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Acute brain failure in severe sepsis: a prospective study in the medical intensive care unit utilizing continuous EEG monitoring

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Take-home message: Nonconvulsive seizures occur in 11 % of patients in the medical ICU with severe sepsis and altered mental status but were not associated with survival or disability at hospital discharge. EEG reactivity, though less frequent in patients on sedation, was associated with mortality through the 1-year follow-up, suggesting that EEG reactivity may be a useful prognostic marker in patients with severe sepsis, but this needs to be validated in larger studies.

Electronic supplementary material
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Abstract *Purpose:* Investigate the prevalence, risk factors and impact of continuous EEG (cEEG) abnormalities on mortality through the 1-year follow-up period in patients with severe sepsis. *Methods:* Prospective, single-center, observational study of consecutive patients admitted with severe sepsis to the Medical ICU at an academic medical center. *Results:* A total of 98 patients with 100 episodes of severe sepsis were included; 49 patients (50%) were female, median age was 60 (IQR 52–74), the median non-neuro APACHE II score was 23.5 (IQR 18–28) and median non-neuro SOFA score was 8 (IQR 6–11). Twenty-five episodes had periodic discharges (PD), of which 11 had nonconvulsive seizures (NCS). No patient had NCS without PD. Prior neurological history was associated with a higher risk of PD or NCS (45 vs. 17%; CI 1.53–10.43), while the non-neuro APACHE II, non-neuro SOFA, severity of cardiovascular shock and presence of sedation during cEEG were associated with a lower risk of PD or NCS. Clinical seizures before cEEG were associated with a higher risk of nonconvulsive status epilepticus (24 vs. 6%; CI 1.42–19.94) while the non-neuro APACHE II and non-neuro SOFA scores were associated with a lower risk. Lack of EEG reactivity was present in 28% of episodes. In the survival analysis, a lack of EEG reactivity was associated with higher 1-year mortality [mean survival time 3.3 (95% CI 1.8–4.9) vs. 7.5 (6.4–8.7) months; $p = 0.002$] but the presence of PD or NCS was not [mean survival time 3.3 (95% CI 1.8–4.9) vs. 7.5 (6.4–8.7) months; $p = 0.592$]. Lack of reactivity was more frequent in patients on continuous sedation during cEEG. In patients with available 1-year data (34% of the episodes), 82% had good functional outcome (mRS ≤ 3, $n = 27$). There were no significant predictors of functional outcome, late cognition, and no patient with complete follow-up data developed late seizure or new epilepsy. *Conclusions:* NCS and PD are common in patients with severe sepsis and altered mental status. They were less frequent among the most

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severely sick patients and were not associated with outcome in this study. Lack of EEG reactivity was more frequent in patients on continuous sedation and was associated with mortality up to 1 year after discharge. Larger studies are needed to confirm these findings in a broader population and to further evaluate long-term cognitive outcome, risk of late seizure and epilepsy.

Keywords Septic encephalopathy · Critical Care · Periodic discharges · Nonconconvulsive seizures · Continuous EEG · Reactivity

Introduction

Sepsis is a major health problem, affecting nearly 750,000 people a year in the US. Mortality reaches 30 % and many patients are left with long-term disability [1]. Acute brain dysfunction, including delirium and coma, occurs in a more than 70 % of critically ill patients and is associated with worse outcome and cognitive decline [2]. Nonconvulsive seizures (NCS) and periodic discharges (PD) are common in patients with critical illness [3–8], require EEG monitoring to be detected and are associated with poor outcome [3, 5, 7–14]. Sepsis is a risk factor for both NCS and PD, including nonconvulsive status epilepticus (NCSE) [6, 7]; however, the prevalence of NCS, NCSE and PD in patients with sepsis has not been defined in a prospective study. In addition, it is uncertain whether these EEG findings impact outcome or are simply a marker of disease severity. Reactivity of the EEG to external stimulation has emerged as a good prognostic factor in patients with acute brain injury [15, 16] and encephalopathy [17]. Its usefulness in sepsis has received little attention [14]. The aims of this study were to determine the prevalence, predictors and prognostic significance of NCS, PD and EEG reactivity in a prospective cohort of patients with sepsis-associated brain dysfunction. Our hypothesis was that the presence of NCS, including NCSE, as well as a lack of EEG reactivity would be associated with worse outcome.

Materials and methods

Study population

In this longitudinal cohort study, we screened 1283 patients admitted between November 2009 and February 2011 to the 24-bed medical intensive care unit (MICU) at Columbia University Medical Center, New York-Presbyterian Hospital. The study was confined to the MICU and did not screen all patients with SIRS and/or sepsis admitted to the entire hospital. Patients were identified through a daily screening of the electronic medical of all patients in the MICU using a standard definition of sepsis [18]. Patients were eligible if they had either severe sepsis (i.e., infection, including pneumonia, with evidence of organ dysfunction) or septic shock (i.e., severe sepsis with persistent hypotension requiring vasopressors after adequate fluid resuscitation) [18] and underwent continuous EEG monitoring (cEEG) for at least 12 h as part of their routine clinical care for the evaluation of encephalopathy. Based on prior results showing the high prevalence of PD and NCS in patients with sepsis-associated encephalopathy from our center [7], cEEG was part of the standard, protocoled evaluation of these patients throughout the study time period. Patients with a known acute primary neurological diagnosis (reason for admission or diagnosed in the last 30 days) as well as patients with severe baseline cognitive impairment and those with a life expectancy of less than 48 h were excluded. See the study Consort diagram for further details (Supplementary Fig. 1). Approval of this prospective, observational cohort study was granted by the Columbia University Medical Center Institutional Review Board (IRB).

Clinical variables

Sources of data included direct discussion with the primary ICU team, review of the electronic medical record and of the raw EEG data. Patient's demographic characteristics were recorded, including age, gender, medical history (including diabetes, chronic renal failure, and chronic hepatic failure), admission date, admission diagnosis and neurologic history (ischemic or hemorrhagic stroke, epilepsy, dementia and brain surgery), admission non-neuro APACHE II (APACHE II minus GCS) and admission non-neuro sequential organ failure assessment (SOFA; SOFA minus GCS) score. The non-neuro APACHE II and SOFA scores were used to minimize the influence of the neurologic component (Glascow Coma Scale score; GCS) on the overall illness severity score since, by design, the cohort consisted of patients with marked encephalopathy. Clinical data recorded at the initiation of cEEG included suspected clinical seizure (s), coma (defined as GCS $\leq$ 8), circulatory shock during cEEG [SOFA-cardiovascular component score (CV)], presence of acute renal failure (creatinine >2 mg/dl or >50 % increase from baseline), acute hepatic failure (bilirubin >2 mg/dl), source of sepsis, temperature while on cEEG and white blood cell count while on cEEG. We also collected data on sedation,

timing and duration of cEEG, and the patients' neurological status on the day of initiation of cEEG. Continuous infusions of sedation were defined as the presence of an hourly rate of lorazepam, midazolam, propofol, fentanyl and/or dexmedetomidine during cEEG monitoring. The presence or absence of clinical seizures prior to cEEG was based on reports of spontaneous abnormal episodic motor activity.

Continuous EEG recordings

Continuous digital video-EEG–ECG recordings were obtained using 21 standard scalp electrodes placed with the use of collodion by certified EEG technicians according to the international 10–20 system and reviewed by a board-certified electroencephalographers, including re-review for this study by the first author (also board-eligible). Per protocol, EEG technicians checked lead placement twice daily and performed routine maintenance as needed to ensure signal integrity. The presence of convulsive seizures (CSzs), convulsive status epilepticus (CSE), NCS, NCSE, and periodic discharges [PD; including generalized periodic discharges (GPD), lateralized periodic discharges (LPD), bilaterally independent periodic discharges (BIPD) and GPD with triphasic morphology] were recorded. Previously described definitions of convulsive and nonconvulsive seizures were used [19]. PD were defined according to the most recent version of the ACNS Terminology for Critical Care EEG [20]. Additionally, PD greater than 2.5 Hz or PD less than or equal to 2.5 Hz with EEG and clinical improvement after IV AEDs, were considered NCSE. PD between 1 and 2.5 Hz with EEG improvement but no clear clinical improvement after IV AEDs, or with fluctuation without definite evolution, were considered possible NCSE [21]. Reactivity was defined as a change in any direction in background frequency and/or amplitude following external stimulation using a standardized stimulation protocol at our institution (see Supplmentary Table 1). Appearance of EMG activity alone was not considered to be EEG reactivity.

Outcome measures

The primary outcome was mortality at discharge, and at 6 months and 1 year after discharge. Secondary outcome was disability as measured by the modified Rankin Scale (mRS; poor functional outcome was defined as a mRS ≥ 4 at the same time points) [22]. Though patients with severe sepsis and septic shock do not have presumed structural brain injury, they exhibit acute brain failure, thus making the mRS an appropriate assessment tool to use in this population. The telephone interview for cognitive status (TICS) is a validated in-person and by telephone assessment of cognition for the detection of cognitive impairment [23, 24]. We administered the TICS at hospital discharge and the various follow-up timepoints. In addition, we used telephone interviews and clinical chart reviews to obtain outcome information on seizures, epilepsy and functional independence.

Statistical analysis

Data were analyzed with SPSS 19.0 software (Chicago, IL, USA), using Student's *t* test or Mann–Whitney *U* test for continuous variables and the Chi-square test for categorical variables. Univariate analysis was performed to identify significant predictors of NCS (including NCSE) or PD. The relationship between EEG reactivity and 1-year survival and between NCS or PD and 1-year survival were independently assessed with Kaplan–Meier curves and log rank test.

Results

Study sample

During the study period, 98 patients experienced 100 consecutive episodes of severe sepsis and were monitored with cEEG. Ninety-four patients were eligible but not enrolled. Reasons for not enrolling included goals of care (e.g., comfort measures only), imminent death or surgery, rapidly improving neurologic exam, or too unstable for EEG hookup (see Supplementary Fig. 1).

Patient baseline characteristics (see Table 1)

For the majority of episodes ($n = 83$), patients were admitted to the MICU with sepsis, while the remaining episodes developed sepsis while in the MICU. For 71 episodes, patients were comatose at the time of cEEG placement. The high non-neuro APACHE II [23.5 (IQR 18–28)] and non-neuro SOFA [8 (IQR 6–11)] scores predicted that the cohort would have significant mortality. The non-neuro APACHE II for patients not enrolled [24 (IQR 19–34)] was not significantly different from those who were enrolled. The majority of cEEGs ($n = 59$) were recorded on a continuous infusion of sedation, including those with antiepileptic properties ($n = 45$), and were associated with higher median admission non-neuro APACHE II [8 (6–12) vs. 7 (4–10); $p = 0.03$] and non-neuro SOFA scores [19 (10–28) vs. 16 (8–24), $p = 0.01$]. Most episodes ($n = 91$) involved intubated patients. Given the small numbers, we were unable to look at different types of sedation as the majority of episodes included patients on benzodiazepines, opiates or both,

Table 1 Patient characteristics ($n = 100$ episodes, 98 patients)

Characteristic	
Age, years	60 (52–74)
Female	50
Neurological status at hook-up	
Coma	76
GCS score	6 (3–8)
Primary diagnosis on admission to ICU	
Sepsis	84
Other (toxic-metabolic, GIB)	14
Non-neuro APACHE-II on admission to ICU	23.5 (18–28)
Non-neuro SOFA on admission to ICU	8 (6–11)
Suspected clinical seizure prior to cEEG	29
Days to cEEG	0 (0–3)
Duration of cEEG	
Days	2 (2–3)
Hours	41 (24–56)
Continuous infusion of sedation during cEEG	59
Continuous infusion of sedation with benzodiazepine/propofol	45
SOFA-CV during cEEG	3 (1–3)
Mechanically ventilated during episode of sepsis *n*	91
Days	11 (5–24)
ICU length of stay	17 (9–24)
Hospital length of stay	31 (17–52)

Data are presented as *n* or median (IQR)

Non-neuro APACHE-II acute physiology and chronic health evaluation II minus the GCS component, *cEEG* continuous electroencephalography, *GCS* glascow coma scale score, *GIB* gastrointestinal bleed, *IQR* interquartile range, *Non-neuro SOFA* sequential organ failure assessment score minus the GCS component, *SOFA-CV* SOFA–cardiovascular component score

with only a few on dexmedetomidine ($n = 3$) or propofol ($n = 1$) without a benzodiazepine or opiate.

Clinical predictors of NCS or PD on EEG (see Table 2)

The median time to cEEG was 1 day with a median duration of cEEG of 41 h (IQR 24–56). Of the 100 episodes in 98 patients, 25 had NCS or PD, of which 14 had PD only and 11 had both NCS and PD. No patients had NCS without the presence of PD. Only one patient with seizure had overt clinical manifestations, while the remainder had subtle or no manifestation. Half (52 %) of episodes with PD had GPD only, while 28 % had LPD only and 20 % had both GPD and LPD. All episodes of NCS were consistent with either definite ($n = 2$) or possible ($n = 9$) NCSE. The majority of NCSE were generalized ($n = 8$). All patients with NCSE (either definite or possible) were treated with AEDs. Examples of NCSE and PD are shown in Supplementary Figs. 2a (NCSE) and 2b (GPD).

In the univariate analysis, a prior neurological history (stroke, epilepsy, dementia, tumor, remote neurosurgery) was associated with an increased risk of NCS or PD (seen in 45 % of those with prior neurological history vs. 17 % without). Non-neuro APACHE II and non-neuro SOFA on ICU admission as well as continuous infusion of sedation and circulatory shock during cEEG (SOFA-CV), were significantly associated with a decreased risk of developing NCS or PD.

Clinical predictors of NCS and NCSE (see Table 3)

In the univariate analysis, non-neuro APACHE II, non-neuro SOFA were associated with a decreased risk of developing NCS or NCSE while a suspected clinical seizure prior to cEEG was associated with an increased risk of developing NCS or NCSE (24 vs. 6 %).

Clinical predictors of lack of reactivity on EEG (see Table 4)

Statistically significant clinical predictors of lack of EEG reactivity included presence of sedation as well as circulatory shock during cEEG (SOFA-CV). In addition, coma at the time of cEEG tended to be associated with lack of reactivity (33 vs. 13 %).

Mortality and prognostic significance of EEG findings (see Fig. 1)

Discharge survival was 56 % (55/98), while 1-year survival was 36 % (35/98). In the survival analysis, a lack of EEG reactivity was associated with higher 1-year mortality [mean survival time 3.3 (95 % CI 1.8–4.9) vs. 7.5 (6.4–8.7) months; $p = 0.002$]. Of survivors (35) through the 1 year follow-up period, 13 % (5/35) lacked EEG reactivity while the remaining 87 % had reactivity. The proportion of survivors with good outcome (mRS ≤ 3) was the same in patients without reactivity [4/5 (80 %)] as with reactivity [23/28 (80 %)]. Data was available for 33 or the 35 survivors. Presence of NCS or PD was not associated with 1-year mortality [mean survival time 3.3 (95 % CI 1.8–4.9) vs. 7.5 (6.4–8.7) months; $p = 0.592$].

Functional and cognitive outcome and late seizures in survivors (see Supplementary Table 2)

Of the 35 survivors through the 1-year follow-up, functional outcome was available in 33. Eighty-two percent ($n = 27$) of survivors had good functional outcome at follow-up (mRS ≤ 3). Lack of reactivity, NCS or PD were not associated with functional outcome in survivors (see Supplementary Table 2). Cognitive outcome was available in 17 patients (see Supplementary Table 2). Median TICS was 29.5 (IQR 26.5–33), consistent with mild cognitive dysfunction. No associations between NCSE, NCS, PD, or lack of reactivity and cognitive

Table 2 Clinical predictors of NCS or PD, $n = 100$ episodes

Clinical characteristics	NCS or PD		Univariate		
	No ($n = 75$)	Yes ($n = 25$)	*P*	OR	95 % CI
Age >60	27	10		1.83	0.72–4.65
Female	36	14		1.38	0.56–3.43
Neurological history	16	13		4.0	1.53–10.43
Medical history					
Diabetes	20	11		2.16	0.84–5.54
Chronic renal failure	25	7		0.79	0.29–2.11
Chronic liver failure	16	7		1.43	0.51–4.03
History of transplant	8	4		1.60	0.44–5.83
Non-neuro APACHE II on admission to ICU	25 (18–29)	19 (17–24.25)	0.042		
Non-neuro SOFA on admission to ICU	8 (7–11.75)	6 (4–7.2)	0.001		
Coma at start of cEEG	59	17		0.58	0.21–1.58
Suspected clinical seizure before cEEG	18	11		2.5	0.96–6.40
Continuous infusion of sedation during cEEG	49	10		0.35	0.14–0.90
Continuous infusion of benzodiazepine/propofol	40	5		0.22	0.07–0.64
SOFA-CV during cEEG	3 (1–3)	1 (1–2.25)	0.008		
Temperature	99 (98.2–100.3)	99.1 (98.4–101)	0.45		
WBC	15 (6.25–21)	13 (7–21.25)	0.95		
Pneumonia	42	13		0.85	0.34–2.11
Acute kidney injury	56	21		1.78	0.54–5.85
Acute liver injury	40	9		0.49	0.19–1.25

Data are presented as either *n* or median (IQR)
Non-neuro APACHE-II acute physiology and chronic health evaluation II minus the GCS component, *cEEG* continuous electroencephalography, *NCS* nonconvulsive seizures, *PD* periodic discharges, *Non-neuro SOFA* sequential organ failure assessment score without the GCS component, minus the GCS component, *SOFA-CV* SOFA cardiovascular component score, *WBC* white blood cell count

Table 3 Clinical predictors of NCSE, $n = 100$ episodes

Clinical Characteristics	NCSE		Univariate		
	No ($n = 89$)	Yes ($n = 11$)	*P*	OR	95 % CI
Age >60	46	7		1.64	0.45–5.98
Female	44	6		1.23	0.35–4.32
Neurological history	24	5		2.26	0.63–8.08
Medical history					
Diabetes	26	5		2.02	0.57–7.20
Chronic renal failure	31	1		0.19	0.02–1.53
Chronic liver failure	18	3		1.48	0.36–6.15
History of transplant	10	2		1.77	0.33–9.30
Non-neuro APACHE II on admission to ICU	24.5 (18–29)	17 (16–22)	0.03		
Non-neuro SOFA on admission to ICU	8 (6–11)	4 (3–10)	0.04		
Coma at start of cEEG	68	8		0.82	0.20–3.39
Suspected clinical seizure before cEEG	22	7		5.33	1.42–19.94
Continuous infusion of sedation during cEEG	54	5		0.67	0.18–2.47
Continuous infusion of benzodiazepine/propofol	43	2		0.27	0.06–1.36
SOFA-CV during cEEG	3 (1–3)	1 (0–3)	0.17		
Temperature	99.2 (98.4–100.5)	98.5 (97.2–101)	0.55		
WBC	14 (7–21)	17 (9–22)	0.61		
Pneumonia	50	5		0.8	0.22–2.96
Acute kidney injury	68	9		1.39	0.28–6.94
Acute liver injury	43	6		1.28	0.36–4.51

Data are presented as either *n* or median (IQR)
Non-neuro APACHE-II acute physiology and chronic health evaluation II minus the GCS component, *cEEG* continuous electroencephalography, *NCSE* nonconvulsive status epilepticus, *SOFA* sequential organ failure assessment score minus the GCS component, *SOFA-CV* SOFA cardiovascular component score, *WBC* white blood cell count

outcome were found, although the sample size was small. Only one patient had seizures 1 year after discharge but he had known epilepsy prior to his sepsis episode. Thus, there were no new cases of late seizure or epilepsy in the 17 patients alive at 1 year who had complete follow-up data.

Table 4 Clinical predictors of reactivity, $n = 100$ episodes

Clinical characteristics	Reactivity		Univariate		
	No ($n = 28$)	Yes ($n = 72$)	*P*	OR	95 % CI
Age >60	11	42		2.16	0.89–5.28
Female	15	35		0.82	0.34–1.97
Neurological history	6	23		1.72	0.61–4.82
Medical history					
Diabetes	10	21		0.74	0.29–1.87
Chronic renal failure	11	21		0.64	0.25–1.59
Chronic liver failure	8	13		0.55	0.20–1.52
History of transplant	2	10		2.10	0.43–10.24
Non-neuro APACHE II on admission to ICU	26 (18.5–30)	22 (17–27.5)	0.13		
Non-neuro SOFA on admission to ICU	8.5 (7–12.5)	8 (5–10)	0.09		
Coma at start of cEEG	25	51		0.29	0.79–1.07
Suspected clinical seizure before cEEG	8	21		1.03	0.39–2.7
Continuous infusion of sedation during cEEG	22	37		0.29	0.11–0.80
Continuous infusion of benzodiazepine/propofol	18	27		0.33	0.13–0.83
SOFA-CV during cEEG	3 (1–3.5)	2 (1–3)	0.02		
Temperature	98.8 (97.9–100.4)	99.2 (98.4–100.5)	0.25		
WBC	17.5 (6.5–25)	14 (7–20.5)	0.28		
Pneumonia	13	42		1.6	0.67–3.89
Acute kidney injury	24	53		0.46	0.14–1.51
Acute liver injury	15	34		0.77	0.32–1.86

Data are presented as either *n* or median (IQR)

Non-neuro Non-neuro APACHE-II Acute physiology and chronic health evaluation II minus the GCS component, *cEEG* continuous electroencephalography, *SOFA* sequential organ failure assessment score minus the GCS component, *SOFA-CV* SOFA cardiovascular component score, *WBC* white blood cell count

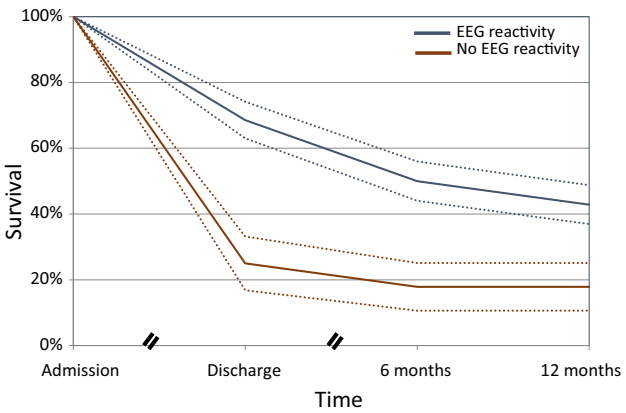

Fig. 1 Kaplan–Meier survival curve showing mortality from admission through the 1-year follow-up for patients with and without EEG reactivity ($n = 98$). *Dashed lines* 95 % confidence intervals

Discussion

In our prospective cohort of patients with severe sepsis (median non-neuro APACHE-II score and of 23.5 and non-neuro SOFA of 8) and acute brain dysfunction (76 % with GCS ≤8 on admission), the prevalence of NCS or PD was 25 %, with 11 % having NCS. The only statistically significant risk factor for developing NCS or PD was a prior history of neurologic disease, while clinical seizures prior to monitoring were associated with NCS and possible NCSE. Factors during treatment of sepsis that were associated with NCS or PD were lower non-neuro APACHE II and lower non-neuro SOFA scores (less severely ill), lack of need for sedation and lack of need for vasoactive medications. Lack of EEG reactivity, which was more common in patients on continuous sedation, was observed in 28 % of episodes. Additionally, lack of EEG reactivity was associated with higher mortality at both discharge and 1-year follow-up. Due to the small number of survivors (only 36 % were alive at 1 year), we were underpowered and found no predictors of functional or cognitive outcome. No patient developed new epilepsy after their episode of sepsis.

Our study confirms the high rate of NCS and PD observed in this population in previous retrospective studies [6, 7, 14, 25], but we could not replicate the previously reported strong association between NCS and/or PD and mortality [6, 7]. Unlike prior studies, our study was exclusively composed of patients with sepsis (vs. 37 % [6] and 60 % [7]) who had severe multi-organ dysfunction. In comparison to previous work, 76 % of episodes occurred in comatose patients (vs. 55 % [6] and 48 % [7]), with a significant proportion (77 %) having acute kidney injury (vs. 65 % [6] and 52 % [7]). Though a prior neurological history was a significant predictor of NCS or PD in our cohort, only 29 % of septic episodes were associated with a prior neurologic history (vs. 47 % [6]). Given the

retrospective nature of prior studies, an illness severity score was not provided and thus cannot be compared with our cohort [6, 7]. However, based on the comparable variables outlined above, our population was more severely ill.

We found that PD, NCS and NCSE were associated with lower illness severity scores and a lower need for sedation and vasopressors. This, and previous evidence that sepsis and coma are associated with a greater risk of PD, NCS and NCSE [6, 7], may suggest that PD, NCS and NCSE occur in a subgroup of patients with an intermediate degree of encephalopathy. More severe brain dysfunction, associated with more severe sepsis, might prevent the development of such discharges, at least as can be visualized on scalp EEG. Brain hypoxia and acidosis have been shown to occur in advanced stages of sepsis [26] and have been associated with fewer acute seizures in animal models [27, 28]. Previous studies have shown that many patients with severe brain injury exhibit seizures and PD that are not visible on scalp EEG but only on intracranial electrodes [29]. One hypothesis for this may be that these patients have multifocal, poorly synchronized seizures or seizure-like discharges that are not seen on scalp as they do not involve a large enough area of synchronized cortex. An additional hypothesis is that patients on sedation require more vasopressors and have fewer NCS and PD as a result of sedatives, which often include drugs with antiepileptic properties. The statistically significant associations between higher illness severity scores, presence of sedation, need for vasopressors and decreased NCS and PD are intriguing. However, since these variables have statistically significant associations with one another, it is impossible to tease out a chain of causality. We cannot differentiate whether sedation is responsible for vasopressor use or whether it is a marker of illness severity (e.g., management of ventilator asynchrony). Additionally, we cannot clarify whether sedation accounts for a decreased rate of NCS and PD or whether it is a reflection of a sick brain's inability to generate discharges or seizures. These findings suggest that further studies need to include a broader population (including less severely ill patients) and more advanced neurophysiology to fully analyze the impact of PD, NCS and NCSE in sepsis.

An important finding of our study is that lack of EEG reactivity during the first days of sepsis was associated with mortality at both discharge and 1 year. EEG reactivity has been shown to be a predictor of better outcome in hypoxic-ischemic and traumatic brain injury [30, 31]. To the best of our knowledge, this is the first time that reactivity has been shown to be predictive of outcome in a population of critically ill patients with a non-neurological primary diagnosis. Though lack of EEG reactivity predicted mortality, it did not predict functional outcome. Clinical–EEG correlations suggest that the reactivity of the EEG to external simulation is dependent on the preservation of brainstem structures mediating arousal responses, such as the ascending reticular formation, but does not necessarily reflect higher cortical function [32, 33]. These findings further stress the importance of secondary brain dysfunction, and perhaps specifically of brainstem dysfunction, in medical critical illness. The absence of brainstem reflexes has been previously shown to predict mortality in critically ill patients [34]. Finally, we found that sedation was associated with decreased NCS or PD and a lack of EEG reactivity. It is possible that sedation is a confounder for reactivity testing during cEEG. However, an additional explanation, as observed in prior studies [35, 36], is that continuous sedation is associated with increased mortality. Though it may seem contradictory that the APACHE II was not predictive of outcome in this cohort, it was not developed or validated in a group of severely sick patients. The original APACHE II cohort only included 7 % of patients with an APACHE $\geq$31 [37] thus limiting its generalizability to predict mortality in a population comprised of very sick patients such as this one.

This study has several limitations including the single center population, the severity of illness, and the relatively small number of patients surviving. CEEG monitoring was clinically indicated in patients whose neurological exam seemed to have a clinical mismatch with the severity of their sickness. Thus, we included a higher proportion of patients with more severe encephalopathy, which is an inherent bias of our study. However, its prospective nature and systematic screening and enrollment allowed for the reliable identification of patients as well as an attempt at follow-up with detailed cognitive outcome. No attempt was made to quantify the burden of electrographic patterns, which may be a key factor [6, 38]. Another limitation is the lack of consensus criteria for reactivity. Although our definition is similar to the ones used in prior studies [31], its inter-rater agreement has never been studied or compared to quantitative EEG analysis or evoked responses. These would be important elements to include in further studies. We did not perform in depth functional assessments and though we performed cognitive assessments using the TICS, few patients participated or were alive at 1 year. Thus, we lacked the sensitivity to detect predictors of cognitive impairment, mainly if PD, NCS and NCSE have an effect on long-term cognitive sequelae. Further studies should include a comprehensive neuropsychological assessment if possible. Lastly, no patients developed new epilepsy. Although this suggests new epilepsy is infrequent after sepsis, even with acute NCS or PD, our phone interview may have lacked sensitivity for seizures. We cannot make any comment on predictors of late seizures or epilepsy. There is recent literature that suggests seizure burden is associated with an increased risk of neurologic decline [38, 39] as well as an increased risk of subsequently diagnosed epilepsy [39]. These findings are important and

need to be validated in larger multicenter studies including adult patients.

Conclusions

In this prospective analysis of critically ill septic patients with altered mental status who underwent cEEG as part of their routine clinical care, NCS (11 %) and PD (25 %) were frequent. The vast majority of seizures were non-convulsive and all patients who had NCS also had PD. NCS or PD were not associated with patient's survival or disability at discharge or follow-up, suggesting that, in severe sepsis and septic shock, NCS and PD do not contribute substantially to the overall outcome or that their contribution is offset by other factors. This is the first study to show that lack of EEG reactivity was not only more frequent in patients on continuous sedation but was associated with increased mortality in patients with sepsis. Our findings underly the importance of brain dysfunction in medical critical illness. Further research is needed to clarify the mechanisms and implications of brain dysfunction secondary to sepsis in order to develop potential interventions aimed at improving long-term functional and cognitive outcomes. In addition, a much larger sample size is needed to assess the prevalence and risk factors for later epilepsy. cEEG has the power to detect both ictal and inter-ictal EEG patterns but also conveys a tremendous amount of physiologic information. Future clinical trials using cEEG and other real-time, continuous, non-invasive (or invasive) monitors will be critical to understanding primary brain dysfunction as well as reducing the risk of secondary brain injury in vulnerable ICU survivors of sepsis.

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