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Review

Conventional and quantitative EEG in status epilepticus

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ABSTRACT

Purpose: To summarize the use of continuous electroencephalographic monitoring (cEEG) in the diagnosis and management of pediatric convulsive status epilepticus (CSE) and subsequent non-convulsive seizures (NCS) with a focus on available guidelines and infrastructure. In addition, we provide an overview of quantitative EEG (QEEG) for the identification of NCS in critically ill children.

Methods: We performed a review of the medical literature on the use of cEEG and QEEG in pediatric CSE. This included published guideline, consensus statements, and literature focused on the use of cEEG and QEEG to detect NCS.

Results: cEEG monitoring is recommended for prompt recognition of ongoing seizures that may be subtle, masked by pharmacologic paralysis, and or converted from convulsive seizures to NCS after administration of anti-seizure medications. Evidence indicating that high seizure burden is associated with worse outcome has motivated prompt recognition and management of NCS. The American Clinical Neurophysiology Society's consensus statement recommends a minimum of 24 h to exclude electrographic seizures, while the Neurocritical Care Society's guideline suggests 48 h in patients that are comatose. The use of QEEG amongst electroencephalographers and critical care medicine providers is increasing for NCS detection in critically ill children. The sensitivity and specificity of QEEG to detect NCS ranges from 65 to 83% and 65–92%, respectively.

Conclusion: The use of cEEG is important to the diagnosis and treatment of NCS or subtle clinical seizures after pediatric CSE. QEEG allows cEEG data to be reviewed and interpreted quickly and is a useful tool for detection of NCS after CSE.

1. Introduction

Convulsive status epilepticus (CSE) is a common neurologic emergency in childhood and one of the most common reasons for admission to the pediatric intensive care unit [1,2]. CSE is defined as a prolonged convulsive seizure or multiple seizures without return to the baseline level of functioning between seizures. The estimated incidence of pediatric CSE is 20 cases per 100,000 children per year with a mortality ranging from 0 to 11% [3–14]. Mortality is higher (4–22%) with symptomatic than idiopathic etiologies and when seizures do not cease after administration of first-line anti-seizure medications and become refractory [15–17]. Although the initial seizure is often readily identifiable as a convulsion, after treatment is initiated seizures may persist with subtle behavioral manifestations such as confusion, subtle motor manifestations, or simply unresponsiveness. Thus, patients presenting with CSE are at high risk of non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE) [18–24].

The principles of management rely on medical stabilization, prompt recognition and treatment of seizures, and simultaneous evaluation and management of the underlying etiology [25–29]. There is evidence that prolonged seizures are unlikely to terminate without anti-seizure medication and can lead to neuronal injury even in absence of continued clinical manifestations [11,30,31]. In addition, both prolonged seizures and anti-seizure medications may compromise respiratory function, leading to intubation and pharmacologic paralysis. Greater awareness of subtle and non-convulsive seizures has increased demand for continuous EEG monitoring (cEEG) in intensive care units [32,33], resulting in workload challenges for many clinical electroencephalography groups. This in turn has led to research and implementation of quantitative EEG (QEEG) analysis and automated seizure detection algorithms to facilitate seizure detection. This review discusses the utility of cEEG in CSE with a focus on infrastructure development and the use of QEEG analysis in the pediatric intensive care unit.

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Table 1
Risk of NCS/NCSE after CSE.

Author	Subjects	Clinical seizures as predictors of ES/ESE
Jette et al. 2006	N = 204 ES 36% (74) CS before cEEG 54% (110/204)	CS before NCS in 34% (69/204)
Abend et al. 2011	N = 550 ES 30% (162) ESE 36% (59/162)	CS prior to EEG <i>Multivariable analysis</i> Seizures 2.62(1.5–4.59) Status epilepticus 0.97(0.46–2.04)
Williams et al. 2011	N = 122 ES 39% (47)	Diagnosis of status epilepticus/seizures Chi ² (Likelihood ratio) 5(0.026)
McCoy et al. 2011	N = 121 ES- 32% (39) 72% (28)-NCS only 18% (7)-NCS and CS 10% (4)-CS only	Predictors of NCS <i>Multivariable analysis</i> Prior in hospital convulsive seizures 3.22(1.01–10.29) IED on EEG 4.42(1.69–11.56)
Payne et al. 2014	N = 259 ES 36% (93) 9% (23) ESE	Hourly seizure burden for clinical seizure < 20%–98% (41/42) 20–50%–86% (24/28) > 50%–96% (22/23) Clinical seizures in the acute presentation had a higher maximum hourly seizure burden
Sanchez Fernandez et al. 2016	N = 98 with CSE ES- 33% (32) ESE- 47% (15/32)	Risk factors for ES after CSE IED-60% (59)- Pearson X ² = 14.77 Prior epilepsy-57%(56)-Pearson X ²
Sansevere et al. 2017	N = 414 ES 25% (102/414) ESE 12% (12/102) NCSE 25% (3/12)	ES after clinical seizure/status-33% (59/179), compared to other indications 18% (43/235)

CS (Clinical seizure), ES (Electrographic seizures), ESE (Electrographic status epilepticus), NCS (Nonconvulsive seizure), NCSE (Nonconvulsive status epilepticus), IED (Interictal epileptiform discharge).

2. cEEG monitoring in status epilepticus

2.1. Stages of status epilepticus

Over time, the definition of status epilepticus has evolved [34–36]. The International League Against Epilepsy defines status epilepticus based on two distinct time points. The first time point (t1) designates the time at which a seizure becomes continuous or abnormally prolonged, while the second time point (t2) designates the time at which there is a risk for long-term consequences [35]. This conceptual definition coincides with the terms early or impending status epilepticus (seizure > 5 min) and established status epilepticus (seizure > 30 min) [27,35]. As a convulsive seizure become prolonged, subtle stages of status epilepticus frequently occur such that the clear convulsive manifestations becomes less apparent, the patient is in a comatose or encephalopathic state, and the clinical manifestations of seizures are subtle if present at all. In addition, as status epilepticus evolves to become established, the likelihood of spontaneous resolution is low and the risk of seizures becoming refractory increases [37,38]. Five distinct electroencephalographic stages of CSE have been described in animal models and humans [39]. The first stage is characterized by distinct electrographic seizures followed by interictal slowing. The second stage is characterized by seizures merging with waxing and waning rhythmic ictal discharges. The third phase is characterized by continuous ictal discharges. The fourth stage is characterized by low voltage regions of suppression. The fifth stage is characterized by periodic discharges on a suppressed background and sometimes evolving to electro-cerebral silence. Since being described initially in 1990, there have been descriptions describing the first two stages in humans [40], and all stages were described in a critically ill adult after the family decided to not escalate treatment due to the overall medical condition [41].

2.2. Guidelines and recommendations

The American Clinical Neurophysiology Society's (ACNS) consensus statement on cEEG in critically ill adults and children recommends that

cEEG be initiated as soon as possible to identify non-convulsive seizures and non-convulsive status epilepticus if there is persistently abnormal mental status following generalized CSE or other clinically evident seizures [42]. The Neurocritical Care Society's (NCS) guideline for the treatment of status epilepticus recommends that cEEG be initiated within one hour of suspected SE in all patients [27]. Both guidelines cite the utility of cEEG in the identification of subtle and non-convulsive seizures, and also to guide treatment of refractory status epilepticus (RSE). In addition to cEEG, the NCS guideline recommends early and aggressive treatment of children presenting with CSE and supports the use of continuous intravenous anti-seizure infusions when necessary [27]. A retrospective cross sectional descriptive study of patients entered in the Kid's Inpatient Database from 2010 to 2012 assessing the use of cEEG in high risk children and neonates (ECMO, TBI, HIE, cardiac arrest, and cardiac surgery) in the United States suggests that cEEG was underutilized for electroencephalographic seizure detection in critically ill children prior to publication of the ACNS consensus statement in 2015 and around the time of publication of the NCS guideline in 2012, citing an overall use of 6% in this subset [43]. This study does not assess the use of cEEG for CSE.

2.3. Risk of subtle and non-convulsive seizures

Several studies indicate that the risk of non-convulsive seizures after convulsive seizures is high [18–24]. Clinical manifestations of ongoing seizures often become more and more subtle over time, especially following the administration of anti-seizure medications, and the use of sedative and paralytic medications may completely mask the clinical manifestations of seizures. Several pediatric studies assessing NCSE in the pediatric ICU have confirmed the association of prolonged or multiple clinical seizures as a risk factor for subsequent development of NCS and NCSE [19,21,22,24,44–47], (see Table 1). A multicenter pediatric study examined 98 children with CSE who underwent cEEG. Electrographic seizures were identified in 32 children (33%) with 11 children (34%) having EEG-only seizures. Factors associated with occurrence of electroencephalographic seizures after CSE were a previous

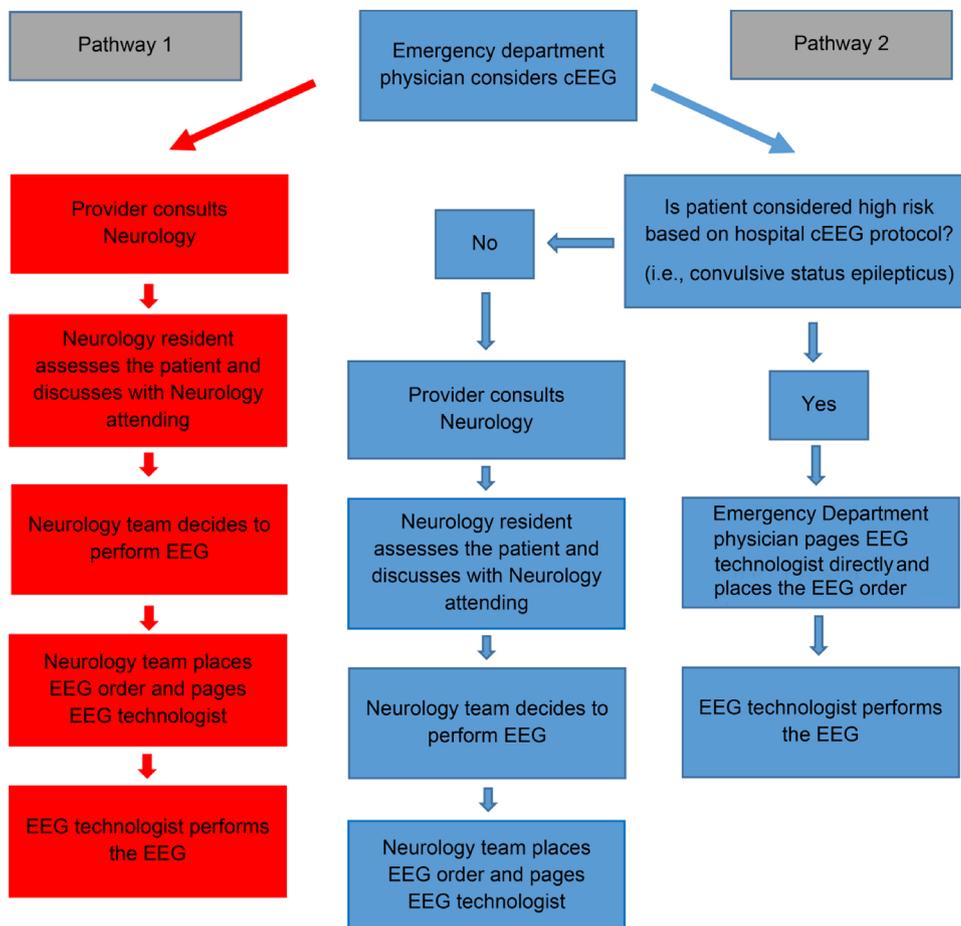


Fig. 1. Proposed pathway for cEEG monitoring in convulsive status epilepticus. Pathway 1 is an example of the typical communication pathway necessary to perform cEEG. Pathway 2 is a proposed strategy to improve time to cEEG initiation for high risk patient populations that includes pediatric patients presenting with convulsive status epilepticus.

diagnosis of epilepsy and inter-ictal epileptiform discharges on the EEG [24]. In addition to the morbidity and mortality associated with pediatric CSE, studies suggest that NCSE and high seizure burden also impact patient outcomes [19,23,48–50]. Two pediatric studies have shown associations between high seizure burden and unfavorable developmental outcomes. The first study assessed follow-up data on 60 of 137 (44%) subjects who had been normal prior to admission with electroencephalographic seizures in 12 subjects and electroencephalographic status epilepticus in 14 subjects. After multivariable analyses, electroencephalographic status epilepticus was associated with an increased risk of unfavorable Glasgow Outcome Scale scores (OR 6.36, $p = 0.01$) and lower Pediatric Quality of Life Inventory scores (23 points lower, $p = 0.001$), whereas electroencephalographic seizures were not associated with worse outcomes [48]. The second study assessed 259 neonates and children including 93 with electroencephalographic seizures and 23 with electroencephalographic status epilepticus. The probability of neurologic decline rose sharply above a maximum seizure burden of 20% per hour (12 min). After a multivariable analysis, the odds of neurologic decline increased by 1.13 (95%CI 1.05–1.21) for every 1% increase in maximum seizure burden [19]. Despite these findings, a causal link between seizure burden and outcome has not yet been proven, and it remains to be established that more timely seizure identification and aggressive management will reduce seizure burden and improve neurobehavioral outcomes.

3. Logistics of cEEG monitoring

3.1. Infrastructure

Continuous EEG is a resource intensive procedure. Policies regarding cEEG timing and duration have a large impact on the available

institutional resources. The optimal duration of cEEG monitoring depends on the probability of seizure detection and the impact that seizure identification and management may have on outcome. A survey of tertiary care hospitals in the United States and Canada showed that 31% of institutions had clinical ICU EEG pathways. Prior to cEEG initiation, 36% of institutions required a neurology consult, 53% of institutions required a phone discussion, and 10% did not require any neurology input. An EEG technologist was available to perform cEEG in 89% of institutions, with 21% having in-hospital technologists after usual daytime hours. The cEEG was reviewed within the first hour by a technologist at 65% of institutions and by an attending physician at 79% of institutions [32].

Developing the infrastructure required to enable prompt cEEG initiation and interpretation is particularly important in situations in which early seizure detection is important. Recent studies have focused on the impact that early detection and treatment of seizures may have on seizure burden and outcome. A pediatric cohort assessing the early treatment of refractory CSE in 218 patients aged 1 month to 21 years showed that a patients receiving first-line antiseizure medications after 10 min of seizure onset had a longer overall convulsive seizure duration when compared to patients receiving first-line antiseizure medication before 10 min [51]. In addition, a study in 625 neonates and children found that a delay between ICU admission and cEEG initiation was associated with mortality [52].

Efforts to improve time to cEEG initiation and time to seizure treatment have focused on refining clinical pathways, communication strategies, and care processes. One study evaluated 41 patients prior to and 21 patients post implementation of a pathway optimizing communication and anti-seizure management. After the pathway was implemented, the median time to treatment decreased from 139 min (IQR 71, 189) to 64 min (IQR 50, 101; $p = 0.0006$). In addition, after

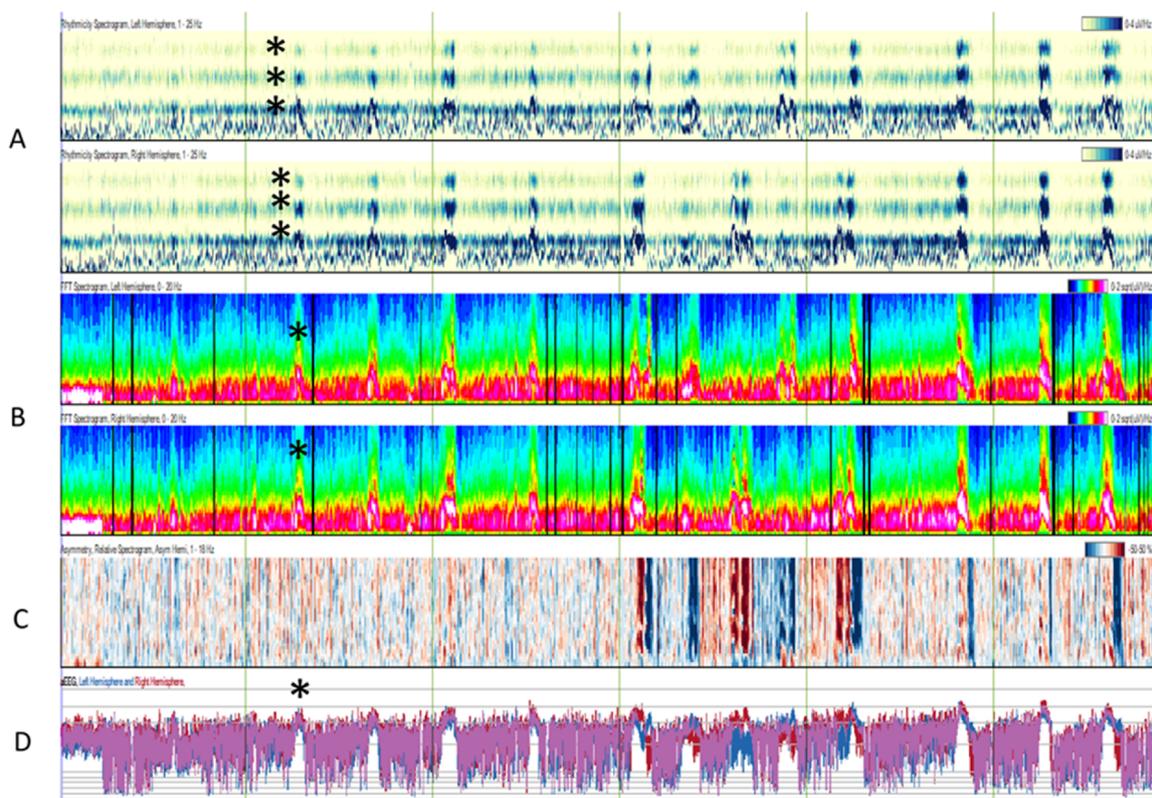


Fig. 2. Quantitative EEG display (left/right hemispheric montage).

This is an example of a 2-year-old boy, who presented in CSE leading to NCSE after intubation. Panel A shows the rhythmicity spectrogram for the left (above) and right hemisphere (below). Panel B shows the CSA/FFT spectrogram for the left (above) and right hemisphere (below), while panel D shows the left and right hemisphere amplitude EEG (aEEG) superimposed on one another. The asterisks (*) denote examples of seizure activity. The seizures are not well visualized on the asymmetry spectrogram. The display is condensed to review a 2-hour period.

pathway implementation there was a higher likelihood of seizure termination following administration of the initial anti-seizure medication (67% vs. 27%, $p = 0.002$) [53]. The ACNS consensus statement recommends development of institution specific pathways given available resources, 42 and Fig. 1 provides an example of a proposed pathway.

3.2. Duration of cEEG monitoring

The optimal duration of cEEG monitoring should be long enough to either confirm or exclude seizures in a high proportion of subjects at risk, while still making reasonable use of institutional resources. The ACNS consensus statement recommends performing cEEG for a minimum of 24 h to exclude seizures while the NCS guideline suggests cEEG for 48 h in patients that are comatose [27,42]. Several single and multicenter pediatric studies confirm that the highest yield for seizure detection is in the initial 24 h of cEEG [20,44–47,54]. Several studies have also aimed to identify predictors of seizures based on early EEG findings. A single center study of 414 pediatric patients with and without epilepsy found seizures occurred in 40% of patients with epileptiform discharges present compared to 25% of the full cohort [47]. EEG background features and salient clinical details may help guide individualized cEEG monitoring strategies to guide limited cEEG resources to the patients most likely to benefit. A multicenter study of 11 tertiary care centers evaluated clinical and EEG features as seizure predictors. Clinical features included a convulsive seizure prior to cEEG monitoring while background EEG features focusing on degrees of abnormality and presence or absence of epileptiform discharges. The model was validated prospectively with a sensitivity of 59% and specificity of 81% [55]. Models can be tailored to individual centers since there may be wide variation in patient characteristics and seizures prevalence when compared to multicenter and tertiary care center

experiences. The cost of unnecessary monitoring must be taken into consideration to allow for better allocation of resources. Cost effectiveness studies have evaluated the cost of cEEG, while assessing the duration of cEEG that is cost effective but will have the greatest impact on clinical care based on the probability of seizure detection [56,57]. One study found that 24 h was most cost effective cEEG monitoring strategy based on a substantially higher cost for 48 h of cEEG monitoring given that the longer duration would only identify 4% more children with electrographic status epilepticus while requiring a large number of patients to undergo an extra day of cEEG [57].

4. EEG patterns after convulsive status epilepticus

Upon initiation of cEEG during or after CSE, there are distinct patterns that are often encountered based on underlying etiology and oftentimes treatment. Identification of these patterns (i.e., lateralized periodic discharges, generalized periodic discharges) may be useful in determining prognosis, estimating the risk of further seizures, and providing insight into the underlying CSE etiology [58]. A pediatric study of 279 children with status epilepticus found generalized periodic discharges (GPDs, formerly GPEDs [58]) as anesthetic agents were lifted in 10 patients upon review of EEG reports. Continuous EEG data was available for 6 out of the 10 patients. Five of the 6 patients had NCS identified within 48 h after GPDs were detected [59]. This study suggested that early EEG findings and patterns after CSE have been controlled may serve as biomarkers for continued clinical seizure and overall prognosis.

In addition, EEG findings can help decipher the etiology of a convulsive seizures or CSE and may help guide management tailored to the suspected etiology. An example of this is identification of lateralized periodic discharges. A study looking at 44 children with LPDs found

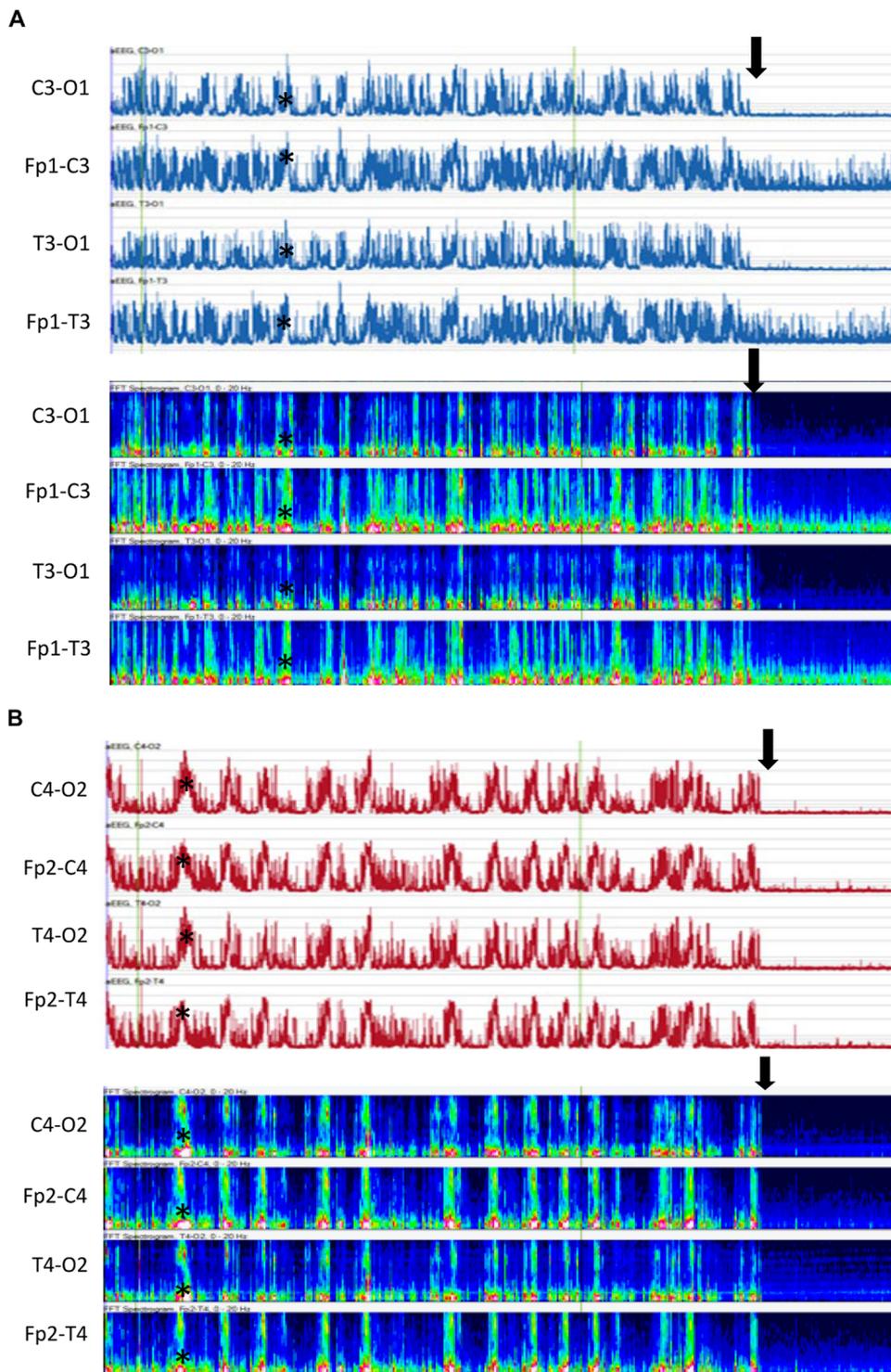


Fig. 3. A. (double distance A–P bipolar montage) B. (double distance A–P bipolar montage).

This is an example of a neonate born at 34 weeks with NCSE responding to a dose of Fosphenytoin. Fig. 3A shows individual electrode pairs from the left hemisphere, while Fig. 3B shows individual electrode pairs from the right hemisphere. The top panels represent the aEEG, while the bottom panels show the corresponding CSA/FFT spectrogram. Recurrent seizures involving multiple brain regions but with right hemispheric predominance are well visualized. The asterisks (*) marks examples of seizure activity. The black arrow denotes resolution of NCSE after a bolus of Fosphenytoin.

that 64% had a central nervous system infection, which was most commonly herpes simplex virus [60]. While herpes simplex virus is thought to be the most common etiology in a setting of concern for infection while identifying LPDs, other infectious etiologies have been described [61].

The ictal nature of periodic and rhythmic patterns in critically ill patients remains unclear and is characterized as being part of the ictal-interictal continuum (IIC) a phrase introduced by Pohlmann-Eden et al in 1996 [62]. While a consensus on the definition of the IIC does not exist, it represents periodic and rhythmic patterns that do not meet criteria for NCSE and do not have the typical components of an

electrographic seizure. A recent study of adults evaluated features of rhythmic and periodic patterns to assess ictal features. LPDs with or without a Plus modifier, lateralized rhythmic delta (LRDA), and GPDs were each associated with seizures while generalized rhythmic delta (GRDA) was not [63]. Similar studies have not been performed in children. The Salzburg criteria published in 2015, defines electrographic seizures and NCSE [64]. Epileptiform discharges > 2.5 Hz, a pattern with spatiotemporal evolution or subtle clinical signs associated with epileptiform discharges or rhythmic activity are defined as ictal patterns. In addition, it suggests performing an anti-seizure medication treatment trial in instances where clear ictal criteria are not met,

Table 2
Sensitivity of qEEG by providers.

Pediatric studies		
Stewart et al. 2010	Cohort: 27 cEEG with 553 seizures. Display: CDSA (8 channel) and aEEG. Reviewers: 3 neurophysiologists	Median sensitivity: CDSA 83.3%; aEEG-81.5% Median false positive rate(n/h): CDSA 0.06; aEEG 0.05
Pensirikul et al. 2013	Cohort: 21 cEEG from PICU. Display: CDSA Reviewers: 8 neurophysiologists	Sensitivity Group A (64.8%) and Group B (75%) Specificity Group A (92.3%) and Group B (78.2%).
Topjian et al. 2015	Cohort: 100 CDSA images from CA survivors (30% with seizures) Display: CDSA Reviewers: 20 critical care physicians and 19 critical care nurses	Overall Sensitivity 70% (95% CI, 67%–73%) Specificity 68% (95% CI, 67%–70%) PPV/NPV 46%/86%
Du Pont-Thibodeau et al. 2017	100 aEEG 100 aEEG + CDSA Reviewers: Pediatric critical care providers	aEEG Sensitivity-77%(95% CI, 73–80%) Specificity-65%(95% CI 62–67%) NPV-88%(95% CI 86–90%) PPV- 46%(95% CI 43–49%) aEEG + CDSA Sensitivity-77%(95% CI, 74–81%) Specificity-68%(95% CI 66–71%) NPV-89%(95% CI 87–90%) PPV- 49%(95% CI 46–52%)

specifically for epileptiform discharges $> .5$ Hz, but < 2.5 Hz, that may or may not be fluctuating based on ACNS critical care criteria. Approaches to treatment of the IIC have been proposed but there is no widely accepted, standardized, or evidence-based approach available [65,66].

5. Quantitative EEG

Continuous real time monitoring of raw conventional EEG tracings is sometimes necessary in the pediatric ICU. This can be challenging due to the volume of information and increasing numbers of studies with limited cEEG equipment and personnel. While visual analysis of conventional EEG continues to be the standard approach to EEG assessment, the use of QEEG analysis is increasing and becoming a useful complementary tool. This technology allows an electroencephalographer or bedside caregiver to view real time EEG data that is compressed over time, providing a ‘snapshot’ that gives an overview of a patient’s brain activity, thereby speeding interpretation and allowing an electroencephalographer or EEG technologist to monitor multiple patients simultaneously [67–69]. QEEG can be based on amplitude in the form of amplitude integrated EEG (aEEG) and envelope trends which provide the median amplitude of background activity. In addition, QEEG can focus on power over time at various frequencies [70], referred to as compressed spectral array (CSA), density spectral array (DSA), and color density spectral array (CDSA). In addition, there are proprietary rhythmicity spectrograms and seizure detection algorithms. Figs. 2 and 3 provide examples of QEEG displays.

Several studies have evaluated the use of QEEG in clinical practice. The first study included 330 pediatric and adult neurologists and showed the use of QEEG software to be uncommon. No QEEG use was reported by 66% of respondents, while among those who used QEEG the most techniques were CSA (18%) and aEEG (13%). [18]. A later survey of 58 pediatric centers in the United States and Canada found QEEG trend analysis to be used at 49% of institutions with bedside use and review in 14% [32]. A recent survey of 97 adult and pediatric clinical neurophysiologists found that 77% use QEEG for clinical care and that seizure detection was the most common use (92%). For seizure detection, the most popular trend used was the rhythmicity spectrogram (61%) followed by automated seizure detectors (55%), and CDSA (47%). In addition, 21% of respondents described that non-neurophysiologists were involved in QEEG interpretation [71]. Thus, available

literature suggests that while QEEG use varies by center, its overall use is increasing for seizure detection among critically ill children.

As the use of QEEG has increased, several adult and pediatric studies have evaluated the accuracy of this tool for seizure detection (Table 2) [72]. One pediatric study transformed 27 EEG recordings with 553 discrete seizures into aEEG and CDSA displays. Three board-certified neurophysiologists without prior experience with these techniques reviewed the trends. The median sensitivity for all recordings across the three reviewers was 83% for CDSA and 82% using aEEG. In addition, 11% of seizures were missed on both displays with the percent of seizures missed being significantly higher with CDSA (21%) than aEEG (14%, $p = 0.003$) [73]. A second pediatric study converted 21 consecutive EEGs tracings to CDSA for seizure identification. Two groups of electroencephalographers reviewed the QEEG images: Group A saw them in random order while Group B was provided with an answer as to whether the initial QEEG image for a patient contained seizures or not (as if someone had reviewed the conventional EEG to help guide QEEG use). Sensitivity was not significantly different between the two groups whereas specificity was different (92% vs. 78%, $P < 0.001$) [74]. The study concluded that while CDSA is a useful screening tool, it will not identify all seizures and false positives may occur.

As QEEG has become available, there has been great interest regarding the interpretation of QEEG by non-neurophysiologists [75–79]. A pediatric study assessed the accuracy of interpretation of CDSA for seizure detection after cardiac arrest among pediatric critical care providers including attending physicians, trainees, and nursing staff. After viewing a tutorial on the use of CDSA 39 critical care providers reviewed 100 CDSA images. The CDSA seizure detection sensitivity was 70%, positive predictive value was 46%, and negative predictive value was 86%. This study concluded that CDSA interpretation by critical care providers may be useful after a brief training [75]. A recent prospective adult study evaluated the role of critical care nurses’ ability to detect seizures using CSA. In this study 33 neuro-intensive care unit nurses and four neurophysiologists reviewed 42-hour CSA segments for seizures after a brief training session. Nurse seizure detection accuracy was 56% with a sensitivity of 74% and a false positive rate of 1 per 3.2 h. Neurophysiologist detection accuracy was 68% with a sensitivity of 66% and false positive rate of 1-per-6.4 h [79]. These studies suggest that while there is room for improvement regarding sensitivity, non-neurophysiologists have a vital role in using QEEG to detect seizures. In addition, accuracy will likely improve with review of the raw data. The

studies to date have relied on carefully selected EEG segments. Further investigation is needed to determine the role of QEEG amongst providers in real-time clinical practice.

6. Conclusions

CSE is a common neurologic emergency requiring prompt recognition and treatment. Continuous EEG monitoring is important in management of CSE to detect continued electroencephalographic seizures after cessation of clinically evident seizures. Continuous EEG is necessary for treatment of refractory status epilepticus and guidance of continuous anesthetic infusions. In addition, EEG background features can be helpful in determining the risk of persisting electrographic seizures, can aid in prognosis, and can sometimes guide diagnostic studies and treatment of suspected underlying etiologies. Finally, QEEG is a rapidly-developing and useful tool for non-convulsive seizure detection since it allows EEG data to be viewed and interpreted quickly by neurophysiologists, EEG technologists, and bedside clinicians.

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