Continuous electroencephalography for seizures and status epilepticus

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Purpose of review
To discuss the use of continuous video-electroencephalographic (cEEG) monitoring among critically ill children at risk for electrographic seizures and status epilepticus.

Recent findings
Recent reports have demonstrated the growing, but heterogeneous, use of cEEG monitoring among North American pediatric institutions, and provided evidence for the high prevalence of subclinical seizures, particularly among encephalopathic patients with acute brain injury. Increasing seizure burden and status epilepticus have been shown to be independently associated with worse short-term and long-term outcomes.

Summary
Certain high-risk children frequently experience electrographic seizures and status epilepticus, often without clinical signs, necessitating the use of cEEG monitoring for their diagnosis and management. Although an increasing electrographic seizure burden and status epilepticus are independently associated with worse outcome, further studies are needed to determine whether aggressive use of antiepileptic drugs to reduce seizure burden can improve outcome.

Keywords
child, continuous video-electroencephalographic monitoring, critical illness, seizures, status epilepticus

INTRODUCTION

The use of continuous video-electroencephalography (cEEG) for the detection of seizures and management of status epilepticus is rapidly increasing and becoming standard practice at many academic pediatric centers in North America [1▪]. Despite the widespread use of cEEG monitoring, few institutions have implemented clinical pathways to define how and when to use this costly and resource-intensive investigation [2▪]. Among those centers that have developed guidelines, large institutional heterogeneity exists [1▪]. This review presents the growing body of evidence available to help guide the use of cEEG monitoring for detecting seizures and status epilepticus in children.

CLASSIFICATION OF SEIZURES IN THE ICU

Seizures among critically ill children are commonly classified according to their clinical and electrographic characteristics (Fig. 1). Electrographic seizures are defined by their EEG features, as any rhythmic electrographic pattern lasting at least 10 s (or shorter if associated with clinical change) with a clear onset and offset, and evolution in frequency, amplitude, or morphology [3]. Electrographic seizures may or may not be accompanied by clinical signs. Electroclinical seizures refer to electrographic seizures that are accompanied by any clinical correlate, including motor, sensory, or autonomic changes. Electroclinical seizures may be readily apparent to bedside observers, but more often in the ICU setting their clinical manifestations may be extremely subtle, such that these seizures are missed by bedside caregivers and are only noted upon review of a time-locked video recording. When electrographic seizures occur without any discernible clinical correlate, they are termed subclinical, or EEG-only seizures. As discussed below, subclinical

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KEY POINTS

- Electrographic seizures and status epilepticus are common among encephalopathic critically ill children.
- The vast majority of these seizures are subclinical and therefore require cEEG monitoring for their diagnosis.
- Certain clinical and EEG characteristics can help predict risk for seizures and may be used to allocate scarce cEEG monitoring resources.
- The majority of seizures begin within the first 24 h of cEEG monitoring.
- Seizures are independently associated with worse outcome in critically ill children, but further study is needed to determine whether aggressive treatment to reduce seizure burden can improve outcomes.

seizures represent the majority of seizures in the ICU and often occur in the setting of an acute encephalopathy secondary to central nervous system pathology (e.g., infection, status epilepticus, trauma), sedation, paralysis, or frequently a combination of the above. Therefore, cEEG monitoring is required to accurately quantify the burden of subclinical seizures and subtle electroclinical seizures among critically ill children.

Electrographic status epilepticus is classically defined as either a single prolonged electrographic seizure lasting at least 30 min or recurrent seizures totalling at least 30 min in any 1-hour period [4▪▪,5▪▪]. However, emerging evidence that neurological injury can occur before 30 min have elapsed, and evidence that delay to initiation of seizure treatment results in greater treatment resistance, has led to an 'operational' definition of status epilepticus as any electrographic seizure lasting at least 5 min [6]. Status epilepticus is commonly classified as either convulsive, when rhythmic limb movements are apparent, or nonconvulsive, when they are not present [6].

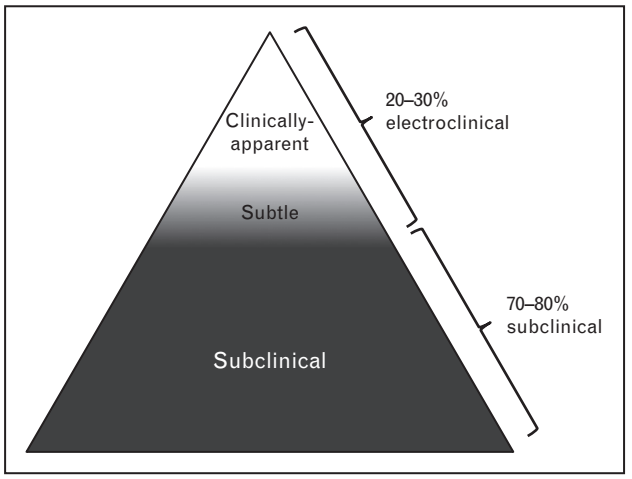

FIGURE 1. Classification of seizures in the pediatric intensive care unit. Electrographic seizures that are clinically apparent or have subtle clinical manifestations are termed electroclinical seizures, whereas those without clinical manifestations are called subclinical seizures. The majority of electrographic seizures are subclinical, and therefore require continuous electroencephalography monitoring for their detection.

PREVALENCE OF SEIZURES AND STATUS EPILEPTICUS IN THE PEDIATRIC ICU

Seizures are common among critically ill children [4▪▪,5▪▪,7–15]. Observational studies of children undergoing cEEG monitoring in the pediatric ICU (PICU) have identified electrographic seizures in 7–46% (Fig. 2a) [4▪▪,5▪▪,7–13] and status epilepticus in 1–23% of patients (Fig. 2b) [4▪▪,5▪▪,9–13]. Most studies have assessed seizure prevalence among children who underwent cEEG monitoring on the request of a treating physician, usually according to institutional guidelines. Given the fact that clinical guidelines for cEEG monitoring and patient characteristics differ between institutions, it is not surprising that the prevalence of seizures varied from 16 to 42% in a recent multicenter study [1▪]. Two prospective research studies have attempted to overcome the selection bias inherent in studies of clinically monitored patients by systematically screening all children admitted to the pediatric ICU (PICU) and performing cEEG monitoring on a research basis in all comatose children [12,13]. The seizure prevalence in these research studies varied between 7 and 25%, again likely due to difference in characteristics of ICU populations being studied, such as coma etiology and illness severity.

The majority of electrographic seizures in the PICU are either subclinical or are accompanied by only very subtle clinical signs, and would likely go undetected without cEEG monitoring. Studies have observed that 70–100% of encephalopathic children who experience electrographic seizures will experience some subclinical seizures, and 29–83% of these children will experience exclusively subclinical seizures (Fig. 2a) [4▪▪,5▪▪,7–13]. Furthermore, these studies report that all children with status epilepticus experience some subclinical seizures, and that at least a third of children with status epilepticus experience exclusively subclinical seizures (Fig. 2b) [4▪▪,5▪▪,9–13].

Taken together, the above studies provide conclusive evidence that seizures and status epilepticus in critically ill children cannot be accurately

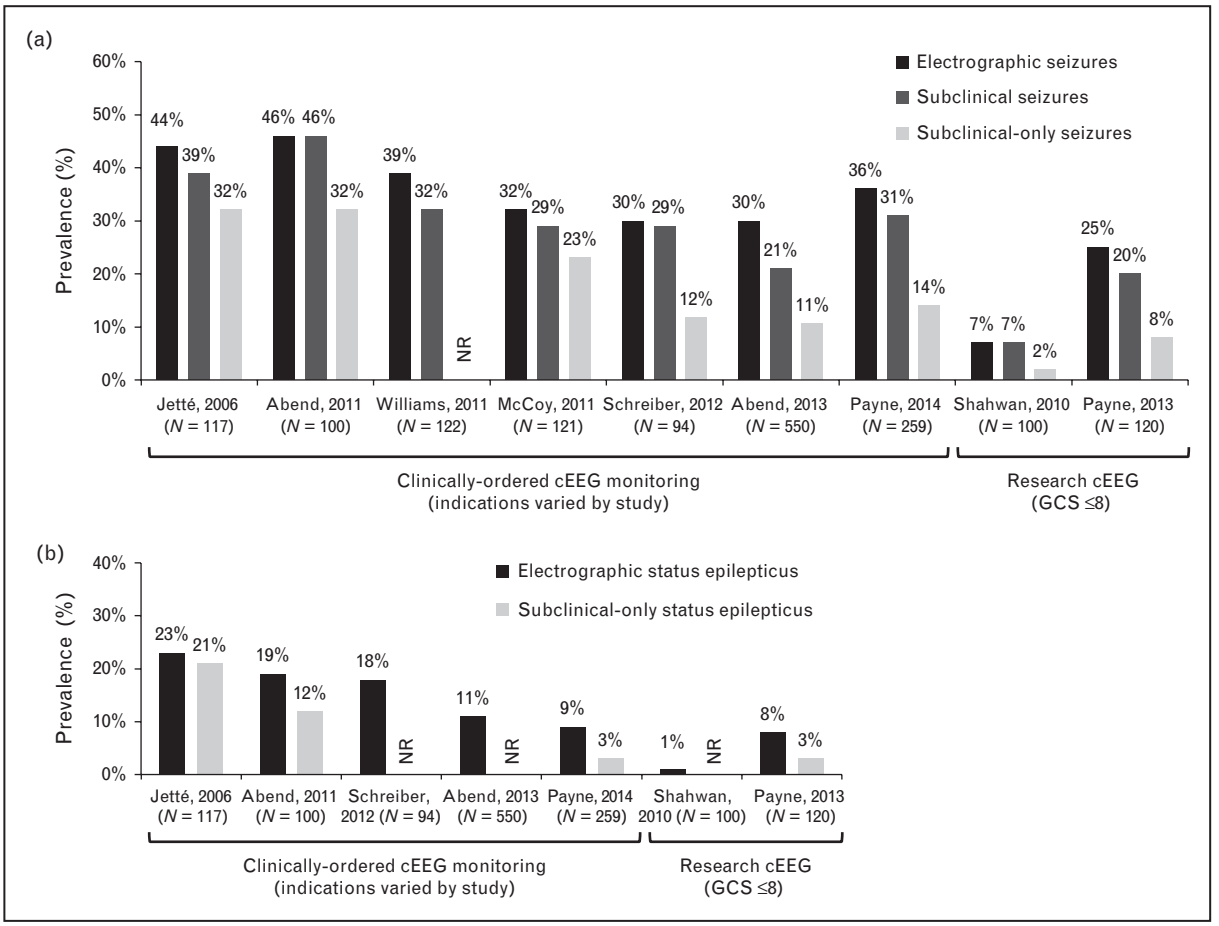

FIGURE 2. Prevalence of electrographic seizures and status epilepticus among critically ill children. Prevalence of electrographic seizures (a) and electrographic status epilepticus (b) among cohort studies of critically ill infants and children undergoing cEEG monitoring. cEEG monitoring was either clinically ordered per institutional guidelines [4▪▪,5▪▪,7–11], or performed as part of research studies of comatose children (Glasgow Coma Scale ≤8) [12,13]. Status epilepticus was defined as 30 min of continuous seizures or 30 min of cumulative seizure activity in 1 h. cEEG, continuous video-electroencephalography; NR, not reported.

diagnosed, let alone effectively treated, without cEEG monitoring.

WHICH CHILDREN SHOULD UNDERGO CEEG MONITORING?

Common clinical indications for cEEG monitoring in the PICU include the following:

(1) established seizures/status epilepticus, to guide titration of antiepileptic drug therapy;
(2) screening for subclinical seizures among patients deemed to be at high risk, for example;
  (a) suspected encephalitis (bacterial, viral, or autoimmune);
  (b) hypoxic ischemic encephalopathy (e.g., neonates, cardiac arrest, near drowning);
  (c) traumatic brain injury (especially nonaccidental);
  (d) stroke (ischemic or hemorrhagic);
(3) screening for seizures among patients who are paralyzed and deemed to be at risk for seizures (e.g., those undergoing extracorporeal membrane oxygenation);
(4) characterization of paroxysmal events suspected to represent electrographic seizures.

However, clinical care pathways and guidelines vary substantially by institution [1▪]. In a recent 11-center study of 550 children, the stated indication for cEEG monitoring was encephalopathy with possible seizures in 67% of patients, event characterization in 38% of patients, and management of refractory status epilepticus in 11% of patients [1▪]. Importantly, the clinical utility of cEEG monitoring is not limited to the detection of electrographic seizures. Equally useful is the ability of cEEG to clarify whether suspicious paroxysmal events (e.g., posturing, apnea) in fact represent electrographic seizures. The increased diagnostic accuracy provided

by cEEG monitoring has the potential to reduce inappropriate antiepileptic drug use and possibly shorten length of stay [1▪,7,8,12]. In addition to the above clinical indications, some institutional guidelines recommend cEEG monitoring under specific clinical circumstances, such as extracorporeal membrane oxygenation, therapeutic hypothermia, and postoperatively following surgery for congenital heart disease.

Studies of broad groups of critically ill children who underwent cEEG monitoring for the above clinical indications have demonstrated several consistent clinical and EEG risk factors for electrographic seizures (Table 1) [4▪▪,5▪▪,7–11,14,16▪]. The most consistent clinical factors associated with electrographic seizures include persistent encephalopathy (be it on a medical ward or in the PICU), younger age (infants <2 to 3 years), and the presence of clinical seizures prior to cEEG monitoring, particularly convulsive status epilepticus [17▪].

Studies that applied cEEG monitoring to specific subpopulations have identified several other patient groups at high risk for electrographic seizures. This includes 63% of children with suspected encephalitis [18▪], 47% of those suffering a hypoxic brain injury following cardiac arrest [19], 11–20% of infants undergoing cardiac surgery [20,21], and 21% of children undergoing treatment with extra corporeal membrane oxygenation [22]. In addition, electrographic seizures have been observed in 43–57% of children following traumatic brain injury, particularly following abusive brain trauma and when a concomitant hemorrhage is identified [23▪,24,25]. Furthermore, seizures are very frequently identified following childhood stroke and often represent the presenting symptom [26–28,29▪]. Electrographic seizures are especially common following a hemorrhagic stroke but also frequently occur after an arterial or venous ischemic infarct [28,29▪]. In fact, among a cohort of children who suffered a spontaneous intracerebral hemorrhage, 48% experienced acute symptomatic seizures, and 28% of those who underwent cEEG monitoring had subclinical-only seizures [29▪]. Finally, 34–48% of neonates undergoing therapeutic hypothermia for hypoxic ischemic encephalopathy have been reported to experience electrographic seizures or status epilepticus, justifying recent guidelines recommending at least 24 h of cEEG monitoring in this population [16▪,30,31].

EEG features consistently associated with a greater risk for developing electrographic seizures include an abnormal EEG background (particularly burst suppression or complete suppression), and the presence of interictal epileptiform discharges, particularly periodic discharges (Table 1). Generalized periodic discharges are particularly strongly associated with electrographic seizures and status epilepticus [13,32,33]. In adults, the absence of interictal epileptiform discharges during the first 30 min of a continuous EEG recording is highly predictive of subsequent seizure freedom [34], findings that likely also apply to children.

Efforts are currently underway to develop clinical prediction rules that may be applied to well defined cohorts of patients to estimate their risk for electrographic seizures [13]. Ideally, these rules would identify those children at greatest risk for seizures and status epilepticus, permitting optimal allocation of often-scarce cEEG monitoring resources.

Table 1. Patient characteristics associated with electrographic seizures

Clinical characteristics	EEG characteristics
Persistent encephalopathy	Abnormal background activity (e.g., burst suppression or suppression)
Younger age (<2 to 3 years)	Lack of background reactivity
Clinical seizures or status epilepticus before starting cEEG monitoring	Interictal epileptiform discharges, particularly periodic discharges
Diagnosis of an acute structural brain injury	
Prior diagnosis of epilepsy	

The table is based on data obtained from numerous observational clinical studies in neonates and children [4▪▪,5▪▪,7–11,14,16▪]. cEEG, continuous video-electroencephalography.

WHAT IS THE OPTIMAL DURATION OF CONTINUOUS VIDEO-ELECTROENCEPHALOGRAPHIC MONITORING?

Only half of critically ill children undergoing cEEG monitoring experience their first electrographic seizure during the initial hour of monitoring [5▪▪,7–13]. Therefore, a routine 20–30 min EEG recording will fail to identify the majority of children who go on to develop seizures, justifying the need for cEEG monitoring to accurately diagnose seizures and quantify seizure burden.

There is considerable interinstitution variability in the timing and duration of cEEG monitoring [2▪,35], but guidelines have recommended that the duration of cEEG monitoring be at least 48 h following an acute brain insult in comatose patients and for 24 h after cessation of electrographic seizures and weaning of antiepileptic drugs [6]. The timing of cEEG monitoring initiation will depend on available institutional resources (e.g., after-hours coverage by EEG technologists) and perceived clinical urgency.

In general, cEEG monitoring should be initiated urgently when the indication is suspected subclinical seizures or status epilepticus in an encephalopathic child known to be at risk (see above).

At our institution, the duration of cEEG monitoring is individualized; however, we typically monitor patients for at least 24–48 h and discontinue monitoring when patients have remained seizure-free for 24 h and they are off all antiepileptic drug infusions and paralytic agents. Continuous EEG monitoring is discontinued prior to 24 h when patients regain consciousness permitting confident clinical assessment for seizures, or when several typical paroxysmal events suspicious for seizures have been captured. Neonates and children who are undergoing therapeutic hypothermia for hypoxic ischemic encephalopathy generally receive 72 h of cEEG monitoring, since they have been shown to be at risk for late-onset seizures during rewarming [16▪,19]. Furthermore, even in the absence of seizures, we may extend the duration of cEEG monitoring when EEG characteristics known to be highly associated with seizures are present (e.g., burst suppression background, frequent interictal epileptiform, or periodic discharges).

Further studies are required to determine the optimal duration of cEEG monitoring in a given child, which will likely depend on a combination of specific clinical parameters (e.g., age, etiology of encephalopathy, ongoing treatment), their initial EEG characteristics, and available institutional resources. Slight variations in cEEG monitoring strategies can have a major impact on the yield of seizure identification and resource utilization [36].

TECHNICAL CONSIDERATIONS

Currently, conventional full-montage EEG is the most accurate technique for identifying electrographic seizures and distinguishing seizures from the many forms of EEG artifact that may occur in the ICU setting. Time-locked video is essential to identifying the subtle clinical manifestations of seizures, to determine sources of physiologic and nonphysiologic artifact, and to confirm whether a given clinical behavior represents an electrographic seizure. Reduced EEG montages have not been well studied in children, but they likely should be used with caution. Studies in adults have demonstrated that some reduced EEG montages permit reasonably accurate seizure detection (e.g., a seven-electrode montage) [37], whereas others do not (e.g., a hairline montage) [38,39]. In the neonatal ICU, the use of one-channel or two-channel amplitude integrated EEG-based cerebral function monitors has gained widespread acceptance for the assessment of EEG background, but their utility for seizure identification remains a matter of debate [40–42]. There is no doubt that recording EEG using fewer electrodes limits the extent of cortex being monitored, reducing the ability to detect electrographic seizures and accurately distinguish seizures from artifacts.

Electrode application should be performed by a registered EEG technologist according to the international 10–20 system and fixed with paste or collodion adhesive. Although not well studied in children, computed tomography and MRI-compatible EEG electrodes may be considered, as they diminish the need to temporarily disconnect patients from cEEG [43–45].

EEG interpretation should be performed by individuals with formal training and certification in clinical neurophysiology. The frequency with which a cEEG recording is reviewed varies extensively by institution and is highly dependent on institutional resources [2▪]. Our cEEG monitoring service operates 24/7, but the cEEG is not interpreted continuously. When a patient is started on cEEG, the recording is reviewed within the first 30 min, and a clinical priority level is assigned to guide the frequency of subsequent review. For example, patients in status epilepticus in whom we are titrating antiseizure medications are reviewed at least every hour, or often continuously, until seizure control is achieved (priority 1). Patients who are deemed to be at risk for subclinical seizures are reviewed at least every 4–6 h (priority 2). Patients who are deemed to be at very low risk for seizures, or in whom the goal is to characterize clinical events suspected to represent seizures, are reviewed at least every 12 h (priority 3). In addition to routine review, 'spot' review of the cEEG is performed whenever ICU caregivers notify us of suspicious clinical activity. Effective communication between our neuromonitoring service and the ICU has been of paramount importance in ensuring timely and efficient cEEG utilization.

At many institutions, qualified EEG technologists are often unavailable after normal working hours. Creative strategies can be applied to enable after-hours electrode application. For instance, ICU nurses can be taught to apply a limited array of EEG electrodes or an electrode cap, until an EEG technologist becomes available to apply a conventional electrode montage. Quantitative EEG trending algorithms (e.g., amplitude-integrated EEG, color density spectral array) that time compress and simplify the EEG display can help speed up EEG interpretation by clinical neurophysiologists and enable bedside caregivers to more easily screen for seizures [46–48]. However, reliance on quantitative EEG trending alone is not recommended because

seizures can be missed (particularly short-duration or low-amplitude seizures), and various artifacts may be mistaken for seizures, resulting in false-positives [46,48]. Finally, much effort is being devoted to developing computerized automated EEG seizure detection software [49,50]; however, until now the accuracy of such algorithms has been insufficient to replace clinical interpretation.

IMPACT OF SEIZURES ON OUTCOMES

Much of the rationale for cEEG monitoring and treatment of electrographic seizures rests on the premise that electrographic seizures, especially when prolonged, are not merely a biomarker of brain injury, but independently contribute to injury of the developing brain. There is a growing body of clinical evidence in neonates [51] and children [5▪▪,15,52▪▪,53,54] that electrographic seizures are independently associated with worse short-term neurological outcome. A recent cohort study of critically ill children demonstrated that increasing electrographic seizure burden was independently associated with neurological decline, even after controlling for diagnosis and illness severity [5▪▪]. A seizure burden greater than 12 min in a given hour was associated with a greater probability and magnitude of neurological decline. Electrographic status epilepticus has been associated with both increased risk of short-term neurological decline and mortality [52▪▪], as well as unfavorable long-term global outcome, lower health-related quality of life scores, and an increased risk of subsequently diagnosed epilepsy [55▪▪]. Among infants with congenital heart disease, the occurrence of clinical and electrographic seizures in the postoperative period has also been associated with worse long-term outcomes [56,57].

Despite the above evidence for an independent association between increasing seizure burden and worse neurological outcome, it remains to be seen whether prompt identification and treatment of seizures can safely lower seizure burden and improve outcomes [5▪▪,53]. The potential for subclinical seizures to cause harm is likely to depend on both the seizure burden and the type and severity of the underlying brain injury [58]. Nevertheless, current consensus guidelines advocate the use of cEEG monitoring to detect and manage status epilepticus in critically ill children and recommend that both clinical and electrographic seizure activity be controlled as quickly as possible [6].

CONCLUSION

Electrographic seizures and status epilepticus are common among critically ill children and frequently manifest with subtle or no clinical signs. Therefore, optimal management of seizures and status epilepticus requires the use of cEEG monitoring. Although cEEG monitoring approaches differ between institutions, most centers perform at least 24 h of cEEG in encephalopathic critically ill children with acute brain injury who are deemed to be at risk for seizures. Growing evidence that electrographic seizures are independently associated with worse outcome supports the use of cEEG monitoring and prompt treatment of electrographic seizures. Even if such treatment results in only modest improvements in outcome, these may represent a substantial lifetime benefit to the child, their family, and society.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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A retrospective study of 550 consecutive critically ill children from 11 centers, describing the heterogeneous use of cEEG monitoring between institutions and subsequent implications for future multicenter collaborative trials.

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