnosis and prognosis, and child has been referred for intervention services and follow-up for careful developmental monitoring to mitigate the longterm effects of early brain injury.

Conditions Treated by a Neonatal Neurocritical Care Service. Unlike adults, the majority of neonates that are evaluated by a neurocritical care service have a primary medical diagnosis as the reason for admission, including complications of prematurity and congenital heard malformation.[6,7] The most common conditions treated within a neonatal neurocritical care service are encephalopathy and seizures, usually due to global

hypoxic-ischemic injury, focal arterial and venous infarcts, intracranial hemorrhage and infection.[6,8]

Development of a Neurointensive Care Nursery (NICN)

Over the past decade, neurointensive care nurseries and neonatal neurocritical care services have opened at a number of centers. They are also an exciting paradigm shift in neonatal intensive care with the potential to influence how all neonates at risk for brain injury receive care. They represent a well-coordinated, multidisciplinary approach to "brain focused care," but require a considerable assembly of clinical expertise and commitment of institutional resources.

Neonatal Neurocritical Care patients can range from well appearing babies with only subclinical symptoms to profoundly ill neonates with multisystem organ dysfunction. But unlike adult and pediatric neurocritical care patient populations, half of NICN patients are admitted for medical issues other than a primary neurological disorder, placing greater emphasis on the care of the baby as a whole.[6,7] Co-morbidities may include hemodynamic collapse, electrolytes and metabolic derangements, coagulopathy, systemic and CNS infection, and cardiorespiratory failure requiring extracorporeal life support (ECLS/ECMO).[9] Thus, many Neonatal Neurocritical Care Programs are in high-acuity NICU settings at larger tertiary care hospitals with pediatric surgical and subspecialty support; and often Centers of Excellence in pediatric neurologic care. We describe the evolution of the first NICN at University of California at San Francisco (UCSF) in April 2008 as a road map for the development of NICN Programs.

<u>Initial Planning and Program Proposal</u>

In the spring of 2007, leaders from the Divisions of Neonatology and Pediatric Neurology at UCSF committed to develop a model of co-managed care to leverage emerging advances in neuromonitoring, neuroimaging, treatment and prevention to improve outcomes for neonates at risk for brain injury. Stakeholders from neonatology, child neurology, neonatal nursing, neurophysiology/epileptology, neuroradiology, developmental and follow-up care convened several planning meetings. These discussions helped identify the core leadership group as well as the services and protocols required to support an interdisciplinary neonatal neurocritical care service. The specific aim of the Program was to improve neurodevelopmental outcomes in newborns at risk of neurological disability. A proposal for strategic support was submitted to the UCSF Medical Center as well as philanthropic organizations for initial funding and the Neurointensive Care Nursery (NICN) at UCSF opened in July 2008.

Building the team

A key step in development of the NICN model of care was the addition of a dedicated neonatal neurologist to help “co-manage” babies with the neonatologist. This was a significant staffing commitment by the Department of Neurology, but changed the role of the neurologist from occasional consultant to an active member of the neonatal critical care team. The neurologist could now be involved in the care of the baby from the point of admission or initial diagnosis of a neurologic problem through to discharge. This brought a full-time neurological perspective to the ICN team to help perform comprehensive neuro evaluations and exams, facilitate diagnosis and management of seizures, interpret neuroimaging and neuromonitoring data, discuss prognosis with families, and provide continuity of care after discharge from the intensive care nursery.

This is supported by evidence that having a dedicated neonatal neurologist partner with the team at a tertiary care NICU can result in a greater number of neurology consults with a wider variety of diagnoses.[10]

Another essential component of the NICN was commitment from neonatal nursing, including a cohort of specially trained NICN nurses. All ICN nurses received some additional NICN training as part of Annual Review. But a cohort of nurses with interest in NICN care volunteered to completed additional training on common neurologic conditions affecting neonates, with a focus on pathophysiology, clinical presentation, diagnostic tests, treatment protocols and integration of neurologic monitoring into daily bedside care. Special competency-based training modules were also created to maintain and verify nursing skills. Once an adequate cohort was trained, two (2) NICN nurses were scheduled each nursing shift to respond to neurologic emergencies, ensure NICN protocols were appropriately followed, and act as a resource for brain-focused care to other nursing colleagues. NICN nurses play a critical role at the bedside with the ability to recognize acute changes in neurologic status, then rapidly implement appropriate protocols or continue to monitor patients to prevent secondary injury.[11]

The role of NICN Director was shared between a neonatologist and neonatal neurologist. Other dedicated NICN specific roles included a NICN Program Coordinator and Nurse Educator. Existing services used frequently by the NICN but shared with other services included neuroimaging (US, MRI) and neurophysiology/epileptology (vEEG). Other services shared with the ICN included pharmacy, nutrition, OT/PT, child life, social work, spiritual and palliative care, and developmental specialists from the

Newborn Individualized Developmental Care and Assessment Program (NIDCAP). All were considered stakeholders and were invited to participate in weekly NICN working group meetings.

Organizational Structure and Provider Guidelines

A core principle of the NICN program is a multidisciplinary approach to care (**Figure 1**).

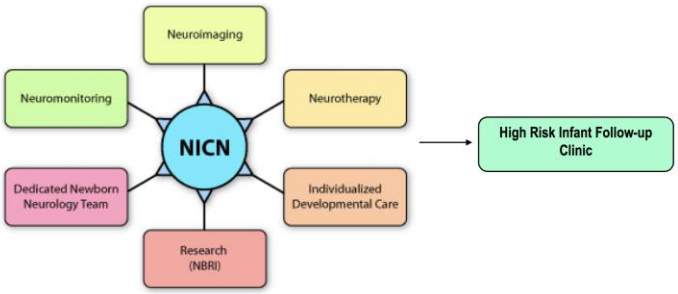

Figure 1. Organizational Structure of the NICN

A working group of the various stakeholders met weekly to identify important clinical workflows and help develop clinical practice guidelines and protocols related to the NICN population. In addition to neonatology, neonatal neurology and neonatal nursing, the working group included neurophysiology/epilepsy, neuroimaging, neurosurgery, developmental care, PT/OT, nutrition, social work, case management and high-risk infant follow-up.[12] The working group identified key practices related to NICN workflows, which were then developed into evidence-based guidelines and protocols (**Table 1**).

Table 1. NICN Provider Guidelines & Protocols

- NICN/ICN Co-management Guidelines
- Neonatal Neurologic Exam
- Neurologic Care for the ‘At-Risk’ Newborn
- Therapeutic Hypothermia Protocol (Inborn Babies)
- Therapeutic Hypothermia Protocol (Outborn Babies)
- Therapeutic Hypothermia and FEN Management
- Therapeutic Hypothermia and Pulmonary Hypertension
- Therapeutic Hypothermia and ECMO
- Therapeutic Hypothermia Transport Guidelines
- Therapeutic Hypothermia Early Exit Guidelines
- Late Identification of Encephalopathy and HIE
- Seizure management
- Triage System for EEG Interpretation
- Stroke Management Guidelines
- Post Hemorrhagic Hydrocephalus Guidelines
- Myelomeningocoele Patient Care Guidelines
- Conventional (cEEG) Monitoring Guidelines
- Amplitude-integrated (aEEG) Monitoring Guidelines
- EEG Interpretation
- NIRS Monitoring Guidelines
- NICN Evaluation in Cardiac Patients
- MRI Ordering of Study Scans
- MRI Evaluation in Cardiac Patients
- Guidelines for Preterm Newborn Imaging
- Guidelines for Preterm Newborn Monitoring
- NICN Discharge planning
- Pediatric Brain Death Determination

Protocol guided care

Protocol guided care brings consistency of approach to the management of NICN patients. Standardization also improves our ability to conduct meaningful clinical investigations by minimizing variability in this high-acuity population of patients. Protocols and practice guidelines were incorporated into provider training, nursing competencies and Annual Review for NICN nurses. They were also disseminated to affiliated delivery hospitals through the Neonatal Outreach Education Program, as well as by regional collaborative workshops. Working together through regional collaboratives, protocols were shared and contributed to the development of a California

Statewide HIE screening campaign,[13] as well as the adoption of California Statewide standards for programs providing therapeutic hypothermia to neonates.[14,15]

New provider guidelines and protocols are created while existing guidelines are continuously updated after practice-based feedback discussed during NICN leadership group meetings. The NICN leadership group also supports ongoing clinical research projects, develops education and training programs, monitors programmatic outcomes and quality improvement, provides peer-support for staff and conducts outreach education for referring hospitals.

The Evidence for Neonatal Neurocritical Care

There is increasing evidence that an NICN approach can improve care for neonates with neurological conditions.

Availability of a Neonatal Neurologist. Most published reports of neonatal neurocritical care programs include involvement of a neurologist with special expertise in neonatal neurology.[6,7,10,12,16] Mulkey and Swearingen specifically evaluated the impact of having a dedicated neonatal neurologist at a single neonatal intensive care nursery. When comparing the period post-neonatal neurologist to the period pre-neonatal neurologist, there were twice the number of consultations and twice the number of visits per patient as well as increased use of video-EEG and a larger variety in types of patients evaluated.[10]

Neuromonitoring. The utilization of neuromonitoring using continuous prolonged video-EEG studies within the neuro-intensive care nursery varies widely with reported rates between 35-67%, [6,7,10] which may depend on use of American Clinical Neurophysiology Society guidelines for monitoring or the definition of what constitutes a NICN patient.[17] Several studies show a positive impact of increased use of video-EEG within a neonatal neurocritical care program. Wietstock et al evaluated the yield of continuous video-EEG and showed that electrographic seizures were captured in 26% (with 24% of those having seizures with no clinical correlate) and in 13%, clinical seizures were suspected but ruled out based on normal video-EEG monitoring.[18] The same group showed a substantial decrease in the use of phenobarbital (on average 30mg/kg less) for neonates with encephalopathy and seizures after implementation of continuous video-EEG throughout the period of therapeutic hypothermia and rewarming and within the context of an NICN,[19] as well as increased detection of EEG seizures without clinical correlate.[20]

Bashir et al similarly evaluated the use of continuous video-EEG within the context of a neurocritical care service and also found improved EEG seizure detection, decreased overall phenobarbital doses and reduced use of anti-seizure medication at the time of discharge home.[16]

Treatment Pathways. Harris et al describe a treatment algorithm for neonatal status epilepticus that was developed and endorsed by neonatologists, neurologists and pharmacists.[21] They describe an estimated absolute reduction in seizures progressing to status epilepticus of 10%, as well as a decreased length of stay after implementation of the algorithm. Limitations of the study include small sample size, lack of randomization and limited statistical analysis, nonetheless, it demonstrates that treatment algorithms may improve seizure treatment.

Preventing Brain injury

Intraventricular Hemorrhage (IVH) Prevention Bundles. IVH and periventricular hemorrhagic infarction (PVHI) are common complications of premature birth and are associated with adverse neurodevelopmental outcomes.[22] "IVH prevention bundles" have emerged in the qualitative literature as important tools for reducing morbidity associated with IVH. Measures include delayed cord clamping, minimizing handling, midline head positioning, limiting infusion rates, and frequent multidisciplinary assessments.[23-25]

Infection. Preventing hospital-acquired infection is an important measure of quality of care. Infection acquired in the neurocritical care unit has been addressed in the adult literature.[26] The topic of infection control in the neonatal NICN is particularly important

given the relationship between sepsis and necrotizing enterocolitis and brain injury (and particularly white matter injury) and developmental outcome in preterm neonates.[27,28]

Preventing Secondary Brain Injury. Preventing secondary injury has played an important role in adult neurocritical care and there is increasing evidence that attention to basic physiology is also important for neonates with brain injury. Optimizing brain metabolic environment and perfusion are the focus of secondary injury prevention. The neonatal neurocritical care service has a role to play to monitor and manage temperature, carbon dioxide and glucose, as well as oxygenation and blood pressure (**Table 2**).

Temperature. Targeted temperature management (TTM) is often used in the neurocritical care unit to minimize secondary brain injury after trauma, hypoxia-ischemia, stroke and hemorrhage, and can lead to improved outcomes, with the strongest evidence for adult cardiac arrest and neonatal hypoxic-ischemic encephalopathy.[29,30] TTM can include therapeutic hypothermia, active normothermia and fever treatment. A primary mechanism by which TTM can prevent secondary brain injury is by reducing metabolic demand (and thereby reducing processes that can be regulated by metabolic rate such as inflammation and free radical production).

Therapeutic hypothermia for neonatal encephalopathy presumed due to hypoxia-ischemia has been standard of care for almost a decade, with evidence for reduced death and disability at 18-22 months, as well as higher rates of normal outcome and lower rates of death and disability persisting until school age.[31,32] Wyatt et al reported that neonates enrolled in the CoolCap trial who had temperatures at least 38^{o}C had a higher risk of death and disability, even among those who received cooling and, therefore, prevention of pyrexia is paramount.[33]

Ventilation. Cerebral perfusion is related to CO_2 such that hypocapnia can lead to vasoconstriction and reduced cerebral blood flow. Secondary analyses of large randomized controlled trials of hypothermia show higher rate of death and disability among neonates with lower CO_2 in the first 72 hours or increased cumulative exposure to hypocarbia.[34,35] The results held true for both moderate and severe encephalopathy as well as after adjusting for pH, amplitude-integrated electroencephalogram background and seizures, birth weight, Apgar at 5 min, and cooling status.[34]

Glucose management. Although neonates typically tolerate lower glucose values than older children or adults, hypoglycemia can cause de novo brain injury in neonates.[36] A secondary analysis of CoolCap study showed that neonates with normal glucose measures had the lowest rates of death and disability, as compared to those with hypoglycemia (highest rate of death or disability) and hyperglycemia (intermediate).[37] Tam et al reported an increased risk of brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy who had hypoglycemia within the first 24 hours after birth.[38] The role of active glucose management, especially for hyperglycemia, is uncertain, although carefully monitoring and minimizing both hypoglycemia and fluctuations glucose levels in the brain injured patient is probably warranted.

Oxygenation and blood pressure management have been extensively studied in preterm neonates, particularly during the first “golden hour” after birth.[25] Both high and low oxygen saturation can have toxic effects. A Cochrane review of the major trials of oxygen management during hospitalization concluded a higher rate of death with lower target oxygen saturation (85-89%) and higher rate of retinopathy of prematurity with higher target oxygen saturation (90-95%).[39] Adequate blood pressure is required to maintain brain perfusion; low blood pressure and rapid infusions have been linked to

intraventricular hemorrhage.[40] The role of PDA in regulation of CBF in the preterm infant is uncertain. Together, these studies suggest that close attention to and management of basic physiologic measures are important to neonatal brain health, however well designed studies of management pathways are needed to definitively determine whether active management to maintain normal physiologic values can impact outcome.

Table 1: Brain focused care to prevent secondary brain injury

Parameter	**Approach**

Temperature	• Targeted temperature management:
	  ○ Implement hypothermia as indicated for neonatal encephalopathy due to hypoxia-ischemia
	  ○ Maintain normothermia if hypothermia is not indicated
	  ○ Treat fever

Ventilation	• Maintain normal CO_2 and avoid hypocapnia
Glucose	• Maintain normoglycemia: avoid both hypo and hyperglycemia
Blood pressure	• Maintain normal blood pressure • Cerebral autoregulation may be impaired

Developmental care. Preterm neonates <37 weeks gestational age at birth are at very high risk for long term motor, cognitive and behavioral problems, even in children without

acute brain injury. The role of developmental care interventions (e.g. kangaroo care, various parent involvement programs, newborn individualized developmental care program, NIDCAP, and massage, among others) have been widely studied with some evidence for benefit, although it is uncertain which elements beyond enhanced holding, touching and parent involvement are keys to improved neurodevelopment.[41] The extent to which term neonates with brain injury may benefit from a similar approach is not known, however early involvement of physical and occupational therapy and parent education about enriched environments is warranted[42], and moreover, such interventions can provide valuable assessment information.

Conclusions and Future Directions

This review has described evolution of the NICN (or, Neuro-NICU), a model of care that is becoming more widely adopted at many regional centers of excellence. In the NICN of the future, new technologies will enhance clinical protocols and precision medicine for infants at risk for neurological injury. These include (1) functional MRI, (2) continuous neurophysiological assessment with machine learning tools to make bedside EEG reading more robust and accessible, and (3) whole genomic approaches to rapidly diagnose patients with neurogenetic or severe metabolic conditions. Genome diagnosis is particularly relevant to consider in the context of neonatal seizures. Indeed, we expect genome sequencing will become routine to stratify patients for appropriate drug treatments, such as oxcarbazepine or carbamazepine for *KCNQ2* mutation causing encephalopathy.[43]

The NICN model is generally considered by clinicians to be an advance in bedside care. The NICN model empowers staff to use the latest tools in the treatment of infants at risk for neurological injury. We have seen encouraging data from hypothermia trials and new

neuroprotective trials are likely to provide additional treatments. An added substantial benefit is providing comprehensive information for counseling families that face difficult decisions. However, the big test question for the NICN/Neuro-NICU model is: Does it improve long-term outcomes? The answer will come from long term follow up and therefore a decision to develop a NICN program should ideally be matched with a commitment to follow children through school age and beyond to definitively show this model provides enduring benefit to patients.

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