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# Continuous Video EEG Monitoring for Electrographic Seizure Diagnosis in Neonates: A Single Center Study

**SO Wietstock, MD**[1,2], **SL Bonifacio, MD**[2], **JE Sullivan, MD**[1,2], **KB Nash, MD**[1,2], and **HC Glass, MDCM**[1,2]

[1]Department of Neurology, University of California San Francisco Benioff Children's Hospital, San Francisco, CA, USA

[2]Department of Pediatrics, University of California San Francisco Benioff Children's Hospital, San Francisco, CA, USA

## Abstract

The objective of this study was to determine the diagnostic yield of continuous video-electroencephalography (cEEG) monitoring in critically ill neonates in the setting of a novel, university-based Neonatal Neurocritical Care Service. Patient demographic characteristics, indication for seizure monitoring, and presence of electrographic seizures were obtained by chart review. Among 595 patients cared for by the Neonatal Neurocritical Care Service, 400 (67%) received cEEG. The median duration of cEEG monitoring was 49 (IQR: 22 to 87) hours. Electrographic seizures were captured in 105/400 (26% of monitored patients) and of those, 25/105 (24%) had no clinical correlate. In addition, 52/400 subjects (13%) were monitored due to paroxysmal events concerning for seizures, but never had electrographic seizures. cEEG monitoring helped confirm or rule out ongoing seizures in more than one third of the cases. This finding helps to support the use of cEEG in critically ill neonates.

### Keywords

Neurocritical Care; Infant; Critical care; EEG; Electroencephalogram; Neonatal seizures; Epilepsy; Neonatal Encephalopathy; Hypoxic-Ischemic Encephalopathy

**Address correspondence to:** Hannah C. Glass, MDCM, MAS, University of California San Francisco, Departments of Pediatrics & Neurology, 675 Nelson Rising Lane, Sandler Neurosciences Bldg. Room 414C San Francisco, CA 94158-0663. Phone: 415-514-3277. Fax: 415-476-3428. Hannah.Glass@ucsf.edu.

**Author contributions**

Wietstock, SO MD - Drafted and revised the manuscript for content, participated in study concept and design, planned and performed analysis and interpretation of data, performed statistical analysis, and approved the submitted manuscript.

Bonifacio, SL MD - Revised the manuscript for content, assisted with interpretation of data, and approved the submitted manuscript.

Sullivan J MD - Revised the manuscript for content, participated in study concept and design, assisted with interpretation of data, and approved the submitted manuscript.

Nash KB MD - Revised the manuscript for content, assisted with interpretation of data, and approved the submitted manuscript.

Glass HC MDCM – Drafted and revised the manuscript for content, participated in study concept and design, planned and performed analysis and interpretation of data, performed statistical analysis, and approved the submitted manuscript.

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**Declaration of conflicting interests**

None

**Ethical approval**

The UCSF Committee on Human Research approved waiver of consent and data collection.

## INTRODUCTION

Continuous electroencephalographic (cEEG) monitoring is the gold standard for accurate detection of seizures, as well as seizure management in the Intensive Care Unit.[1–3] The clinical treatment paradigm in centers where cEEG is not used is to treat those neonates with paroxysmal events that are suspicious for seizures, with or without EEG confirmation, with phenobarbital,[4–7] and often for several months.[8] Since paroxysmal events in neonates may or may not represent seizures,[9] and electrographic seizures may have no discernable clinical correlate,[10] this approach fails to adequately diagnose seizures and exposes neonates to possible harm, either by medication overuse for paroxysmal events that have no electrographic correlate, or under-treatment of seizures without clinical manifestations. Monitoring with cEEG can refine seizure management by accurately diagnosing electrographic seizures and optimizing treatment for those patients who truly need medication.

Although cEEG is recommended as the gold standard, there is limited evidence about the yield of capturing electrographic seizures by monitoring a broad population of critically ill neonates. Past studies report the yield of capturing electrographic seizures via cEEG in neonates with hypoxic-ischemic encephalopathy at 34–65%.[11–13] Studies that examine a broader population in the pediatric[14] and adult ICU[15] show that up to 20–30% of patients have electrographic seizures, many of which are subclinical and would remain undetected without monitoring.

The aim of this 4.5-year, single-center, observational study of 595 neonates admitted to the Neonatal Intensive Care Unit and evaluated by the Neonatal Neurocritical Care Service was to examine the yield of cEEG since the initiation of our monitoring program, as well as to examine risk factors for electrographic seizures. Since the risk for seizures is highest in infancy,[16] and neonates display frequent dissociation between clinical and electrographic events,[10,17] we hypothesized that the proportion of neonates with seizures detected as part of clinical cEEG monitoring would be at least as high as in pediatric and adult populations.

## METHODS

### Subjects

Neonates admitted to the University of California, San Francisco Neonatal Intensive Care Unit from July 2008 to December 2012, whom the Neonatal Neurocritical Care Service evaluated,[18] were prospectively enrolled into a database and considered for inclusion in this study. Clinical data were compiled prospectively in a systematic manner using pre-determined variable definitions. The UCSF Committee on Human Research approved waiver of consent and data collection. A subset of subjects was previously reported.[13,19]

### Selection

All neonates monitored with cEEG for clinical indications during the study period were evaluated by the Neonatal Neurocritical Care Service, entered into the Neuro-Intensive Care Nursery database, and formed the study cohort. Neonates who received cEEG monitoring

for non-clinical reasons (i.e., research study) were excluded from the study. Indications for consultation by the Neonatal Neurocritical Care Service are described elsewhere.[18] There were no other exclusion criteria.

## Measurements

cEEG was applied by a trained technician according to the international 10–20 system. Modified montage aEEG was displayed at the bedside and full montage was available for remote review by the neurophysiologist (Nicolet, Natus, San Carlos, CA). The decision to monitor with cEEG was based on local guidelines and at the ultimate discretion of the attending neurologist and neonatologist. Guidelines for monitoring were developed by our service in 2008 and are similar to those published by the ACNS in 2011.[4] Indications for cEEG were as follows: (1) to assess the differential diagnosis of paroxysmal events (i.e., patients with one or more clinical events that are concerning for seizure), (2) to detect seizures in high-risk populations (including acute encephalopathy, need for ECMO, intracranial infection or bleeding), and/or (3) to assess for background abnormalities during acute encephalopathy. Our guidelines included cEEG for all neonates treated with therapeutic hypothermia from the time of admission through re-warming. The recommended duration of cEEG monitoring was to capture suspected events, until *at least* 24 hours after resolution of electrographic seizures, and/or until the completion of rewarming for neonates undergoing therapeutic hypothermia. Among neonates who were monitored for a primary indication of paroxysmal event concerning for seizure, 44% had at least event captured on EEG.

Patient demographic characteristics and indication(s) for monitoring were extracted from the database and chart review. Electrographic seizure diagnosis was based on clinical EEG reports written by neurophysiologists, who used a standard definition for electrographic seizures (repetitive, evolving, and stereotyped pattern, with a definite beginning and end, with a minimum duration of 10 seconds and a minimal amplitude of 2 microvolts). A neonatal neurologist (HCG) determined the seizure etiology after patient discharge from hospital and based on medical and nursing documentation of the clinical history, laboratory evaluations, electroencephalogram interpretation, and MRI results.

Seizure treatment was at the discretion of the treating neonatologist and neurologist, and was typically initiated in the following clinical scenarios: after a clinical event that was suspicious for seizure that occurred prior to initiation of monitoring, or for confirmed electrographic seizure(s). Our clinical practice is to treat seizures with electrographic correlate, to discontinue seizure medications in neonates without confirmed electrographic seizures, and not to treat prophylactically or to achieve a specific target level.

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at University of California, San Francisco.[20]

## Analysis

Study results are presented as actual numbers with percentages, or medians with interquartile ranges. The chi-squared or Fisher exact test was used to examine the difference

between two proportions. The Wilcoxon rank-sum test was used to compare medians. Statistical analyses were performed using Stata 12 (StataCorp, College Station, Texas) and p-values < 0.05 were considered significant.

## RESULTS

The Neonatal Neurocritical Care Service cared for 595 neonates over the 4.5-year observation period (July 2008 to December 2012). The majority was born at term (66%), and was referred from an outside hospital (67%). There was no sex preponderance among the population and 14% died before hospital discharge. Therapeutic hypothermia was initiated in 30% of subjects and completed in 25%. Among the neonates seen by the Neonatal Neurocritical Care Service, 67% (400/595) received clinically indicated cEEG (Table 1), including all those who received therapeutic hypothermia. Most children had two or more indications for monitoring: paroxysmal event concerning for seizure 192/400 (48%), encephalopathy 217/400 (54%), and high risk population 267/400 (67%).

The median duration of cEEG monitoring was 49 (IQR 22 to 87) hours. Neonates who received therapeutic hypothermia for hypoxic-ischemic encephalopathy (HIE) were monitored for a median duration of 85 (IQR 71 to 96) hours.

### Identification of Seizures

Electrographic seizures were captured in 105/400 subjects (26%) and, of those, 25/105 (24%) had electrographic seizures that never had a clinical correlate and never had clinical events prior to EEG monitoring that were suspicious for seizures. In addition, 52/400 (13%) of subjects had clinical events that were concerning for seizure, but had no seizures detected by cEEG (either due to resolution of events prior to placement or continuation of events that had no EEG correlate). Phenobarbital was administered prior to monitoring in 93/400 (23%) of patients overall, and among 38/51 (75%) of patients who were monitored due to paroxysmal events suspicious for seizures but for whom cEEG never confirmed seizures.

Electrographic seizure rates were assessed by common indications for monitoring (Table 2). Seizure occurrence by diagnosis is presented in Table 3. Seizures were most common in neonates with HIE and stroke. Subclinical seizures were most often seen in neonates with HIE.

### Risk Factors for Electrographic Seizures

Neonates of primiparous mothers were more likely to have electrographic seizures (RR 1.4, 95% CI 1.2 – 1.7, p<0.005), as were neonates who were monitored for an indication of paroxysmal event concerning for seizure (RR 1.4 95% CI 1.0 – 2.0, p=0.04), whereas mode of delivery, sex, transfer from a referring hospital, and gestational age at birth were not significantly associated with electrographic seizures.

## DISCUSSION

Two-thirds of a large cohort of 595 neonates evaluated by the Neonatal Neurocritical Care Service received cEEG monitoring for a median duration of two days.[21] The yield of

monitoring was high: twenty-five percent had electrographic seizures and of those, a quarter had only subclinical seizures. Furthermore, cEEG monitoring permitted exclusion of electrographic seizures in 13% of monitored subjects who had one or more clinical events prior to EEG monitoring that were concerning for seizures. Risk factors for electrographic seizures were maternal primiparity and paroxysmal event concerning for seizure as the indication for monitoring.

The yield of cEEG was similar to what has been reported in adult and pediatric ICU populations undergoing clinically indicated cEEG. Claassen *et al* evaluated 110 adult subjects who underwent cEEG monitoring and reported a 19% detection rate, with the highest risk among those with coma, age <18 years, prior history of epilepsy or convulsive seizures prior to monitoring.[15] Abend *et al* reported electrographic seizures among 30% of pediatric patients consecutively admitted to the Pediatric Intensive Care Unit who received cEEG at 11 sites across North America.[14] Risk factors for electrographic seizures included younger age, abnormal interictal EEG, and clinical seizures prior to cEEG monitoring or a diagnosis of epilepsy prior to monitoring. Three prior studies have reported seizure rates of 34–65% among neonates with HIE who were treated with therapeutic hypothermia and monitored with cEEG,[11–13] which suggests that there may be a higher yield for monitoring among cooled neonates.

Our findings have important clinical management implications: monitoring yielded results that could be used to guide seizure medication management in more than one third of subjects, including the 26% of neonates who had electrographic seizures and the 13% of neonates who had paroxysmal events but no electrographic seizures. For neonates with electrographic confirmation of seizures, monitoring permits accurate titration of medication to effect, as well as discontinuation of medication after resolution of acute symptomatic seizures. In neonates with paroxysmal events that have resolved without electroclinical dissociation, or have no electrographic correlate, monitoring may inform a decision to discontinue of medications. Since phenobarbital may be harmful to the developing brain,[22] discontinuation of anti-seizure medications in patients without confirmed EEG seizures could, in theory, lead to improved functional outcomes. Our findings are similar to those from a broader pediatric population, which show that cEEG affected clinical management in more than half of monitored children.[23]

In 2011, the American Clinical Neurophysiology Society (ACNS) published cEEG monitoring guidelines that are similar to those used by our center.[21] Although cEEG is widely recommended,[24,25] most centers have failed to adopt the ACNS guidelines due to substantial barriers, which include the need for readily available specialized equipment, technicians, and neurophysiologists for rapid initiation and interpretation.

Although data were drawn from a large cohort of critically ill neonates, this study is not without its limitations. First, it was not possible to assess the impact of screening aEEG, as charts did not contain formalized documentation of aEEG results. Thus, we could not determine the added utility of cEEG in addition to aEEG, or vice versa. Second, it is possible that the population of monitored neonates was subject to screening bias as all subjects treated with therapeutic hypothermia for HIE were monitored through cooling and

rewarming. Thus, the distribution of seizure etiologies may over-represent this subgroup. Third, detection of electrographic seizures was subject to the timing of cEEG initiation and duration. As a result, it was not possible to confirm whether some of the clinical events that were suspicious for seizure may have had an electrographic correlate, as not all were captured on cEEG. Fourth, subjects were entered into the database following consultation with our Neonatal Neurocritical Care Service. Subjects who were not identified as being high risk for neurological conditions may not have received consultation and monitoring, and therefore, it is possible that we did not capture some of the lowest risk subjects that are encompassed by the guidelines. Lastly, seizures were determined by clinical report rather than blinded review, which may slightly reduce the accuracy of seizure detection including determination of seizures without clinical correlate. The potential benefit of this approach is that the results are more widely generalizable to clinical practice at other centers. In addition, the absolute value of the diagnostic yield is difficult to interpret at this time, as there is no clear acceptable threshold at which cost of screening and benefit of diagnosis balance.

## CONCLUSION

The Neonatal Neurocritical Care Service monitored more than half of its patients with cEEG according to guidelines that are similar to those recommended by the ACNS,[21] and detected electrographic seizures among 26% of monitored neonates. In addition, cEEG allowed physicians to rule out presence or persistence of electrographic seizures in an additional 13% of neonates who presented with paroxysmal events concerning for seizure. We believe that this diagnostic yield is clinically significant, supporting use of the ACNS guidelines so that medication use can be appropriately tailored to accurate seizure diagnosis. The current seizure management paradigm at most centers is to treat those neonates with clinical events that are suspicious for seizures, with or without confirmation of electrographic seizures, typically with phenobarbital,[4–7] and often for several months.[8] This approach fails to adequately diagnose seizures, and exposes neonates to possible harm, either by medication overuse or under-treatment of seizures without clinical manifestations. More work is needed to determine the cost *versus* benefit of cEEG, as well as its impact on long-term neurodevelopmental outcomes.

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**Table 1**

Characteristics of 400 neonates seen by UCSF Neonatal Neurocritical Care Service from July 2008 to December 2012 who were monitored using continuous video-EEG (cEEG).

| | **Video-EEG Monitoring (N=400)** |
|---|---|
| Male sex | 225 (56%) |
| Gestational age | |
| -Preterm (<34 weeks) | 61 (15%) |
| -Late Preterm (34 to <37 weeks) | 43 (11%) |
| -Term (>37weeks) | 296 (74%) |
| Transferred from outside hospital | 303 (76%) |
| Length of stay, days | 10 (6 to 25) |
| Death before hospital discharge | 55 (14%) |

Values are given in terms of n (%) or median (interquartile range)

**Table 2**

Proportion of 400 neonates who were monitored with continuous video-EEG (cEEG) with electrographic seizures by indication for monitoring.

| Indication for seizure monitoring | Proportion with EEG Seizures | 95% Confidence Interval |
|---|---|---|
| Paroxysmal event concerning for seizure | 60/192 (31%) | 25–38% |
| Encephalopathy | 38/169 (22%) | 17–30% |
| High-risk clinical condition | 64/268 (24%) | 19–29% |
| Paroxysmal event and encephalopathy | 12/48 (25%) | 14–40% |

## Table 3

Electrographic seizure occurrence by diagnosis among 400 neonates monitored using continuous video-EEG (cEEG, subjects can have multiple diagnoses).

| Diagnosis | N | EEG Seizure(s) n(%) | Only EEG Seizures without Clinical Correlate N(%) |
|---|---|---|---|
| Hypoxic ischemic encephalopathy | 212 | 61 (29%) | 22 (10%) |
| Ischemic stroke (arterial and venous) | 43 | 25 (58%) | 1 (2%) |
| Intracranial hemorrhage* | 39 | 11 (28%) | 2 (5%) |
| Brain malformation | 27 | 4 (15%) | 2 (7%) |
| Syndromic/Dysmorphic | 22 | 2 (9%) | 0 |
| Intracranial infection | 7 | 2 (29%) | 0 |
| SSRI exposure | 7 | 0 | 0 |
| Neonatal onset epilepsy | 6 | 5 (83%) | 0 |

* Excludes asymptomatic subdural hemorrhages

Values are given in terms of n (%).