PEDIATRIC NEUROMONITORING

Review of Noninvasive Neuromonitoring Modalities in Children II: EEG, qEEG



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Abstract

Critically ill children with acute neurologic dysfunction are at risk for a variety of complications that can be detected by noninvasive bedside neuromonitoring. Continuous electroencephalography (cEEG) is the most widely available and utilized form of neuromonitoring in the pediatric intensive care unit. In this article, we review the role of cEEG and the emerging role of quantitative EEG (qEEG) in this patient population. cEEG has long been established as the gold standard for detecting seizures in critically ill children and assessing treatment response, and its role in background assessment and neuroprognostication after brain injury is also discussed. We explore the emerging utility of both cEEG and qEEG as biomarkers of degree of cerebral dysfunction after specific injuries and their ability to detect both neurologic deterioration and improvement.

Keywords: Continuous electroencephalography, Quantitative electroencephalography, Critical care neuromonitoring, Seizure, Status epilepticus, Encephalopathy

Introduction

One in six admissions to pediatric intensive care units (ICUs) is attributable to an acute brain disorder [1]. The nervous system is also susceptible to secondary insult related to a primary systemic illness. Neurological dys-function during pediatric critical illness manifests in several ways, including seizures and encaphalopathy. Underlying etiologies can include ischemia, hemorrhage, cerebral edema, metabolic injury, and infection. Detection of neurologic dysfunction classically relies on the neurologic examination; however, the ICU environment limits clinical detection of neurological dysfunction because sedation, analgesia, and neuromuscular blockade, which are required to ensure patient comfort and facilitate life-sustaining therapies, interfere with neurologic assessment [2, 3].

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Electroencephalography (EEG) serves as a noninvasive bedside neuromonitoring tool that provides high spatial and temporal resolution of brain activity. Continuous EEG (cEEG) yields an uninterrupted stream of brain activity data. Running cEEGs on multiple patients per day for several days in an ICU results in large quantities of data, and not all institutions have around-the-clock support for review and interpretation of the EEGs. Analytical and visualization tools termed quantitative EEG (qEEG) transform the raw digital EEG into its waveform components (e.g., amplitude and frequency), allowing for quantification of EEG features and time-condensed displays. The ability to view large amounts of data at one time allow detection of subtle changes that may occur over hours and are not easily noted on second-by-second review of the raw EEG. This makes qEEG particularly appealing for application in critical care and has the potential to increase efficiency and allow for bedside monitoring and interpretation.

This article provides a broad overview of the technical aspects and clinical applications of cEEG and qEEG in the pediatric ICU.

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cEEG Monitoring

Technical Aspects of cEEG Monitoring

The EEG recording is obtained by applying electrodes to the scalp and measuring the electrical activity of the underlying brain. The activity measured represents a summation of excitatory and inhibitory postsynaptic potentials of predominantly superficial cortical neurons. A cortical area of at least 6 cm² of synchronous neuronal activity is required to generate an epileptiform discharge detectable on scalp EEG [4, 5].

Electrode disks or cups are typically made of silver chloride or gold and require removal and reapplication for emergent brain imaging with either computed tomography or magnetic resonance imaging (MRI) because of electrode artifact and risk of thermal burns in the case of MRI. Imaging-compatible electrodes are available [6, 7]. cEEG is typically recorded using the International 10-20 System which includes 21 electrodes [8]. Limited electrode arrays or montages can be used in the ICU. The neonatal "double distance" montage uses fewer electrodes to account for smaller neonatal head size [9]. A limited array may also be used when a patient is anticipated to need cEEG monitoring for several days to reduce the number of sites at risk of skin breakdown. Risk factors for electrode-related skin injury include critical illness, longer duration of monitoring, age less than 1 year, fever, lack of headwrap, and need for vasoactive support [10-12]. The skin should be checked daily, and scalp rest should be provided if breakdown is identified. Some centers perform scheduled scalp rest at protocolized intervals regardless of skin findings. Synchronous video recording is recommended for cEEG [13] to allow for the detection of clinical seizures, artifacts caused by movement or electrical components, and observation of the patient's clinical state.

The minimum recommended written reporting rate of the ICU EEG is once every 24 h and when there is a significant change. Verbal communication of results to the clinical team should occur at least twice a day [14].

Indications for cEEG Monitoring

Indications for ICU cEEG include seizure monitoring [15–23], background pattern assessment, neuroprognostication, and detection of new brain injury [24–29]. cEEG indications are outlined in critical care policy statements and society guidelines [9, 30–37].

Background Assessment

EEG background activity is used to assess the patient's baseline level of brain activity. It can be used to confirm alterations in consciousness, determine a patient's ability to cycle between awake and sleep states, assess for reactivity, grade depth of sedation, and detect focal abnormalities [27, 30, 38, 39]. If diffuse background abnormalities are detected, this is often summarized in EEG reports as a graded severity of cerebral dysfunction or consistent with a degree of encephalopathy.

cEEG assessment of background has been studied and validated for numerous conditions resulting in acute brain injury. For perhaps the most widely described patient population-children who remain comatose after cardiac arrest (CA)-a cEEG background category of normal, slow-disorganized, discontinuous, burst suppression, and attenuated-featureless has strong interrater agreement [40] and a specificity as high as 95% for predicting unfavorable neurologic outcome [27]. cEEG has also been used to grade degree of encephalopathy in conjunction with the neurologic examination to detect clinical worsening. In children with acute liver failure who develop hepatic encephalopathy, an initial EEG on admission was predictive of outcomes such as survival and liver transplantation [29, 41]. A similar assessment, applied in children with altered mental status or concerns for seizures who received chimeric antigen receptor T cell therapy, demonstrated that EEG background correlated with the clinical examination measured by the Cornell Assessment of Pediatric Delirium [42].

A recent study surveyed members of the Critical Care EEG Monitoring Research Consortium (CCEMRC) to determine the common features used by adult and pediatric EEG readers to grade cerebral dysfunction [43]. Common features (used by >90% of respondents) included posterior dominant rhythm, predominant awake frequencies, and reactivity. Interrater agreement among the respondents grading the background of 40 EEGs was fair. Thus, although recognition of distinct EEG background patterns has good reliability, translation of these features into a graded level of "cerebral dysfunction" has limitations due to variability in interpretation. Standardization through use of a common schema may reduce variability in reporting. Based on the adult grading system, Table 1 proposes a potential framework for categorizing electrographic cerebral dysfunction in children.

Seizure Detection

Detection of seizures is the most frequent indication for pediatric ICU cEEG [44, 45], with seizure incidence in the ICU ranging from 10 to 47% [15, 19, 44, 46–53]. Seizures may be defined as "clinical" if there is an observable change during the seizure or as "nonconvulsive" if there is no observed motor activity. The term "subclinical" is often avoided in ICU EEG terminology because the clinical impact of seizures on awareness is often unknown during critical illness [14]. "Electrographic seizures" refers to seizures observed on EEG, and "electrographic-only" refers to seizures visible on EEG without

Table 1 Troposed pediatric cerebrar dystanction grading sea	scale
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EEG features	Severity of cerebral dysfunction							
	Normal	Mild	Mild-moderate	Moderate	Moderate- severe	Severe	Lack of cerebral rhythms	
Posterior dominant rhythm (PDR)	Normal for age 2–4 mo, 3–4 Hz By 6 mo, 4–6 Hz By 12 mo, 5–7 Hz By 3 y, 8 Hz By 10 y, >8.5 Hz	Detectable PDR but slower than expected	Features of both mild and moderate dysfunction	Absent	Features of Both Moderate and Severe Dysfunction	Absent	No detect- ible cerebral activity ^a	
Predominant frequencies	Normal admix- ture Normal organi- zation	Diffuse slowing Poor organiza- tion		Diffuse slowing Loss of organiza- tion		Monotonous and limited frequencies ^b Attenuated featureless		
Sleep architec- ture	Present ^c	Present ^c		Absent		Absent		
State changes	Present ^c	Present ^c		Present		Absent or SIRPIDs only		
Reactivity	Present ^c	Present ^c		Present		Absent		
Continuity	Present	Present		Nearly continu- ous		Burst suppressed ^d		

This is a proposed grading scale for cerebral dysfunction in children aged 2 months to 18 years that has not been validated in this age group. Adapted from The Yale Adult Background EEG Grading Scale [43]

EEG electroencephalogram, Hz Hertz, mo months, PDR posterior dominant rhythm, SIRPIDs stimulus-induced rhythmic, periodic, or ictal-appearing discharges, y years ^a This categorization does not imply the EEG was performed to meet minimum technical requirements for assessment of electrocerebral inactivity when using EEG as

an ancillary study for determination of death by neurologic criteria

^b For EEGs that are not burst suppressed

^c EEGs that have limited duration may only demonstrate a single state or may not sufficiently assess reactivity

^d For EEGs that are not attenuated or featureless

any clinical change. Because of the impact of sedation and neuromuscular blockade on the observable manifestations of seizures, cEEG is required for accurate detection of seizures in the ICU [30]. In a study of 98 children presenting with convulsive status epilepticus, 33% had electrographic seizures and one third of those were electrographic-only with no observable clinical component [54]. When comparing analogous conditions, such as acute ischemic stroke or central nervous system infection, children have a higher seizure rate than adults [30], with neonates carrying the highest risk [30, 55–58]. Table 2 reviews seizure rates for children versus adults for the same acute neurologic conditions [20, 30, 56, 59–86].

Evidence suggests that seizure burden (percentage of an hour occupied by seizure) is independently associated with neurodevelopmental outcome [15, 18, 50, 87]. In a prospective single-center study of 259 children in the ICU undergoing cEEG monitoring, neurologic outcome was worse when maximal seizure burden exceeded 20% [18]. Based in part on these findings, the 2021 American Clinical Neurophysiology Society (ACNS) updated the definition of electrographic status epilepticus (ESE) from > 50% over 1 hour to the lower threshold of \geq 20% [14]. This change prompted further consideration of the

Table 2 Seizure rates in hospitalized or critically ill chil-dren versus adults for analogous conditions

Neurologic condition	Children (%)	Adults (%)
CNS infection [25]	16-100	10-33
Moderate to severe TBI [19, 25]	14–70	18-33
Postconvulsive status epilepticus [25]	26–57	48
Acute arterial ischemic stroke [15, 54–63]	16–59	3.3–7
Intraparenchymal hemorrhage [20, 53, 60, 64, 65]	11–100	16-23
Cardiopulmonary bypass [66–69]	8–12	2.4-3
Cardiopulmonary arrest [25]	16–79	10–59
Septic encephalopathy [25]	58	32
Extracorporeal life support [70–75]	17–40	0–6
COVID-19 [76-80]	8–22	0.5-9

CNS, central nervous system; COVID-19, coronavirus disease of 2019; TBI, traumatic brain injury

risk versus benefit calculation for the treatment of ESE. The short-term and long-term impact of antiseizure medications used to treat this lower ESE threshold must be considered as they may add additional risk to outcome by impacting likelihood of hypotension, hypoxia, sedation, and need for mechanical ventilation [88–92]. Further prospective studies are needed to better understand the impact of treatment strategies on outcomes for seizures, ranging from short, infrequent seizures to status epilepticus, in critically ill children.

Epileptiform Patterns and the Ictal-Interictal Continuum

A common challenge of interpreting ICU cEEG is distinguishing which patterns of electrographic discharges and rhythmic activity are "ictal" (seizures) or "interictal" (in between seizures) [93]. It must be recognized that although there are criteria, a spectrum exists. Electrographic patterns with epileptiform features that stand out from the background but lack adequate evolution or clinical correlation consistent with definite seizures represent the ictal-interictal continuum (IIC) [14]. Discharges are considered on the IIC when they last more than 10 seconds and include one of the following: (1) periodic or spike wave discharges occurring at 1-2.5 Hz, (2) periodic or spike wave discharges with additional epileptiform features (e.g., superimposed fast activity) averaging 0.5–1 Hz, or (3) lateralized rhythmic delta activity \geq 1 Hz with features associated with increased risk of seizures [14]. Periodic discharges (PDs) are repetitive waveforms with no more than 3 phases and interdischarge intervals of regular duration. Rhythmic delta activity (RDA) is defined as consecutive, uniform 0.5- to \leq 4-Hz activity without an interval in between (Fig. 1) [14]. The ACNS definition of electrographic seizures and ESE is largely based on the Salzburg consensus criteria [94–96]. A seizure is defined as epileptiform discharges>2.5 Hz for \geq 10 seconds or any pattern \leq 2.5 Hz with clear evolution lasting \geq 10 seconds [14]. If the IIC pattern and there is a clinical improvement in the patient after parenteral antiseizure medication administration, then the pattern is favored to be ictal. ESE occurs when a seizure lasts 10 consecutive minutes or cumulatively \geq 12 min (20%) of a 60-min epoch [14].

Understanding PDs and RDAs as they relate to the IIC, their potential contribution to ongoing brain injury, and the complex underlying physiology that results in these rhythms is crucial to clinical interpretation of ICU EEG. Reported incidence of rhythms on the IIC (PDs and RDA) ranges from 1.2 to 12% in critically ill children [19, 27, 46, 97]. A study of 1399 critically ill children described periodic and rhythmic patterns and IIC patterns and found that 142 (10%) had periodic and rhythmic patterns, and 93 of those 142 (65%) also met criteria for an IIC patterns [98]. Another study of 719 consecutive children demonstrated that electrographic patterns on the IIC were independently associated with worse outcomes as measured by the Glasgow Outcome Scale-Extended Pediatric Version, the Pediatric Cerebral Performance Category score, and mortality [46].

Generalized periodic discharges (GPDs) were present in 21 of 296 (7%) critically ill children in a two-center study [99] and in 43 of 1399 (3%) critically ill children in a single-center study [98]. Common etiologies



include encephalitis and hypoxic-ischemic injury. Seizures occurred in 63–100% of children with GPDs [97– 99]. GPDs also occur in the setting of anesthetic weans (particularly barbiturates), often resolve with time, and can be stimulus induced [100]. Lateralized periodic discharges (LPDs) are associated with acute structural etiologies, including stroke or encephalitis [101–103], with incidence ranging from 0.5 to 7% [97, 98, 103, 104]. LPDs have a strong association with seizures, which occur in 61–100% of pediatric patients with LPDs [97, 101, 105].

The other pattern associated with the IIC is RDA, further categorized as generalized RDA (GRDA), lateralized RDA (LRDA), continuous or intermittent RDA, and RDA with "plus modifiers," including fast activity or superimposed sharps or spikes. Incidence of GRDA is 1.6-2.4%, and GRDA is not associated with seizures [97, 98]. A common ICU pattern is bifrontally predominant intermittent GRDA, associated with nonspecific encephalopathies and midline lesions [106–108], although the latter correlation may be more true in adults than in children [109]. LRDA incidence in critically ill children ranges from 0. to 1.6% but may be underreported [97, 98]. It is often associated with a focal cortical lesion [110, 111]. Association of LRDA with seizure is high. A study of 1399 ICU EEGs detected LRDA in 11 patients, and seven (64%) had seizures [98]. Another study noted that 100% of patients with LRDA developed seizures [97]. The association was highest when rhythm frequency was > 1.5 Hz. While numbers are small, these findings suggest the risk of seizures when LRDA is present may be similar to that of LPDs in children.

These patterns have been studied in greater detail in critically ill adults in far greater numbers, including in an investigation into the clinical significance of each type of rhythm, frequency, plus modifiers, and stimulus-induced patterns [112]. Plus modifiers include superimposed fast activity (+F), which can occur with PDs or RDA; rhythmic activity (+R), which only applies to PDs; and superimposed sharps and spikes (+S), which only applies to RDA [14]. A three-center retrospective study from the CCEMRC studied more than 4,500 critically ill patients monitored on EEG and found that LPDs, LRDA, bilateral independent PDs with and without plus features, and GPDs with plus features conferred an increased risk of seizures, whereas GRDA did not [112].

Brief potentially ictal rhythmic discharges are focal or generalized > 4-Hz rhythmic activity lasting 0.5 to < 10 seconds, which may evolve or demonstrate similar morphology and location as interictal epileptiform discharges or seizures already observed in a particular patient [14, 113]. Critically ill children may also exhibit stimulus-induced rhythmic, periodic, or ictal-appearing discharges (SIRPIDs) [114] (Supplemental Fig. 1). The stimulus can be any alerting stimulus, ranging from auditory to tactile to noxious, and the type of stimulus should be documented when reporting this phenomenon [14, 114]. An early descriptive study of SIRPIDS in children found a high association with seizures and status epilepticus.

Key to the discussion of the clinical implications and treatment strategies of the IIC is the degree to which it may contribute to brain injury. Are these patterns a biomarker of acute injury or do they pose an independent risk of causing new brain injury? When the pattern meets the Salzburg and ACNS criteria for nonconvulsive status epilepticus, it is common practice to treat and evaluate the response to treatment to prevent further neurologic injury. But these criteria rely on a frequency cutoff of > 2.5 Hz to define seizure when there is inadequate evolution to otherwise qualify it as ictal. Studies of cerebral metabolic demand during IIC patterns indicate that the threshold for impending new metabolic injury may occur at lower frequencies. In a study of nine patients with concurrent LPDs and positron emission tomography scans, 1-Hz LPDs increased F-fluorodeoxvglucose (FDG) uptake by 100% compared with LPDs occurring at <1-Hz frequency, and FDG uptake was further increased by>300% for frequencies>1 Hz [115]. A study using invasive measures of cerebral blood flow and brain tissue oxygenation demonstrated increasing cerebral blood flow with every 0.5-Hz increase in LPD frequency, and when discharges surpassed 2-Hz frequency, regional hypoxia was detected [116]. Similarly, periodic discharges after traumatic brain injury are associated with a higher lactate/pyruvate ratio and lower glucose levels [59], supporting the potential for LPDs to contribute to regional metabolic demand in brain injury.

Prognostication After Brain Injury

cEEG is used to assist in the prognostication process and in risk stratification when patients present with acute brain injury or when an underlying illness puts them at risk for neurological complications. Post-CA prognosis is one of the areas with the most active research and best evidence base for both children and adults. For children post CA, the background category (normal, slowdisorganized, discontinuous, burst suppression, and attenuated-featureless) was highly predictive of outcomes [25, 27, 117]. Severely abnormal EEG backgrounds were highly specific for poor neurodevelopmental outcomes, and more benign EEG backgrounds had less specificity but were associated with higher proportions of favorable outcomes. Sleep features on 24-h post-CA EEG (sleep spindles) were associated with favorable outcomes, and conversely, the absence of sleep architecture was associated with unfavorable outcomes [118] and was additive to the prognostic ability compared to background EEG features alone [27]. In pediatric extracorporeal life support, the EEG background category within the first 24 h was highly correlated with survival [24]. Future studies to determine optimal and modifiable predictors of outcomes will likely help improve treatment and prognostication in children.

Duration of cEEG Monitoring

cEEG is a resource-intensive and time-intensive form of neuromonitoring [119-121]. Studies have explored parameters and predictors that can determine the optimal length of monitoring required to identify seizures or clinical deterioration [19, 122–127]. When children have seizures on EEG monitoring in the ICU, about 50% occur in the first hour of recording and 90% occur within the first 24 hour [19, 128]. A study of 719 critically ill children, 184 of whom had electrographic seizures (26%), used clinical and electrographic features to identify the minimum duration of monitoring to achieve a < 5% risk of seizure [129]. Features used in this model included age < 1 year, clinical seizure prior to EEG, and interictal or IIC abnormalities. If a child was > 1 year of age and had no prior seizures or epileptiform EEG activity, an EEG duration of 6 hours was sufficient to reach a risk of < 5%for developing seizures, whereas an infant <1 year with prior clinical seizure required 2.5 days of monitoring based on their model to reach a seizure risk of < 5%. The ACNS recommends a minimum of 24 hours of monitoring in most cases, although shorter or longer duration can be applied depending on the clinical scenario [30]. Risk factors for predicting seizures in pediatric patients include age, clinical seizures prior to EEG, and presence of interictal discharges [19, 129, 130].

Limitations of cEEG

cEEG use can be limited by the amount of resource it requires. This includes in-house technologists to apply the EEG, professionals trained in interpretation reviewing at regular intervals, communication of findings to the clinical team, documentation of the EEG report, and storage of large data files in archives. EEG review is also almost always retrospective, even if reviewed at very frequent intervals, which has its limitations in the acute care setting, where real-time detection of changes in organ function is vital.

Localization of brain dysfunction is limited by the spatial resolution of standard electrode placement. Small abnormalities may not be detectible within the resolution of scalp EEG. EEG findings are not specific to the type of injury that causes abnormalities; for example, LRDA may be present as a postictal rhythm or after an acute stroke. Finally, many necessary treatments in the ICU can impact the EEG signal, including the impact of neuroactive medications and artifacts from ICU equipment, electrical artifact, and movement.

Quantitative EEG

Introduction to qEEG Monitoring

A recent survey of neuromonitoring practices in North America found that 96% of institutions use ICU cEEG [28], with cEEG review by a trained electroencephalographer remaining the gold standard [30]. However, there are practical limitations, such as the time-intensive nature of review and the need for real-time data in the ICU. qEEG allows large amounts of electrographic data to be viewed in a condensed form and can be displayed at the bedside, enabling real-time monitoring of cerebral function. qEEG use in the ICU is growing, increasing from 34% in 2010 to 50% in 2016 [131-133], and two pediatric-specific surveys reported 38-50% qEEG availability [28, 134]. Challenges for the widespread implementation of qEEG in pediatric ICUs include limited age-specific normative value for children, the need for additional software, lack of training in interpretation, and a paucity of data validating appropriate clinical application, making this a tool still under investigation in many scenarios.

Normative Data

Just as other physical parameters, such as blood pressure and heart rate, vary by age, so do the features of the normal EEG. It is essential to have a normative range for comparison with patient data both for clinical care and for research. The frequencies captured with cEEG typically fall into five ranges that are commonly referred to as follows: delta (0.5 to < 4 Hz), theta (4 to < 8 Hz), alpha (8 to < 13 Hz), beta (13 to < 30 Hz), and gamma (> 30 Hz). In a study of qEEG features in pediatric acute liver failure, normative values from 70 pediatric age-grouped normal EEGs were used to create a normative qEEG data set focusing on EEG frequency and relative power. A recent study reported the qEEG features from 1,289 healthy volunteers, including more than 500 pediatric patients (ages 4.5-20 years) [135]. These studies showed high-amplitude, slow-frequency delta power predominated in infants and decreased into childhood, whereas higher frequency power (theta and alpha) increased with age. Children demonstrate frequency admixtures similar to adults beginning in early teenage years [8, 136].

Children in the ICU rarely have completely normal electrographic brain function. Sedating medications commonly contribute to EEG abnormalities [137]. Supplemental Fig. 2 summarizes the impact of commonly used sedatives, anesthetics, and analgesics on the cEEG and qEEG. By altering the electrophysiologic profile of



brain activity, these medications may impact how qEEG is interpreted in the setting of acute neurological injuries. Further work to understand normative parameters in the ICU may help distinguish sedated children with and without neurologic injury. Preliminary experience from adult literature provides some reassurance that these agents do not negate the diagnostic utility of the EEG; in a study of 496 adults post CA, propofol administration and discontinuation did not alter the prognostic value of the post-CA EEG [138].

Building qEEG Trends

All qEEG software relies on processing the raw EEG signal through different computational methods and displays this information visually as time-compressed trends. The primary ways of processing cEEG are based on amplitude and/or frequency over time. Figure 2 provides an overview of the different qEEG trends and their common applications. It should be noted that the trends, color schematics, scales, and axes may vary between different qEEG software companies. We will first describe the features of the major amplitude-focused and frequency-focused trends, and then we will provide an

overview of how trends are commonly used clinically, providing available supporting data in pediatric populations. It should be noted that such data are limited and qEEG remains a largely investigational tool. Large-scale validation studies are needed to better understand its role in pediatric critical care.

Amplitude-Focused Trends

1. Amplitude-integrated EEG

The first iterations of amplitude-integrated EEG (aEEG) came into use in clinical practice in the 1960s–1970s and were used as "cerebral function monitors" in adult patients post CA or in perioperative open-heart surgery neuromonitoring [139, 140]. In recent decades, aEEG has been more commonly used in the neonatal ICU for assessment of neonatal EEG background and seizure detection. At least three electrodes are required to build the aEEG; typically, these include homologous electrode pairs in either the parietal or central regions (traditionally P3–P4) and a ground electrode [141]. Software may offer different electrodes are being used to

build the aEEG, as abnormalities occurring far from the electrodes may not be detected.

The EEG signal is filtered to amplify frequencies between 2 and 20 Hz and emphasize cortically derived rhythms over artifact. The signal is then displayed using semilogarithmic compression, which accounts for the naturally high variation in amplitudes, with the *y*-axis starting linearly from 0 to 10 μ V then logarithmically from 10 to 100 μ V [141–143]. aEEG may be displayed as a single graph or separated by the right and left hemispheres.

2. Envelope trends

These trends are made by plotting the running average of either the median amplitude (envelope trend) or the maximum amplitude (peak envelope) of waveforms between 2 and 20 Hz, displaying amplitude variation over time. Like aEEG, envelope trends may be displayed as a single graph or separated between the right and left hemispheres. This trend can be helpful for detecting qEEG changes during a seizure, as amplitudes typically increase during a seizure, or other neuropathology that particularly affects EEG voltage.

3. Suppression ratio

The suppression ratio displays the percentage of time the EEG signal is below a prespecified amplitude consistent with suppression. For example, if during a 10-second epoch of EEG, eight of the seconds had maximum amplitudes < 5 μ V, the percentage suppression would be 80%. A running average is calculated with percentage suppression on the *y*-axis. This qEEG tool is particularly useful for neurologic conditions that result in background suppression, such as severe hypoxic-ischemic encephalopathy [144], refractory intracranial hypertension, or pharmacologically induced burst suppression [145–148].

Frequency-Focused Trends

Frequency-based trends rely on a Fast Fourier Analysis/ Transform (FFT). This algorithm separates frequency from the time domain into individual oscillatory waveforms. Frequency power is the area under the FFT amplitude curve for each frequency and is displayed as the square of the amplitude (μ V²) [149]. This modality breaks down the EEG into the contributions from each frequency over time. qEEG displays can highlight individual wavelengths (frequency band power) or spectrograms of selected or all EEG channels. These are frequently referred to as a color density spectral array (CDSA) and may be displayed at the bottom of a traditional cEEG recording. Other techniques to analyze the EEG using FFT include measures of asymmetry across brain regions, ratios comparing different frequency bands (e.g., alpha/delta ratio [ADR]), and rhythmicity detection.

1. FFT spectrogram or CDSA

The FFT spectrogram or CDSA displays the power for each frequency over time. Frequencies are displayed on the *y*-axis, time is displayed on the *x*-axis, and power is represented by a color spectrogram that can be adjusted to the user specification depending on the software, but traditionally warm colors, such as red, pink, and white, represent high power, whereas dark blue to black represents low power. The color spectrogram trend is commonly used for seizure identification, as described below, as well as for detection of state changes and effect of anesthetics.

2. Alpha/delta ratio

The ADR is a power ratio of faster alpha frequencies over slower delta frequencies. The ratio is averaged over time and displayed as a line graph, with the γ -axis as the numerical value for the ratio, the left hemisphere classically displayed as a blue line, and the right hemisphere in red. This trend is often applied to detect focal cerebral ischemia based on the principle that as cerebral blood flow decreases, the first electrographic change is a decrease in alpha frequencies, followed by an increase in slower theta then delta frequencies [150]. Because relative alpha and delta frequencies vary inversely in the setting of decreased cerebral perfusion, this ratio amplifies these changes. This contrasts with extracerebral pathology (subdural fluid collection), which would blunt alpha and delta amplitudes similarly, often without a noticeable change in the ratio.

3. Asymmetry index and spectrogram

Asymmetry trends display absolute or relative asymmetries between electrodes in different brain regions, typically between hemispheres. The absolute asymmetry index graphs the absolute difference (0–100%) between the hemispheres as a running average. The relative asymmetry index displays a line graph of the relative asymmetry between regions over time, with index values (– 100 to 100%) on the *y*-axis: negative values when the left hemisphere has more power and positive values when the right hemisphere predominates.

The asymmetry spectrogram relies on FFT to display the comparison of relative power for each frequency as it relates to homologous regions in the contralateral hemisphere. The *y*-axis is power frequency (typically 0-20 Hz), and the color spectrogram displays right hemisphere dominance for a specific frequency as red and left hemisphere dominance for a specific frequency as blue. The darker the color, the greater the hemispheric asymmetry. It can be displayed as a holohemispheric comparison or by region (anterior, posterior, temporal, parasagittal). This trend is particularly helpful at displaying focal abnormalities in the brain, such as seizure or stroke.

4. Rhythmicity spectrogram

The rhythmicity spectrogram (Persyst Development Corporation, Solana Beach, CA) uses a density spectral array that displays greater rhythmicity as denser blue, calculated across sequential groupings of the 1- to 25-Hz frequency bands over time. When used along with automated seizure detection, it can be useful clinically to identify ictal events [151, 152]. However, this trend is susceptible to highlighting nonictal rhythmic patterns, including sleep spindles, or the posterior dominant rhythm and repetitive artifacts (respiratory treatments or patting). Discussion of similar trends to detect rhythmicity offered by specific software is outside the scope of this review.

5. Coherence, entropy, and connectivity

The extent to which two waveforms correlate at a given frequency is coherence [153, 154]. Entropy, on the other hand, describes the inherent disorder or randomness of the waveforms [155]. Measurements of coherence and entropy have been used to measure connectivity between brain regions and quantify brain reactivity. Connectivity between brain regions can rely on amplitude or frequency-focused tools [156]. These methods have been applied in investigations of disorders of consciousness [155, 157–159] and in seizure prediction modelling [160, 161]. Very few data exist for application of these qEEG measures in children.

Clinical Application of qEEG in the Pediatric ICU Seizure Detection

Seizure detection is one of the most common indications for cEEG monitoring in the pediatric ICU, and seizures occur frequently in critically ill children [15, 19, 44, 46–53]. qEEG has the potential to improve timely recognition and treatment of seizures in this vulnerable population. Multiple qEEG trends can detect seizures, depending on the type of seizure (focal versus generalized), location, and duration. CDSA is commonly used. A seizure will appear as a "solid flame" pattern [162, 163]. Power abruptly increases, peaks, and then attenuates during a seizure typically for both fast and slow frequencies, resulting in a flame-like appearance on the color spectrogram (Fig. 3). On an aEEG, if the seizure involves the electrodes used in the aEEG algorithm, the seizure appears as a sudden upward arched pattern because amplitude of the EEG waveform typically increases during the seizure. The envelope trend will also peak during a seizure, as another amplitude-focused trend. In the case of a focal seizure, the asymmetry index and spectrogram can be useful in highlighting laterality of ictal and postictal patterns.

Several studies have reported success in training bedside ICU providers to recognize qEEG seizures after a brief training session, with sensitivity for seizure detection ranging from 73 to 100% [151, 164-170]. In a prospective study of qEEG program initiation, pediatric ICU providers identified 100% (12 of 12) of patients with electrographic seizures recorded using qEEG, with most (67%) of the seizures recognized when a neurophysiologist was not available for interpretation [170]. Eleven patients had false positive identification of seizures, and 64% (7 of 11) received antiseizure medication. A recent 2-year gEEG education and implementation program providing instruction to pediatric ICU nurses found a much lower seizure detection rate at only 10% (1 of 10) with prospective monitoring; however, the frequency of monitoring was not standardized [171].

Another option for rapid seizure recognition in the ICU is the application of commercially available seizure detection algorithms. Several different proprietary algorithms were compared to the gold standard of expert neurophysiologist review [172]. The algorithm from Stellate Harmonie Version 7 (Natus Medical, Middleton, WI, USA) had the highest sensitivity for seizure detection at 92% but a daily false positive rate of 126.3 incorrectly detected events/day, whereas Persyst Version 11 had a balance of sensitivity and the false positive rate: 76% and 5.1 events/day, respectively. False positive rates, unnecessary medication administration, and alarm fatigue are important considerations when implementing bedside use of qEEG for seizure identification, and ideally, a neurophysiologist should be available to confirm findings on raw cEEG.

qEEG may also aid in efficient seizure burden estimation after super refractory status epilepticus (SRSE) [173]. A recent study used a novel seizure detection education approach, allowing review of ten different trends and use of spike detection frequency above or below 3-Hz frequency to help distinguish seizures from the IIC. Novice qEEG readers overestimated seizure burden, identifying about double the number of minutes of confirmed seizures. qEEG experts, on the other hand, were very accurate in their estimate of seizure



Fig. 3 A 9-year-old boy with a left frontotemporal tumor and new onset left hemispheric onset seizures (black arrows). Trend description from top to bottom: rhythmicity spectrogram for left then right hemisphere demonstrates increased rhythmicity over the left hemisphere during seizures. Fast Fourier Transform spectrogram left over right hemisphere shows solid flames best formed over the left during seizures. Asymmetry spectrogram shows greater power over the left hemisphere during seizures (blue color change). Asymmetry indices for slower frequencies (1–5 Hz) over faster frequencies (6–14 Hz) show discrete graph trend toward less positive values during seizures, indicating greater relative power of the left hemisphere. Amplitude-integrated electroencephalography (EEG) shows classic arched pattern during seizures (Color figure online)

burden (3126 minutes by qEEG estimate vs. 3257 minutes by expert raw EEG review). Although this study did not include children, it provided exciting results, suggesting that qEEG can reasonably estimate seizure burden after SRSE.

Assessing Response to Antiseizure Medication and Infusion Titration

qEEG trend panels can aid the ICU provider in assessing patient response to antiseizure medications [174]. For patients with recurrent seizures who are treated with multiple antiseizure medications in a short period of time, review of the qEEG trends can help distinguish which medications were the most effective and thus guide drug selection individualized to the patient response (Fig. 4). The suppression ratio can be used to assess the degree of burst suppression and titrate anesthetic infusions to a specific target for SRSE and refractory intracranial hypertension management.

Background Assessment

The FFT spectrogram or CDSA is used in clinical practice to assess state change and variability. Quantifiable differences in band power on FFT spectrogram are associated with recovery of children post CA [175]. In a study of 69 pediatric post-CA patients with early (<17 hour after return of circulation) and late (>18 hour) EEG, higher power in the gamma, beta, and delta frequencies early in EEG monitoring was predictive of favorable outcomes, and delta and alpha powers were more important predictive features in late EEG. Gamma frequencies are faster than what are traditionally identified as cortically derived frequencies on scalp EEG and often represent myogenic artifact, suggesting that the ability to generate such artifact post CA may be associated with a more favorable outcome. Similarly, the presence of early sleep spindles post CA is associated with favorable outcome [118], which may account for the influence of beta power in the prediction modeling.



The ability to use qEEG to create an objective, linear, real-time measure of encephalopathy compared to subjective intermittent examinations may have substantial advantage in the ICU, as these measures may serve as a live neuromonitoring "vital sign," viewable at bedside. For example, in the setting of pediatric acute liver failure, the assessment and diagnosis of hepatic encephalopathy has treatment implications and influences transplant priority. Hepatic encephalopathy grade and qEEG spectrogram features were compared in 33 children with acute liver failure [41]. qEEG features were both associated with the degree of encephalopathy and outcomes (liver transplant or death). Infants generally had a loss of total power in response to encephalopathy, whereas older children tended to have decreased theta/delta ratios. Figure 5 illustrates the qEEG progression from stage II to stage III hepatic encephalopathy grade, demonstrating how qEEG can be a dynamic measure of brain function.

Although studies are lacking in children, qEEG is being used to better understand and perhaps find a measurable therapeutic target in disorders of consciousness. Having a bedside tool to detect covert consciousness in patients who appear otherwise unresponsive could significantly improve our ability to neuroprognosticate and advise families in the initial days after acute brain injury. One such assessment tool is the "ABCD model," which has been applied in adult patients with disorders of consciousness after CA. The model is predicated on the central thalamus being a hub of networks involved in consciousness and grades four spectral patterns of the EEG on a scale of corticothalamic activity [176]. Patterns range from type A, representing complete electrographic corticothalamic deafferentation, to type D with normal corticothalamic function. Spectral typing correlated with bedside behavioral assessment using the Coma Recovery Scale-Revised and outcome as measured by the Cerebral Performance Category. Another study of 104 adults who had no clinically apparent response to standard examination found that 16 (15%) demonstrated cognitive-motor dissociation, defined as specific regional and frequency band changes in response to two spoken commands [177]. Eight of those patients were following verbal commands by a median of 6 days. Detection of language comprehension in patients with disorders of consciousness has also been demonstrated by identifying patients with time-locked EEG oscillations that correspond to word, phrase, and sentence frequencies, which have been shown to only be present in patients who can comprehend speech [178]. In this study, electrographic evidence of tracking higher-level linguistic structure correlated with better outcome at 3 and 6 months.



corresponded to the patient no longer following commands and progressing to extensor posturing of arms and legs, sustained clonus at the ankles, hyperreflexia, and positive Babinski sign bilaterally (Color figure online)

Detection of Acute Neurologic Decline

qEEG is also used to detect life-threatening neurologic decompensation before becoming irreversible (e.g., cerebral herniation). Two recent publications evaluated qEEG trends for identifying intracranial emergencies prior to clinical deterioration in children [145, 146]. One study used qualitative review of the qEEG by neurophysiologists and the Persyst Z-score trend to create alerts for 10 patients. The Z-score measures deviations from a user-defined and patient-specific baseline. The user can then set an alarm for specified cutoffs beyond this Z-score. Identification of neurologic deterioration using expert qEEG review occurred a median of 5.2 hours before raw EEG changes were detected and a median of 5.5 hours before a clinical change was noted. The Z-score qEEG alert detected the change before expert review in 50% (5 of 10) of the patients. The second study comprised 13 patients with increased intracranial pressure and found that a detectable rise in the suppression ratio occurred a median of 3.1 hours prior to the first clinically detectable change [146].

When cerebral perfusion gradually decreases because of progressive cerebral edema, the qEEG changes may be most apparent in the FFT spectrogram, with initial loss of fast frequencies and gain of slower frequencies, followed by loss of slower frequencies as the ischemic threshold is crossed [150] (Fig. 6).

Focal Cerebral Dysfunction Detection

Critically ill children may be at risk for focal neurologic dysfunction and injury, depending on their underlying disease. For example, children requiring extracorporeal membrane oxygenation are at risk for both focal ischemia and hemorrhage [179-181]. New EEG abnormalities, such as focal slowing or new interictal or ictal activity, can be the first indicator of injury in critically ill children who may otherwise have a limited neurologic examination. The roles of both cEEG and qEEG specifically for detection of ischemia and hemorrhage are reviewed elsewhere in this issue in the article titled "Neuromonitoring in Children With Neurovascular Disorders." A singlecenter study of children with acute unilateral anterior circulation ischemic stroke (n=5) and hemorrhagic stroke (n=6) compared qEEG features between the injured and uninjured hemispheres [182]. Patients with ischemic stroke demonstrated decreased alpha and beta power and lower spectral edge frequency in the injured hemisphere, whereas patients with hemorrhage consistently had a negative correlation between total power and mean arterial blood pressure. The loss of faster frequencies in



the ischemia group has been well described; the negative correlation between total power and blood pressure was postulated to reflect a significant increase in the delta power in the area of the bleed. This may also reflect loss of autoregulation in the affected hemisphere.

Asymmetry spectrograms are particularly helpful for rapidly identifying differences between hemispheres. Persistent changes in asymmetry spectrograms have been associated with unfavorable outcome (morbidity and mortality) in a small pediatric study aimed at predicting neurologic deterioration [145]. Differences in the asymmetry spectrogram appear related to cerebral perfusion, either increased (seizure) or decreased (stroke, post-ictal state), or extracerebral pathology (subdural hemorrhage or superficial scalp swelling). The relative asymmetry between brain regions has long been appreciated to be useful in ischemia detection and stroke recovery in adult patients [183–186], and this trend has been used to monitor cerebral perfusion in pediatric patients undergoing revascularization surgery for moyamoya [187]. Of note, these displays are relative to the contralateral hemisphere or region in question and are susceptible to overemphasis of noncerebral pathology (scalp edema).

The ADR is also used for assessing perfusion and ischemia (Fig. 7). The most common use is screening adult patients for delayed cerebral ischemia after subarachnoid hemorrhage [188, 189]. Studies have also

investigated the utility during carotid endarterectomy [190], mechanical thrombectomy [191], pediatric and adult revascularization for moyamoya [187, 192], and stroke and rehabilitation in adults [185]. Clinical and research applications for individual trends in the pediatric ICU remain open, as well as novel combinations of these trends to for tracking disease trajectory or recovery [193].

Pediatric Macroperiodic Oscillations

More recently, a new periodic pattern on the power spectrogram has been identified in pediatric patients [194]. This pattern oscillated regularly over minutes and has been termed macroperiodic oscillations (MOs) (Fig. 8). In the first description, this pattern was associated with younger patients and oscillated over 2–7 minutes, with the timing consistent within patients. There was a strong association with refractory seizures in patients with acute injury and without preexisting neurologic conditions. A further computational study to measure the strength and spatial distribution of oscillations found MOs in patients not readily identified on clinical review of the qEEG and in patients without seizures. Importantly, the strength and spatial distribution of the MO pattern was associated with clinical outcomes at hospital discharge [195, 196].

A similar oscillatory pattern in neonates with severe hypoxic-ischemic encephalopathy has been described;



Fig. 7 A 10-year-old boy with at-home cardiac arrest requiring extracorporeal membrane oxygenation (ECMO). Hypotension and arrhythmias resulted in hypoperfusion injury around the time of ECMO cannulation (black arrow). The right hemisphere lost delta power, increasing the alpha/ delta ratio (ADR), whereas the left hemisphere lost fast frequencies and gained slow frequencies, resulting in a decrease in ADR (red arrow). Asymmetry spectrogram reflects the increase in delta power over the left hemisphere after cannulation (Color figure online)



this pattern was not clearly associated with seizures but was seen in neonates with more severe background abnormalities and worse neurodevelopmental outcomes [197]. This pattern was termed "pseudo-sawtooth" and described an aEEG cyclical pattern with a cycle duration of 3.3–4.6 minutes consisting of periods of increased amplitude of delta and theta frequencies alternating with profound suppression. This pattern emerged and peaked at a time that closely paralleled the known timing of the secondary phase of brain injury experienced by neonates after hypoxic-ischemic injury, between 6.5 and 28 hours after birth. The authors posited that this may be a biomarker of more severe brain injury and that the rhythmic oscillations may be intrinsic to subcortical structures, emerging when cortical activity is more severely impaired.

Common qEEG Artifacts in the Pediatric ICU

EEG studies in the ICU are prone to artifacts. Most qEEG software offers artifact reduction algorithms, which perform well in removal of artifact from electrical artifact (60 Hz in the United States, 50 Hz in Europe) and myogenic artifact. Less likely to be filtered by artifact reduction are rhythmic patterns such as patting and respiratory therapy artifact, and both can be mistaken for seizures if the raw EEG and video are not reviewed (Fig. 9a). Scalp edema can cause shift asymmetries, depending on head position (Fig. 9b).

Limitations of qEEG

An advantage of qEEG in critical care is that it summarizes large amounts of data that can then be trended over time. However, several minutes of EEG need to be collected to display the initial trends, and several hours may be required to make assessments of features such as state cycling, seizure burden, response to medication, and global improvements or decline. qEEG is not yet ready to be used as an independent tool in pediatric neurocritical care; as such, findings should always be verified with review of the raw EEG.

qEEG software does not currently offer easy integration of patient-related events with the EEG, such as medication administration. Some packages do offer integration of qEEG with continuous variables, such as vital signs, intracranial pressure, end-tidal CO_2 .

Regarding seizure detection, qEEG may miss seizures if the ictal amplitude change is too small, if the seizure is of short duration, or if the seizure is limited to a small area and only detected by a few electrodes [172, 198–200].

Additional limitations include the lack of normative data in critically ill children and the impact of neuroactive medications on qEEG. There are no guidelines for standardized reviewing and reporting of qEEG, many of the patterns have not been studied extensively or validated in children, and formal training in qEEG interpretation is not widely available.

Future Directions

Use of qEEG in clinical practice in the pediatric ICU for brain monitoring is increasing. Continued efforts are ongoing to validate the optimal parameters to detect patterns that are predictive, specific, and clinically actionable. The development of EEG monitoring tools that can be confidently associated with a specific neurologic state, including increased intracranial pressure, hypoperfusion, new ischemia, and status epilepticus, will enable movement of these tools to the bedside for prospective monitoring and interventions that may improve outcomes through early detection, timely intervention, or improved accuracy of prognosis. Multimodal monitoring coupling EEG with other neuromonitoring tools discussed in this article will further advance clinical care in the pediatric ICU.



electroencephalography (EEG) in a 3-month-old with congenital heart disease status post surgical repair. Asymmetry indices and spectrograms demonstrate shifting impact of scalp edema on the EEG signal, with changing asymmetric power at regular intervals, reflecting timed repositioning of the patient by the bedside nurses

Conclusions

cEEG offers high-resolution noninvasive neuromonitoring of critically ill children at risk for neurologic complications. cEEG remains the gold standard for seizure detection and background assessment, and qEEG offers real-time display of time-compressed data, holding promise for detecting neurologic compromise more rapidly than traditional EEG review.

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1007/s12028-023-01686-5.

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Author Contributions

All authors contributed to drafting and editing of the manuscript, and the final manuscript was approved by all authors.

Source of Support

There was no funding for this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical Approval/Informed Consent

Ethical approvals were not sought given that this is an invited review.

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Received: 28 July 2022 Accepted: 30 January 2023 Published online: 22 March 2023

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