Electrographic seizures in pediatric ICU patients

Cohort study of risk factors and mortality

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ABSTRACT

Objectives: We aimed to determine the incidence of electrographic seizures in children in the pediatric intensive care unit who underwent EEG monitoring, risk factors for electrographic seizures, and whether electrographic seizures were associated with increased odds of mortality.

Methods: Eleven sites in North America retrospectively reviewed a total of 550 consecutive children in pediatric intensive care units who underwent EEG monitoring. We collected data on demographics, diagnoses, clinical seizures, mental status at EEG onset, EEG background, interictal epileptiform discharges, electrographic seizures, intensive care unit length of stay, and in-hospital mortality.

Results: Electrographic seizures occurred in 162 of 550 subjects (30%), of which 61 subjects (38%) had electrographic status epilepticus. Electrographic seizures were exclusively subclinical in 59 of 162 subjects (36%). A multivariable logistic regression model showed that independent risk factors for electrographic seizures included younger age, clinical seizures prior to EEG monitoring, an abnormal initial EEG background, interictal epileptiform discharges, and a diagnosis of epilepsy. Subjects with electrographic status epilepticus had greater odds of in-hospital death, even after adjusting for EEG background and neurologic diagnosis category.

Conclusions: Electrographic seizures are common among children in the pediatric intensive care unit, particularly those with specific risk factors. Electrographic status epilepticus occurs in more than one-third of children with electrographic seizures and is associated with higher in-hospital mortality. *Neurology*® 2013;81:383–391

GLOSSARY

CEEG = continuous EEG; **CI** = confidence interval; **IQR** = interquartile range; **OR** = odds ratio; **PICU** = pediatric intensive care unit.

Several single-center studies have reported electrographic seizures in 10%–40% of children who underwent clinically indicated continuous EEG (CEEG) monitoring in the pediatric intensive care unit (PICU) or emergency department.[1–12] The majority of electrographic seizures were not accompanied by any clinical signs,[1,3,8,10–14] even in nonparalyzed patients.[1,14] Therefore, accurate seizure identification requires CEEG. Data obtained from CEEG reportedly affect clinical management in 59% of monitored children, most often by affecting anticonvulsant utilization.[15] Several studies have reported an association between electrographic seizures or status epilepticus and worse outcome,[11,12,16,17] occurring independently of potential confounders related to acute etiology and critical illness severity.[12,16]

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Since electrographic seizures are common and may be associated with worse outcome,[18] an increasing number of children in the PICU are undergoing CEEG. A recent survey of 61 large pediatric hospitals in the United States and Canada reported a 30% increase in the number of monitored PICU patients from 2010 to 2011. In 2011, a median of 10 patients at institutions in the United States and 3 patients at institutions in Canada underwent CEEG per month.[19] Since seemingly small changes in CEEG indications and strategies may have a substantial impact on required CEEG resources,[20] data regarding seizure risk factors are needed to ensure limited neurophysiologic resources are targeted at children most at risk for seizures.

To date, studies of CEEG in children in the PICU have reported on cohorts from single institutions, limiting their generalizability. Therefore, we conducted a multicenter retrospective study of children undergoing CEEG in the PICU to estimate a more precise and generalizable incidence of electrographic seizures, describe electrographic seizure characteristics, identify risk factors for electrographic seizures, and determine whether electrographic seizures or electrographic status epilepticus were associated with higher in-hospital mortality.

METHODS

Study design. This was a retrospective cohort study conducted at 11 sites in the United States and Canada.

Standard protocol approvals, registrations, and patient consents. Each site obtained institutional review board approval.

Patients. Each of the 11 sites provided data for 50 consecutive children aged 1 month to 21 years who underwent CEEG in the PICU. Continuous bedside video CEEG was performed using the international standard 10–20 system of electrode placement and the clinical EEG system at each institution. Children admitted to the PICU for planned epilepsy-related management such as epilepsy surgery or epilepsia partialis continua management were excluded. CEEG required performance of at least 6 hours of EEG recording. If there were multiple CEEG sessions during the same admission, then only data from the first session were included. CEEG interruptions lasting less than 12 hours were considered the same session.

Clinical variables. We collected information on age, sex, prior neurologic diagnoses (including prior epilepsy, epileptic encephalopathy, developmental delay/intellectual disability, and other neurologic diagnoses), acute neurologic disorder, occurrence of clinical seizures or status epilepticus prior to CEEG, mental status at CEEG onset, duration of PICU stay, and in-hospital mortality. Acute neurologic disorders were grouped into 3 general diagnosis categories: 1) epilepsy-related, 2) acute structural (stroke, CNS inflammation or autoimmune disorder, traumatic brain injury, CNS infection, brain malformation, tumor/oncologic, and hypoxic-ischemic encephalopathy), and 3) acute nonstructural (sepsis, metabolic, pharmacologic sedation, toxin, paralytic administration).

EEG variables. EEG data were obtained by an investigator at each center without central review. We collected information on electrographic seizure occurrence and characteristics, initial and typical EEG background category, and occurrence of interictal epileptiform discharges. Electrographic seizures were defined as abnormal, paroxysmal electroencephalographic events that were different from the background, lasted longer than 10 seconds (or shorter if associated with a clinical seizure), had a plausible electrographic field, and evolved in morphology and spatial distribution. Electrographic seizures were classified as electrographic status epilepticus if any single seizure lasted longer than 30 minutes or if recurrent seizures together lasted for more than 30 minutes in any 1-hour epoch (50% seizure burden). Electrographic seizure characteristics included typical duration, proportion with clinical correlate, and anatomical localization at onset and maximal extent. Subclinical seizures were defined as electrographic seizures without clinical signs on video review.

Statistical collection and analyses. Data were collected and managed using REDCap (Research Electronic Data Capture), a Web-based electronic data application hosted at the Children's Hospital of Philadelphia Research Institute.[21] Descriptive statistics are presented as medians and interquartile ranges (IQR) for continuous variables and as counts and percentages for categorical variables. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated for potential predictors. Possible risk factors for seizure occurrence were first analyzed by univariate logistic regressions. A 2-sided p value <0.05 was used to denote statistical significance. Variables that were significant in the univariate analyses were then entered into a multivariable logistic regression model. The backward selection method was used to generate a final reduced model. The Hosmer-Lemeshow test was used to test the hypothesis of adequate fit. The same approach was used to analyze mortality and potential correlates of mortality. Fisher exact test was used to test whether the proportion of children with electrographic seizures was different within subcategories of traumatic brain injury, stroke, and hypoxic-ischemic encephalopathy. The Kruskal-Wallis rank test was used to compare PICU length of stay between seizure status categories, with subsequent bivariate comparisons performed using the Wilcoxon rank sum test. All statistics were performed using STATA/SE (version 12.0, Stata Corp., TX).

RESULTS

A total of 550 subjects were included, of whom 295 were boys (54%). The median age was 36.5 months (IQR 9 months–10.2 years). To provide data on 50 consecutive subjects, sites required a median of 416 days (IQR 194–655 days). The CEEG duration was <12 hours in 16% (88 of 550), 12–24 hours in 34% (187 of 550), 24–48 hours in 23% (129 of 550), 48–72 hours in 8% (44 of 550), >72 hours in 17% (94 of 550), and unknown in 1% (8 of 550).

Incidence of electrographic seizures. Electrographic seizures occurred in 30% of subjects (162 of 550). Among subjects with electrographic seizures, 38% (61 of 162) had electrographic status epilepticus, which was categorized as continuous seizure activity lasting ≥30 minutes in 46% (28 of 61), recurrent seizures occupying more than 30 minutes within an hour in 51% (31 of 61), and unreported in 3% (2 of 61). Table 1 provides

Table 1 Electrographic seizure characteristics

Electrographic seizure characteristic	n (%)
Typical seizure duration (n = 158)	
10–59 s	60 (38)
1–5 min	63 (40)
6–30 min	25 (16)
>30 min	10 (6)
Clinical correlate (n = 162)	
All (100%)	43 (27)
Most (50%–99%)	22 (14)
Some (1%–49%)	33 (20)
None (0%)	59 (35)
Unknown	5 (3)
Seizure onset localization (n = 162)	
Focal	86 (53)
Multifocal	30 (19)
Generalized	39 (24)
Unknown	7 (4)
Seizure maximal spread localization (n = 162)	
Focal-unilateral	80 (49)
Bilateral	76 (47)
Unknown	6 (4)

Table 2 Electrographic seizure occurrence by diagnosis

Diagnosis (n)[a]	Electrographic seizures present, %	Electrographic seizures absent, %
Sepsis (19)	58	42
Epilepsy (159)	48	52
Brain malformation (24)	38	62
CNS inflammation or autoimmune disorder (24)	33	67
Stroke (33)	30	70
Traumatic brain injury (61)	30	70
Metabolic (59)	29	71
CNS infection (28)	29	71
Unknown (14)	21	78
Tumor/oncologic (21)	19	81
Hypoxic-ischemic encephalopathy (73)	18	82
Pharmacologic sedation—no known neurologic problem (15)	13	87
Toxin (8)	13	87
Paralytic administration (26)	8	92

[a] Subjects could have more than one diagnosis.

electrographic seizure characteristics including duration, clinical correlate, and localization.

Risk factors for electrographic seizures. Seizure occurrence by acute diagnosis is shown in table 2. Subanalyses were performed for several acute diagnoses. Among the 19 subjects with sepsis, electrographic seizures occurred in 6 of 12 subjects (50%) without any other neurologic diagnosis and 5 of 7 subjects (71%) with another neurologic diagnosis. Electrographic seizures were more common in children with abusive (58%, 14 of 24) than accidental (9%, 3 of 33) traumatic brain injury ($p < 0.001$). There was no difference in electrographic seizure occurrence in children with ischemic stroke (31%, 5 of 16), hemorrhagic stroke (30%, 3 of 7), and sinovenous thrombosis (67%, 2 of 3) ($p = 0.51$). There was no difference in electrographic seizure occurrence in children with hypoxic-ischemic encephalopathy secondary to cardiac arrest (20%, 10 of 49), near drowning (14%, 1 of 7), or with an etiology categorized as other (18%, 2 of 11) ($p = 1.0$).

The median age of children without seizures was 42 months (IQR 12.6–144 months) and with seizures was 23 months (IQR 5–87 months) ($p = 0.002$). Clinical seizures or status epilepticus occurred prior to CEEG in 48% (180 of 377) without seizures and 79% (125 of 159) with seizures (OR 4.02, 95% CI 2.62–6.17). The initial EEG background was normal in 22% (87 of 388) without seizures and 4% (7 of 162) with seizures (OR 6.40, 95% CI 2.94–13.89). Interictal epileptiform discharges occurred in 28% (110 of 388) without seizures and 75% (120 of 159) with seizures (OR 7.78, 95% CI 5.10–11.86). An epilepsy-related diagnosis was present in 21% (83 of 388) without seizures and 50% (81 of 162) with seizures (OR 3.67, 95% CI 2.48–5.43).

Table 3 provides an evaluation of electrographic seizure risk factors. Multivariable analysis showed that risk factors for electrographic seizures were younger age, clinical seizures prior to CEEG, abnormal initial EEG background, presence of interictal epileptiform discharges, and an epilepsy-related diagnosis.

Outcome. Thirteen percent (73 of 550) of subjects died. Death occurred in 12% (46 of 388) without seizures, 12% (12 of 101) with electrographic seizures, and 25% (15 of 61) with electrographic status epilepticus ($p = 0.02$). Table 4 provides an evaluation of in-hospital mortality risk factors. The occurrence of electrographic status epilepticus, an abnormal EEG background, and acute structural or nonstructural neurologic diagnoses were independently associated with mortality. Adjusting for neurologic diagnosis category and EEG background category, the odds of mortality remained higher among subjects with electrographic status epilepticus (OR 2.42, 95% CI

Table 3 Risk factors for electrographic seizures[a]

Variables (electrographic seizure prevalence)	Electrographic seizures present (162 [29.5%]), n (%)	Electrographic seizures absent (388 [70.5%]), n (%)	Univariate analysis		Multivariable analysis		Final reduced model	
			OR (95% CI)	p[b]	OR (95% CI)	p	OR (95% CI)	p
Age, mo, median (IQR)	23 (5, 87)	42 (12.6, 144)	0.99 (0.99–0.99)	0.001	0.99 (0.99–0.99)	0.007	0.99 (0.99–0.99)	0.006[c]
Sex								
Male (26%)	76 (47)	219 (56)	1		1			
Female (34%)	86 (53)	169 (44)	1.47 (1.01–2.12)	0.042	1.37 (0.87–2.20)	0.176		
Prior developmental delay or intellectual disability								
No (24%)	77 (48)	246 (63)	1		1			
Yes (37%)	85 (52)	142 (37)	1.96 (1.35–2.86)	<0.001	0.67 (0.33–1.36)	0.269		
Prior epilepsy diagnosis								
No (22%)	84 (52)	292 (75)	1		1			
Yes (45%)	78 (48)	96 (25)	2.84 (1.93–4.18)	<0.001	1.17 (0.52–2.61)	0.705		
Prior epileptic encephalopathy diagnosis								
No (27%)	132 (81)	359 (93)	1		1			
Yes (51%)	30 (19)	29 (7)	2.79 (1.61–4.83)	<0.001	0.93 (0.43–2.00)	0.854		
Prior neurologic disorder								
No (26%)	102 (81)	283 (73)	1		1			
Yes (18%)	60 (19)	105 (27)	1.60 (1.08–2.36)	0.019	0.83 (0.44–1.57)	0.568		
Clinical seizures prior to EEG								
No (15%)	34 (21)	197 (52)	1		1		1	
Seizures (45%)	93 (58)	114 (30)	4.73 (2.99–7.45)	<0.001	2.62 (1.50–4.59)	0.001	2.56 (1.48–4.44)	0.001[c]
Status epilepticus (33%)	32 (20)	66 (18)	2.81 (1.61–4.91)	<0.001	0.97 (0.46–2.04)	0.943	1.02 (0.49–2.11)	0.966
Mental status at EEG onset								
Normal (33%)	20 (13)	51 (14)	1					
Lethargic/obtunded (33%)	99 (62)	198 (54)	1.28 (0.72–2.26)	0.404				
Comatose (25%)	40 (25)	118 (32)	0.86 (0.46–1.62)	0.65				
Initial EEG background category								
Normal/sleep (7%)	7 (4)	87 (22)	1		1		1	
Slow/disorganized (33%)	112 (69)	225 (58)	6.19 (2.77–13.81)	<0.001	6.08 (1.56–18.36)	<0.001	5.47 (2.06–14.51)	0.001[c]
Discontinuous (34%)	13 (8)	25 (6)	6.46 (2.33–17.94)	<0.001	5.35 (1.56–18.36)	0.008	4.87 (1.45–16.43)	0.011[c]
Burst-suppression (45%)	13 (8)	16 (4)	10.10 (3.49–29.21)	<0.001	13.12 (3.36–51.27)	<0.001	12.93 (3.37–49.58)	<0.001[c]
Attenuated/featureless (33%)	17 (10)	35 (9)	6.04 (2.30–15.82)	<0.001	12.57 (3.80–41.52)	<0.001	10.33 (3.20–33.37)	<0.001[c]

Continued

Table 3 Continued

Variables (electrographic seizure prevalence)	Electrographic seizures present (162 [29.5%]), n (%)	Electrographic seizures absent (388 [70.5%]), n (%)	Univariate analysis		Multivariable analysis		Final reduced model	
			OR (95% CI)	p[b]	OR (95% CI)	p	OR (95% CI)	p
Interictal epileptiform discharges								
Absent (13%)	42 (26)	278 (72)	1		1		1	
Present (52%)	120 (74)	110 (28)	7.78 (5.09–11.88)	<0.001	6.45 (3.85–10.83)	<0.001	5.77 (3.52–9.45)	<0.001[c]
Neurologic diagnosis category								
Epilepsy related (49%)	81 (50)	83 (21)	1		1		1	
Acute structural (24%)	58 (36)	187 (48)	0.32 (0.21–0.49)	<0.001	0.26 (0.12–0.57)	0.001	0.33 (0.18–0.59)	<0.001[c]
Acute nonstructural (16%)	23 (14)	118 (30)	0.20 (0.12–0.34)	<0.001	0.27 (0.12–0.61)	0.002	0.31 (0.16–0.60)	<0.001[c]

Abbreviations: CI = confidence interval; IQR = interquartile range; OR = odds ratio.
[a] Reference group is noted with 1.
[b] Pairwise comparisons with the reference group were performed for variables with >2 categories.
[c] Significant difference.

1.08–5.40) but not subjects with electrographic seizures (OR 1.78, 95% CI 0.80–3.95).

The relationship between electrographic status epilepticus and mortality was further explored within the acute neurologic diagnosis categories. Among subjects with an acute structural disorder, death occurred in 37% (10 of 27) with electrographic status epilepticus and 18% (40 of 218) without electrographic status epilepticus ($p = 0.02$). Among subjects with an acute nonstructural neurologic disorder, death occurred in 33% (4 of 12) with electrographic status epilepticus and 12% (15 of 129) without electrographic status epilepticus ($p = 0.04$). Among subjects with an epilepsy-related disorder, death occurred in 5% (1 of 22) with electrographic status epilepticus and 2% (3 of 142) without electrographic status epilepticus ($p = 0.49$).

PICU length of stay was available for 525 subjects. The median length of stay was 5.5 days (IQR 2–16.5 days) in subjects without electrographic seizures, 8 days (IQR 3–20 days) in subjects with electrographic seizures, and 11 days (IQR 5–29 days) in subjects with electrographic status epilepticus. Length of stay was longer in patients with electrographic status epilepticus compared to both those without seizures ($p = 0.0001$) and those with electrographic seizures but not electrographic status epilepticus ($p = 0.03$). There was no difference between length of stay in subjects with electrographic seizures (not electrographic status epilepticus) vs those without electrographic seizures ($p = 0.06$).

DISCUSSION We present a large retrospective cohort study of electrographic seizures among children in the PICU who underwent clinically ordered CEEG at 11 North American institutions. Electrographic seizures occurred in 30% of children, of whom 38% had electrographic status epilepticus.

Prior single-center studies have reported varying incidences of electrographic seizures or electrographic status epilepticus, ranging from 7% to 48% of monitored children.[1–12] This variability is likely due to the smaller size of these cohorts, variability in case mix across institutions, and interinstitution variability in CEEG indications. Furthermore, previous studies were performed over nearly a decade, during which CEEG indications and other components of critical care have evolved. The larger size of the present cohort permits a more precise estimate of seizure incidence and more detailed risk factor analyses with narrower OR CIs. The multicenter design provides more generalizable results.

This study provides an estimate of electrographic seizure incidence that is within the range suggested by smaller single-center studies, and confirms that a large proportion of children in the PICU are experiencing

Table 4 Risk factors for in-hospital mortality[a]

Variables (death prevalence)	Dead 73 (13%), n (%)	Alive 477 (87%), n (%)	Univariate analysis		Multivariable/final reduced model[b]	
			Mortality OR (95% CI)	p[c]	Mortality OR (95% CI)	p
Age, mo, median (IQR)	13 (3, 91)	40 (11, 125)	0.99 (0.99–1.00)	0.159		
Sex						
Male (12%)	36 (49)	259 (54)	1			
Female (15%)	37 (51)	218 (46)	1.22 (0.75–1.99)	0.427		
Prior developmental delay or intellectual disability						
No (14%)	43 (63)	265 (57)	1			
Yes (11%)	25 (37)	202 (43)	0.76 (0.45–1.29)	0.313		
Prior neurologic disorder						
No (14%)	52 (72)	331 (70)	1			
Yes (12%)	20 (28)	145 (30)	0.88 (0.51–1.52)	0.6444		
Seizure category						
No (12%)	46 (63)	342 (72)	1		1	
Seizures (12%)	12 (16)	89 (19)	1.00 (0.51–1.97)	0.994	1.78 (0.80–3.95)	0.157
Status epilepticus (25%)	15 (21)	46 (10)	2.42 (1.25–4.69)	0.008	2.42 (1.08–5.40)	0.032[d]
Typical EEG background category						
Normal/sleep (1%)	1 (1)	91 (19)	1		1	
Slow/disorganized (8%)	28 (37)	304 (64)	7.78 (1.04–58.14)	0.046	8.41 (1.11–63.66)	0.039[d]
Discontinuous (18%)	8 (11)	37 (8)	19.68 (2.38–162.89)	0.006	17.00 (1.97–146.83)	0.01[d]
Burst-suppression (31%)	8 (11)	18 (4)	40.44 (4.76–343.57)	0.001	28.47 (3.17–255.54)	0.003[d]
Attenuated/featureless (53%)	30 (40)	27 (6)	101.11 (13.17–776.16)	<0.001	91.54 (11.72–715.17)	<0.001[d]
Neurologic diagnosis category						
Epilepsy related (2%)	4 (5)	160 (34)	1		1	
Acute structural (20%)	50 (68)	195 (41)	10.26 (3.63–29.01)	<0.001	9.63 (3.20–29.03)	<0.001[d]
Acute nonstructural (13%)	19 (26)	122 (26)	6.23 (2.07–18.78)	0.001	8.89 (2.70–29.25)	<0.001[d]

Abbreviations: CI = confidence interval; IQR = interquartile range; OR = odds ratio.
[a] Reference group is noted with 1.
[b] Backwards stepwise regression was attempted to generate a reduced model but did not remove any covariates identified as significant in the initial multivariate logistic regression model.
[c] Pairwise comparisons with the reference group were performed for variables with >2 categories.
[d] Significant difference.

electrographic seizures. Among children with electrographic seizures, 35% had no clinical signs associated with any electrographic seizures and only 27% had clinical signs associated with all electrographic seizures. This is consistent with prior single-center studies that have reported that many electrographic seizures are not accompanied by any clinical signs,[1,3,8,10–14] even in nonparalyzed patients.[1,14] Therefore, CEEG and not only close clinical observation is required to identify electrographic seizures in many patients.

Seemingly small variations in clinical pathways for PICU CEEG can lead to substantial differences in resource utilization.[20] Determining which children are at highest risk for seizures may help optimize utilization of limited CEEG resources. The current study identified risk factors for seizure occurrence including younger age, clinical seizures prior to CEEG, abnormal initial EEG background of any type, presence of interictal epileptiform discharges, and an epilepsy-related diagnosis. These are consistent with risk factors identified in smaller single-center studies, although the associated risk can be better quantified in this larger cohort. Reported clinical risk factors for electrographic seizures in children include younger age,[1,10] preceding convulsive status epilepticus[10] or clinically overt seizures,[11,13] and structural brain injury,[11,13] including traumatic brain injury[10] and hypoxic-ischemic brain injury after cardiac arrest.[9] Reported electrographic risk factors include epileptiform discharges,[10,13] periodic epileptiform discharges,[3] and lack of background reactivity.[3] Most of these studies involved etiologically heterogeneous

cohorts with only a small number of subjects with each etiology.

Sepsis was the diagnosis associated with the highest occurrence of electrographic seizures, and seizures occurred in children with and without other neurologic diagnoses. Encephalopathy in the setting of sepsis is often associated with neurophysiologic and neuroradiologic abnormalities and is likely multifactorial in etiology.[22] A study of septic children demonstrated background patterns on EEG consistent with moderate to severe encephalopathy and elevated serum S100 beta and neuron-specific enolase compared to controls, indicating that neurologic injury may occur with sepsis.[23] A study of adults in a medical intensive care unit reported that about one-third of patients with sepsis had electrographic seizures or periodic epileptiform discharges and the presence of sepsis was the only predictor of electrographic seizures or periodic epileptiform discharges. Furthermore, the presence of electrographic seizures or periodic epileptiform discharges was associated with death or severe disability at hospital discharge.[24] Similarly, in children with convulsive status epilepticus, sepsis is an independent risk factor for death.[21] The current data indicate that electrographic seizures may be common in children with sepsis, and further study is needed to evaluate the impact of these seizures on outcome.

The impact of CEEG and seizure identification on outcomes remains unclear. Presumably, identification of electrographic seizures by CEEG results in at least partially effective treatment and a reduced seizure burden, although this has only been demonstrated in neonates.[25] When surveyed, most neurologists report that when electrographic seizures are identified, they generally initiate anticonvulsants immediately and aim to terminate all electrographic seizures.[26] Similarly, observational studies have reported that CEEG results in anticonvulsant medication changes in about half of critically ill children and adults who undergo CEEG.[15,27] A number of single-center studies have demonstrated an association between electrographic seizures or electrographic status epilepticus and worse outcome in critically ill children.[11,12,14,16,17,28] Our data also indicate that electrographic status epilepticus was associated with higher mortality, even after adjusting for the neurologic diagnosis category and initial EEG background category. However, the current data cannot establish whether electrographic status epilepticus is a modifiable risk factor for mortality or is a nonmodifiable biomarker of severe brain injury leading to mortality. Further study is needed to establish whether optimal seizure identification and management approaches lower the seizure burden without injurious adverse effects, and thereby improve clinical outcomes.

Increasing awareness of the relatively high incidence of electrographic seizures among children in the PICU has led to increasing demand for CEEG,[26] thereby necessitating development of efficient methods for seizure identification such as quantitative EEG tools. In one study, the median sensitivity for seizure identification was 83% using color density spectral array and 82% using amplitude-integrated EEG, but in individual EEG tracings sensitivity varied from 0% to 100%.[29] Another study applying color density spectral array and envelope trend demonstrated that sensitivity for seizure identification depends on user experience, display size, and inherent seizure characteristics such as duration.[30] We found that 38% of electrographic seizures in children in the PICU lasted less than 1 minute, indicating that a substantial proportion of seizures may be "averaged-out" by highly compressed displays. Both this study and a prior single-center study reported worse short-term outcome with electrographic status epilepticus but not electrographic seizures.[16] If these data are replicated in studies with long-term outcome measures, then quantitative EEG methods may not need to identify every brief seizure if they can reliably identify a seizure burden that is sufficient to worsen outcome. There has also been interest in the use of more limited electrode montages in order to permit easier electrode application. However, only about half of the seizures in the present cohort were diffuse at their maximal extent, raising the concern that montages with a highly reduced number of electrodes may not have the spatial sensitivity to identify many electrographic seizures.

This study has several limitations. First, this was a retrospective study of clinically obtained CEEG and clinical practice. Therefore, it is not known whether every patient who met institutional criteria for CEEG actually underwent monitoring. Further, clinical practice likely varied across centers in terms of frequency of CEEG review, the timing of anticonvulsant administration following seizure onset, and anticonvulsant choices, and these factors may all influence outcome. Second, although we employed standard definitions for electrographic seizures and status epilepticus, EEG interpretation was performed by individual neurophysiologists at each center, and not by a central reading group. Third, electrographic status epilepticus represented a composite outcome involving both long seizures and recurrent seizures. These 3 limitations could be improved by future studies that involve prospective screening of all children in the PICU for specified CEEG indications, multireader EEG scoring, and quantification of seizure burden. Fourth, we only assessed outcome as in-hospital mortality and PICU length of stay. Studies are needed with more detailed outcome measures performed after a longer follow-up period.

This multicenter study demonstrates that electrographic seizures occur in about one-third of children

in the PICU who undergo clinically ordered CEEG. Among these children, the seizure burden is often high, with electrographic status epilepticus occurring in about one-third. Many electrographic seizures have no accompanying clinical signs, and thus would not be identified without CEEG. Risk factors for seizure occurrence include younger age, clinical seizures prior to CEEG, abnormal initial EEG background patterns, interictal epileptiform discharges, and an epilepsy-related diagnosis. Electrographic status epilepticus is associated with higher short-term mortality, even after adjusting for neurologic disorder category and EEG background category. Further study is needed to establish an optimal management approach and then determine whether seizure identification and optimized management is associated with improved outcome.

AUTHOR CONTRIBUTIONS

Nicholas S. Abend: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. Daniel H. Arndt: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Jessica L. Carpenter: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Kevin E. Chapman: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Karen M. Cornett: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. William B. Gallentine: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Christopher C. Giza: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Joshua L. Goldstein: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Cecil D. Hahn: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Jason T. Lerner: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data. Tobias Loddenkemper: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Joyce H. Matsumoto: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Kristin McBain: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Kendall B. Nash: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data. Eric Payne: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Sarah M. Sánchez: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Iván Sánchez Fernández: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Justine Shults: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Korwyn Williams: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Amy Yang: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Dennis J. Dlugos: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval.

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Electrographic seizures in pediatric ICU patients: Cohort study of risk factors and mortality

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