Neonatal Neurocritical Care Series

Neuromonitoring in Neonatal Critical Care Part II: Extremely Premature Infants and Critically Ill Neonates

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Impact:

- For extremely premature infants, NIRS monitoring has a potential role in individualized brain-oriented care, and selective use of aEEG and cEEG can assist in seizure detection and prognostication.
- For critically ill neonates, NIRS can monitor cerebral perfusion, oxygen delivery, and extraction associated with disease processes as well as respiratory and hypodynamic management. Selective use of aEEG and cEEG is important in those with high risk of seizures and brain injury.
- Continuous multimodal monitoring as well as monitoring of sleep, sleep wake cycling and autonomic nervous system have promising role in neonatal neurocritical care.

Abstract

Neonatal intensive care has expanded from cardiorespiratory care to a holistic approach emphasizing brain health. To best understand and monitor brain function and physiology in the neonatal intensive care unit (NICU), the most commonly used tools are amplitude integrated EEG (aEEG), full multichannel continuous EEG (cEEG), and near infrared spectroscopy (NIRS). Each of these modalities has unique characteristics and functions. While some of these tools have been the subject of expert consensus statements or guidelines, there is no overarching agreement on the optimal approach to neuromonitoring in the NICU. This work reviews current evidence to assist decision making for the best utilization of these neuromonitoring tools to promote neuroprotective care in extremely premature infants and in critically ill neonates. Neuromonitoring approaches in neonatal encephalopathy and neonates with possible seizures are discussed separately in the companion paper.

Introduction

Bedside neuromonitoring technology is central to providing neurocritical care. Neuromonitoring tools commonly used in the NICU include amplitue integrated electroencephalography (aEEG), multichannel conventional electroencephalography (cEEG) and near-infrared spectroscopy (NIRS). More details of these neuromonitoring tools and their applications in term neonatal encephalopathy and neonatal seizures were described in part I of this review, published in the same issue. In part II, we describe the application of neuromonitoring tools in extremely premature infants, and the critically ill neonate. Also, we provide an overview of the importance of multimodal monitoring as well as sleep and autonomic nervous system monitoring in the NICU. The use of neuromonitoring tools in common NICU scenarios described in this two-part article is summarized in **Table 1.**

Extreme Prematurity

With improved overall survival, the care of extremely preterm infants now focuses on optimizing neurodevelopmental outcomes. Complications of extreme prematurity, such as respiratory distress syndrome or necrotizing enterocolitis (NEC), while not primary neurologic disorders, are nonetheless associated with adverse long-term neurodevelopmental outcomes. Increasingly, the comprehensive care of extremely preterm infants includes neuromonitoring with the goal of neuroprotection.

aEEG in Extremely Preterm Infants in First Days of Life

aEEG can be easily and safely applied in extremely preterm infants. [1] An expected maturation of aEEG background occurs with increasing postmenstrual age. **(Figure 1)** Early aEEG background during the first days of life is predictive of long-term outcomes. [2-7] Abnormalities on aEEG are associated with brain injury, such as intraventricular hemorrhage [8] and later adverse outcomes. [9] Normal features on aEEG, such as cyclicity indicating emerging sleep wake cycling (SWC), are associated with good prognosis. When interpreting aEEG in extremely preterm infants, it is important to recognize that the aEEG may also be impacted by sedative and analgesic medications, hemodynamic changes, carbon dioxide levels, and plasma glucose levels. [10-14] Besides the physiological changes and sedatives, low amplitude artifacts such as ECG and high-frequency oscillatory ventilation (HFOV) can alter background activity or mimic seizures. A systematic review of 10 articles highlighted relatively low and variable sensitivity and specificity in seizure detection. Accuracy and inter-reader agreement were better when aEEG was interpreted by experienced readers with similar level of training.[15] Over the last decades several authors have described aEEG characteristics across gestational and postconceptional age based on continuity (background pattern), lower margin voltage, bandwidth span and cycling (SWC). [7,16] Burdjalov proposed a qualitative scoring system to describe the maturation of neonatal brain and allow an objective comparison of aEEG tracing between different patients and different time points within the same patient. [7] **(Table 2)** A 2 weeks or more delay in Burdjalov scoring has been evaluated as a predictor of adverse outcome.[17] Recently, a stepwise approach was suggested by Deshpande et al. to assess pathological pattern and maturation at bedside. [16] The aim of this stepwise model was to help clinicians to integrate aEEG interpretation in clinical practice for neurological surveillance of preterm infants.

While several studies have demonstrated that early aEEG patterns in extremely preterm infants may predict unfavorable outcomes, there are no studies evaluating whether responding to abnormal aEEG patterns improves long-term outcomes. Thus, for experienced users, aEEG can be a useful tool to assess brain health and to formulate prognosis in extremely preterm infants especially with high risk of brain injury e.g., high grade intraventricular hemorrhage; ongoing studies are needed to determine how aEEG may guide intervention at the bedside.

cEEG in Extremely Preterm Infants

cEEG monitoring is useful for extremely preterm infants when a detailed assessment of cortical function is needed or when aEEG is suggestive of seizures. However, multichannel recordings require special care to optimize safety and signal quality in the youngest preterm infants. [13,18] Although EEG electrode application in this population is challenging due to limited space, humidified incubator, infection control and fragile skin, one study of cEEG in 70 neonates <32 weeks gestational age (GA) and another of 50 neonates <30 weeks GA reported no instances of skin breakdown when using such approach. [19,20] Hydrogel electrodes, EEG caps with electrodes are increasingly available to help easy application and improve the quality of recordings. [19,21] Despite the advances in application of EEG electrodes, skin integrity requires dedicated care.

Prior studies of qualitative EEG analysis showed that visually observed surface positive sharp waves of short duration over the centro-temporal region (PRS waves, positive rolandic sharp) indicated the presence of intraventricular hemorrhage (IVH) and white matter injury in preterm infants. [22,23] Recently, limited data also suggested that cEEG changes may provide early indicators of IVH even prior to ultrasound diagnosis. The analysis of burst morphology revealed

sharper and more asymmetric bursts prior the onset of IVH. [8] Furthermore, cEEG findings can predict neurodevelopmental outcome in extremely preterm infants starting from the first few days of life, and possibly has the highest predictive value closer to term equivalent age. [24,25] Finally, cEEG continues to be the gold standard for detection of seizures in preterm infants. As discussed in part I of this review, caution is needed in the diagnosis of seizures in preterm infants even when EEG is used. Rhythmic EEG patterns due to artifacts from routine care and other rhythmic non-epileptic activities could look like seizures especially on aEEG and need to be interpreted carefully. Moreover, in spite of abundance of seizures in this population and their potential association with adverse outcome, specific guidelines for treating seizures in this population are lacking. [26]

NIRS Monitoring in Preterm Infants

NIRS monitoring is useful in preterm infants for several complementary reasons. First, preterm infants commonly encounter abnormal pulmonary function, and unstable cardiovascular physiology, and receive systemic interventions that can impact cerebral oxygen delivery. Second, the brain of the preterm infant is only four to six millimeters below the skin surface, which minimizes interference from extracerebral tissue and makes NIRS monitoring particularly feasible. Finally, brain injury and neurodevelopmental impairment are frequent within this group, underscoring the need for better understanding of underlying pathophysiology. Therefore, NIRS monitoring of extremely preterm neonates has been adopted as routine practice in some NICUs. [27]

Many studies have explored reference values of NIRS in preterm infants and changes associated with peri/intra-ventricular hemorrhage. [28-32] In extremely preterm infants, it is possible to reduce

the burden of cerebral hypoxia using a combination of NIRS monitoring and an evidence based treatment guideline to adjust cardiorespiratory support during the first three days of life. [33] While this intervention did not significantly reduce brain injury detected by cranial ultrasound or MRI, early EEG, molecular biomarkers of cerebral injury, or two-year neurodevelopmental outcome, [34-36] it offers promising proof of principle for NIRS to individualize brain care. Moreover, NIRS has a potential role in monitoring cerebral perfusion and management of those with post-hemorrhagic ventricular dilatation. [37] Regional cerebral oxygen saturation is progressively impaired with increasing dilatation, and gradually improves following CSF drainage.[38,39]

While not readily available in clinically used devices, another potentially relevant use of NIRS in preterm infants is in the continuous assessment of cerebrovascular reactivity. [40] Disturbance of cerebral autoregulation is thought to be a key factor in perfusion related brain injury, with fluctuations in blood pressure putting the brain at risk of ischemic and hemorrhagic injury. Fluctuating pressure passivity occurs in the majority of very low birth weight infants, [41] and increased passivity in this population has been associated with germinal matrix /intraventricular hemorrhage. [42] A potential role of NIRS could be in assessing the integrity of cerebrovascular reactivity to establish 'patient specific' optimal blood pressure measurements. [43]

While promising, routine use of NIRS in extremely preterm infants is not without potential drawbacks. NIRS monitoring, though non-invasive, requires yet another sensor on fragile skin, disturbs very preterm infants, requires time from nurses and doctors, and has financial costs. Error of measurement or incomplete understanding of the relevant pathophysiology may lead to inappropriate intervention. Commercial devices have different sensitivity to hypoxia, making a generalized approach difficult. [44,45] In addition, several technical issues remain regarding how best to characterize cerebral autoregulation and cerebral vasoreactivity in a broader sense. Large,

randomized trials to demonstrate clinical benefits and potential harms of NIRS-guided care are needed. Currently underway are two such studies: a trial of NIRS during stabilization in the first 15 minutes after birth in 362 neonates born before 32 weeks GA [46] and a pragmatic trial of NIRS in 1600 extremely preterm infants during the first three days of life. [47] The primary outcome of both trials will be survival without major brain injury identified by cranial ultrasound. Pending these results and future studies, clinical NIRS application in extremely preterm infants is limited to experienced centers capable of carefully incorporating NIRS information into their practices.

In summary, aEEG, cEEG, and NIRS each hold great promise and may be useful in select extremely preterm infants. aEEG monitoring in extremely preterm infants can be reserved to those at highest of brain injury and seizures (e.g., high-grade IVH). While prolonged cEEG is currently rarely indicated for extremely preterm infants (e.g., for accurate detection of seizures), it may be useful to perform brief cEEG recordings for detailed assessments of selected patients, such as to assess cortical activity which can assist in prognostication. NIRS monitoring along with treatment guidelines has a protentional utility to reduce burden of cerebral hypoxia within the first 3 days of life, however effect on long term outcome is still unknown. NIRS is recommended in case of respiratory and hemodynamic instability (see section on critically sick neonates) and high grade IVH complicated with posthemorrhagic hydrocephalus especially before and after therapeutic interventions.**(Table 1)** Further evidence is needed before routine use is expanded beyond specialized centers.

Neuromonitoring of Critically Ill Neonate

Many neonates admitted to the NICU without a primary neurological diagnosis are at high risk for developing brain injury. This injury could occur secondary to respiratory or hemodynamic instability that adversely affects brain perfusion and metabolism. Common examples include hemodynamically significant PDA, neonatal shock, respiratory or cardiorespiratory failure, metabolic disorders, neonatal surgery or extracorporeal membrane oxygenation (ECMO). In addition, neonates suffering from neonatal sepsis (with or without meningitis) are at high risk of inflammation-mediated brain injury. Many of these extremely sick neonates receive sedation and neuromuscular paralysis which renders clinical examination unable to detect neurologic change. Neuromonitoring of critically ill neonates allows for identification of alterations in brain function and could give a basis for providing neuroprotective therapies or performing further neurologic evaluation.

aEEG/cEEG Monitoring in the Critically Ill Neonate

EEG monitoring of critically ill neonates allows for detection of neonatal seizures and for identification of compromised brain function. The American Clinical Neurophysiology Society's guideline on cEEG recommends cEEG be considered for neonates at high risk for seizures. These neonates include preterm infants with high grade IVH, those with cardiopulmonary risk factors for acute brain injury such as a need for ECMO, newborns with congenital heart disease (CHD) requiring surgery, severe persistent pulmonary hypertension (PPHN), and suspected CNS infection. [48]

The prevalence of electrographic seizures in critically ill neonates is best described in those requiring ECMO and in those with CHD in the postoperative period. Electrographic seizures have

been detected in 18-23% of infants and children receiving ECMO were associated with mortality and unfavorable outcome. [49,50] Infants with CHD are also at risk for developing seizures during the postoperative period. Electrographic seizures have been reported in 8-10% of infants with CHD who underwent cEEG after cardiac surgery with cardiopulmonary bypass. [51,52] Other causes of neonatal hemodynamic instability, including sepsis and PPHN, have not been as well studied, but are known to result in seizures and brain injury in at least some patients. [53,54]

Beyond seizure identification, cEEG and aEEG may be beneficial for prognostication in critically ill neonates. A study of 150 infants with CHD who underwent aEEG monitoring after cardiac surgery found that a delay in return to a continuous background was associated with increased risk of mortality and worse neurodevelopmental outcome. [55] Similarly, a study of 30 neonates with PPHN and CHD reported higher rates of abnormal neurologic outcome among those with abnormal aEEG background. [56]

Infants with CNS infections are also at high risk for having acute brain injury with long term neurological consequences. Comprehensive EEG analysis incorporating background activity, the absence or presence of abnormal focal activity, positive rolandic sharp waves and seizures predicted death or moderate or severe disability at 1 year of age in a small number of infants treated with severe bacterial meningitis. [53] In line with that, patients with markedly abnormal EEG background during the acute phase of meningitis either died or were neurologically impaired at 10- months follow-up.[57]

Both aEEG and cEEG can help in diagnosing seizures commonly encountered in inborn error of metabolism.[58,59] Moreover infants with inborn error of metabolism frequently have aEEG and cEEG background abnormalities which could have distinctive patterns especially during the metabolic crises. [59] In the review of 25 cases with inborn error of metabolism, 15 infants showed

encephalopathic changes on aEEG. Neuropathological and molecular changes secondary to excitotoxic injury in disorders associated with hyperammonemia are similar to the abnormalities seen in hypoxic- ischemic encephalopathy, so both depressed background pattern and seizures frequently occur. The most severe changes (suppression burst, isoelectric tracing) were seen in urea cycle defects, disorders of energy metabolism and non-ketotic hyperglycinemia. In addition, infants with disorders of pyruvate and mitochondrial energy metabolism showed progression over time in line with clinical deterioration. In contrast in peroxisomal disorders seizures were detected without signs of encephalopathy. [60]

Finally, cEEG/ aEEG can assist in monitoring alterations in partial pressure of CO ($PaCO_2$), glucose level and hemodynamics. Changes in interburst intervals (IBI) indicating a very low voltage brain activity detected by an automated, commercially available algorithm were associated with changes in $PaCO_2$ and plasma glucose levels in preterm infants.[61] The association between high $PaCO_2$ and EEG discontinuity was supported by previous studies as well. [62,63] Other studies reported association between decreased cerebral blood flow [64] and right ventricle cardiac output [10] and depression in EEG activity in preterm infants.

NIRS Monitoring in the Critically Ill Neonate

NIRS has been widely used in pediatric cardiac intensive care units. The spectrum of reference values, critical levels and proper management of this population is beyond the scope of this article but has been reviewed elsewhere. [65] As cerebral oxygen saturation may be used as a marker for cerebral perfusion, oxygen delivery, and extraction, NIRS has a variety of applications for critically ill infants in the NICU. [66] When used in ECMO patients, $rStO_2$ was lower in those who

died or had brain injury than in those who survived without brain injury. [67] NIRS has the potential to monitor the effect of various respiratory interventions on cerebral hemodynamics. [68-70] Increased $rStO_2$ could be a marker of cerebral hyperperfusion accompanying an acute increase in $PaCO_2$, while decreased $rStO_2$ could indicate brain hypoperfusion associated with hypocapnia [71] Furthermore, NIRS may assist in quantifying apneic events significant enough to cause cerebral hypoxia. [72] Apart from respiratory management, NIRS could also have a role in identifying thresholds to treat neonatal hypotension through identification of critical blood pressures associated with low $rStO_2$. [73] In extremely preterm infants, a drop in cerebral $rStO_2$ can indicate hemodynamically significant PDA. [74,75] Evidence suggests that NIRS can assist in detection of clinically significant anemia and might assist in the decision for RBC transfusion. [76-78] Finally, NIRS monitoring could be useful in neonatal sepsis to assess cerebral perfusion. In a small study, cerebral saturation was lower in infants with neonatal sepsis when compared to controls, and lower saturation was associated with worse neurodevelopmental outcome. [79]

In summary, seizures, impaired cardiac output, decreased cerebral blood flow, disturbances in blood glucose and PaCO2 often occur in critically ill infants, that is why it is essential to monitor the well-being of the brain during intensive care. Whether such monitoring will lead to interventions capable of improving outcome is yet to be proven. aEEG monitoring is strongly suggested in critically ill neonates with high risk of brain injury secondary to hemodynamic and respiratory instability; including infants with PPHN, CHD, need for ECMO treatment, septic shock with or without CNS infection, and metabolic crisis. If aEEG is suggestive of seizures or the interpretation of aEEG is uncertain cEEG is indicated. [48,80] NIRS is a surrogate marker of cerebral perfusion and reflects the balance between brain tissue perfusion and oxygen extraction, therefore it has the potential utility in infants with hemodynamic and respiratory instability (e.g.,

hemodynamically significant PDA, PPHN, CHD, ECMO, septic shock), perioperative care and severe anemia. **(Table 1)**

Multimodal Monitoring in the NICU

The integration of aEEG/cEEG and NIRS data with other bedside physiological measures like heart rate, respiratory rate, pulse oximeter and transcutaneous CO_2 monitoring allows for understanding trends in clinical status and better assessment of acute events like seizures. **(Figure 2)** Recent methodological progress has also allowed for the combination of aEEG/cEEG recordings with studies of sensory responses in newborns. In the preterm infant, cortical sensory responses from the subplate-cortex circuitry can be observed at bedside aEEG/cEEG by presenting tactile, visual or auditory stimuli to the preterm infant. [81-83] In a full-term infant, complementing aEEG/cEEG with somatosensory evoked potentials may significantly improve outcome prediction after asphyxia [84] or stroke. [85] Importantly, these multimodal studies can be readily performed using both limited channel aEEG or a full-scale cEEG. [86] Furthermore, their diagnostic information is not affected by hypothermia. [87] Integrity of subcortical pathways may also be assessed at the bedside using other physiological measures, such as assessment of coherence between EEG signal and limb movements. [88] With this methodology already available, widespread uptake of multimodal monitoring will depend on user training and implementation into user-friendly outputs in commonplace brain monitors.

A multimodal approach can combine NIRS, electrographic findings (aEEG/cEEG) with vital signs and hemodynamic parameters to allow better understanding of critically ill patients with high risk of brain injury and to help neurodevelopmental outcome prediction. Deshpande et al conducted a

prospective observational study of 50 extremely premature infants to assess the safety and feasibility of combined cerebral and hemodynamic monitoring with echocardiography, NIRS, aEEG, and brain ultrasound within the first 72 hours of life. The combination of noninvasive bedside monitoring tools was well- tolerated with a low adverse event rate and might allow an early alert of developing IVH. [89] In a recent retrospective study EEG were collected along with simultaneous peripheral oxygen saturation and hear rate recordings and were analyzed at 12 and 24 h of age to predict outcomes at 2 years of age in infants <32 weeks of gestation. The combination of EEG grades with quantitative analysis of HR, SpO_2 and gestational age had the potential to predict death or neurodevelopmental delay but failed to reach statistical significance. [24]

Fractional tissue oxygen extraction calculated from the systemic arterial oxygen saturation (SpO_2) and cerebral venous oxygen saturation ($rStO_2$) (FTOE= ((SpO2- rStO2)/SpO2) × 100) reflects the balance between oxygen delivery and consumption and is more meaningful than absolute value of oxygen delivery. FTOE has the potential to detect changes in cerebral hemodynamics that lead to severe IVH, however the direction of change is controversial in the current literature. [66] In addition acute increase in end-tidal and transcutaneous CO_2 was associated with decreased FTOE as a surrogate marker of increased cerebral perfusion due to elevated CO_2 level. [71,90]

Sepsis accounts for significant mortality and morbidity including brain injury, especially in extremely preterm infants. Multimodal monitoring of vital signs and trends is able to detect physiology changes before clinical deterioration occur. In the era of big data analysis with the ability to extract and process large datasets from the electronic health records and bedside monitors, some predictive algorithms were developed based on continuous multimodal monitoring

e.g. HeRO (Heart Rate Observation) score, the Signal Instability Index (SII), and RALIS which can aid in early diagnosis of sepsis. [91]

The time-synchronized data integration and processing require additional infrastructure and financial resources, but this approach may open up new perspectives in both in research and clinical care.[92]

Sleep and autonomic nervous system monitoring

Neonates spend most of their time in sleep. There are two complementary aspects of neonatal sleep that make monitoring beneficial in the NICU. First, the neuronal activity related to infant sleep is crucial for early neuronal survival, as well as for guiding the growth of brain networks. [93,94] Thus, monitoring to ensure adequate sleep functions as a neuroprotective strategy. Second, the infant's ability to spend time in sleep, or alternate between sleep states is an efficient bedside biomarker of neurological and general physiological stability. Recent studies have shown that the amount of deep sleep [95] or the infant's ability to express SWC [9,96] are strongly predictive of later neurodevelopment. Furthermore, the disruption of sleep duration and quality showed the most profound abnormalities in patient treated in intensive care unit due to the frequency of interventions, frequent alarms, bright lightning and the absence of day-night differentiation. [97] A recent study established that handling of infants in the NICU is administered across all sleep-wake states and associated with both sleep disruption and consequential respiratory events. [98] The pattern of sleep-wake transition in neonatal period can be associated with behavioral and cognitive impairment. [97,99]

Currently, most NICUs do not have dedicated monitoring of sleep states or SWC. However, several indirect bedside methods are already available, with new techniques actively being

developed. While behavioral observation remains the gold standard, [100] it requires substantial expertise and is difficult to assess continuously. Brain monitoring with aEEG allows for observation of the sinusoidal patterns characteristic of SWC. [101] Through observation of very preterm infants (GA 30-34 weeks) by cardio-respiratory monitoring combined with aEEG, it was demonstrated that the more discontinuous parts of the characteristic sinusoidal pattern represent quiet sleep periods, while the more continuous aEEG periods represent wakefulness/active sleep. [102] This finding was further confirmed in a recent study comparing aEEG with polysomnography. [103] Thus, aEEG may offer an opportunity to monitor sleep states. Additional noninvasive methods are emerging to allow monitoring of sleep state based on breathing patterns [104] and heart rate variability indices. [105] Breathing patterns can be measured noninvasively using a movement-sensitive bed mattress or video-analysis, both of which show a high correlation with sleep states.

We need to highlight that some authors recommend assessing 3 reliable physiological parameters including rapid eye movement, body movement and respiration to determine SWC, since cyclicity on aEEG is only reflects the repetitive changes between continuous and discontinuous EEG activity; especially in preterm infants where the immaturity of the neuronal network leads to more frequent indeterminate sleep state. [101]

The autonomic nervous system (ANS) controls the heart rate by creating balance in the sympathetic and parasympathetic nervous systems via norepinephrine and acetylcholine release, resulting in small accelerations and decelerations of heart rate. During quiet sleep characterized by the absence of movements and slow rhythmic breathing parasympathetic predominance was detected with lower time and frequency domain heart rate variability (HRV) metrics compared to active sleep with sympathetic predominance. [106,107] Abnormally low heart rate variability signifies ANS dysfunction and may indicate brain injury besides inflammatory response to sepsis or focal

infection. Preterm infants who later developed cerebral palsy, cognitive and language disfunctions or attention disorders showed altered HRV during active sleep. [108] HRV is also affected by the maturation of ANS, cardiac sympathovagal balance shifts towards parasympathetic dominance during sleep reflecting the maturation of the parasympathetic and vagal systems and cardiorespiratory control. [109] Although heart rate variability indices may be physiologically feasible, HRV metrics are not integrated part of neonatal neurocritical care. To date only heart rate characteristics index (HeRO) monitor is commercially available that analyzes electrocardiogram data in real time utilizing heart rate variability indices in neonatal intensive care to predict sepsis in preterm infants.

In summary, continuous monitoring of sleep and SWC should be an essential component of brain-orientated neonatal care. Current possible approaches to monitoring sleep include routinely available tools, such as aEEG, cEEG, and attention to behavior. Further investigations on HRV are needed since it can provide useful insights into ANS development and functioning. Forthcoming improved monitoring devices will facilitate better assessment and the development of novel nursing protocols to optimize neonatal natural sleep.

Conclusion:

Appropriate use of neuromonitoring holds promise for improving care to high-risk infants. Different monitoring modalities need to be selected according to the clinical condition and individual patient needs:

- For extremely preterm infants, NIRS monitoring in the first three days of life has potential utility, since abnormal cerebral perfusion is associated with higher risk of IVH and

impaired neurodevelopmental outcomes; and cerebral NIRS together with a treatment guideline was able to reduce the burden of hypoxic episodes. However, ongoing clinical trial results are needed. NIRS monitoring has a role in management of post-hemorrhagic ventricular dilatation, The use of aEEG and cEEG in this population should focus on those at highest risk of brain injury and/or seizures and need to be interpreted cautiously.

- Selective use of EEG, NIRS, and multimodal monitoring in critically ill neonates allows for brain-oriented care that has the potential to improve neurodevelopmental outcomes.
- Continuous monitoring of sleep and avoiding sleep interruption can assist in the growth of brain networks. Presence of SWC can be used as a predictor of neurological outcome. In addition, abnormally low heart rate variability during active sleep can be a surrogate marker of ANS dysfunction.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Table 1: Comparison of Neuromonitoring Devices in Different Clinical Scenarios

Condition	aEEG	cEEG	NIRS
Neonatal Encephalopathy	• Useful for screening for inclusion for TH with high sensitivity at 6 hours after birth; should not be used to exclude from TH if otherwise eligible • Positive predictive value improves during cooling and is high starting at 48 hours after birth • Should be continued through cooling and rewarming	• During TH, cEEG monitoring is needed for at least 24 hours to monitor evolution of encephalopathy and to diagnose electrographic only seizures, most common at that timeframe	• Continuous NIRS through cooling and rewarming is helpful as a prognostic tool for injury on MRI as well as outcome
Seizures	• Can be used to screen for seizures and, while not as sensitive as cEEG, it is superior to clinical assessment alone	• The gold standard for detection and diagnosis of seizures • Should be continued until at least 24 hours after last seizure	• Might show alteration of cerebral oxygenation during clinical and subclinical seizures
Extreme Prematurity	• Has potential benefit in monitoring those with highest risk of brain injury and/or seizures e.g., high grade intraventricular hemorrhage	• Consider brief cEEG recording in those at highest risk of brain injury and/or seizures	• Consider monitoring in the first 3 days of life, however, ongoing clinical trials results are needed • IVH complicated with PHVD especially before and after interventions
Critically Sick Neonates	• Consider monitoring for alterations in background brain function and possible seizures in neonates with CHD, PPHN, inborn error of metabolism, sepsis with or without CNS infection or requiring ECMO	• Suggested to be applied in neonates at highest risk for neonatal seizures especially if aEEG is suggestive of seizures.	• Recommended in case of respiratory or hemodynamic instability (e.g., hemodynamically significant PDA, PPHN, CHD, ECMO, septic shock), perioperative care and severe anemia.
Pitfalls	• Low amplitude artifacts (HFOV, ECG), sedative and analgesic medications can alter background activity or mimic seizures • Reliability depends on user expertise	• Electrodes application is challenging in preterm infants due to limited space, humidified incubator, infection control and fragile skin • Requires significant technical and professional resources	• Variation in sensor type and position • Interpret as a trend rather than absolute number due to variability

Abbreviations: CHD: Congenital heart disease; ECG: electrocardiogram; ECMO. extracorporeal membrane oxygenation, HFOV: High-frequency oscillatory ventilation; IVH: Intraventricular hemorrhage; NEC: Necrotizing enterocolitis; PDA: Patent ductus arteriosus; PHVD: Post-hemorrhagic ventricular dilatation, PPHN: Persistent pulmonary hypertension of the newborn, TH: hypothermia

Figures

Figure 1: Maturation of EEG and aEEG with postmenstrual age.

On the right side are single channel conventional EEGs (about 36 seconds of recording) plotted with a speed 10 mm / sec and voltage of 100 μV/ cm, demonstrating progressive decrease in IBI with age (represents the most discontinuous part of the aEEG recording). On the left side are corresponding aEEG (about 6 hours) from the same recordings in a speed of 6 cm/hour. With maturation, the aEEG shows higher amplitude, narrower bandwidth, increased continuity and evolving cyclicity. (Adapted from [110])

Figure 2: Demonstration of the value of multimodal monitoring in a term neonate with severe HIE.

aEEG demonstrates isoelectric pattern superimposed with seven distinct seizures over a period of six hours. With each seizure, there is an increase in heart rate (HR), and a decrease in respiratory rate (RR), systemic oxygen saturation (SpO_2) and regional cerebral saturation (rSO2). This is followed by an increase in transcutaneous pCO_2 level ($tcPCO_2$).

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