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Does continuous video-EEG in patients with altered consciousness improve patient outcome? Current evidence and randomized controlled trial design

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Abstract

Continuous video-EEG (cEEG) is recommended in patients with altered consciousness; as compared to routine EEG (rEEG, lasting <30 minutes) it improves seizure detection, but is time- and resource consuming. While North American centers increasingly implement cEEG, most other (including European) hospitals have insufficient resources. Only one study suggested that cEEG could improve outcome in adults, and a recent assessment challenged this view. This paper reviews current evidence on the added value for cEEG in clinical terms, and described a design for a prospective study.

In a multicenter randomized clinical trial (NCT03129438), adults with GCS ≤11 will be randomized 1:1 to cEEG for 30-48 hours or two rEEG, assessed through standardized ACNS guidelines. The primary outcome will be mortality at six months, assessed blindly. Secondary outcomes will explore functional status at four weeks and six months, ICU length of stay, infection rates, and hospitalization costs. Using a 2-sided approach with power of 0.8, and α error of 0.05, 2x174 patients are needed to detect an absolute survival difference of 14%, suggested by the single available study on the topic.

This study should help clarifying if cEEG has a significant impact on outcome and define its cost effectiveness. If the trial will result positive, it will encourage broader implementation of cEEG with consecutive substantial impact on health care and resource allocations. If not, it may offer a rationale to design a larger trial, and -least for smaller centers- to avoid widespread implementation of cEEG, rationalizing personnel and device costs.

Continous EEG in patients with altered consciousness: current evidence

In the last decade, continuous video-EEG (cEEG) has been increasingly used in intensive care units (ICUs), particularly in North America [1-3]. The ICUs represent an environment prone to considerable potential morbidity and mortality due to underlying critical diseases, not only involving primarily the brain, such as severe brain trauma, intracranial hemorrhage, subarachnoid hemorrhage, or ischemic stroke, but also in case of secondary brain injury or dysfunction, as in patients with post-cardiac arrest encephalopathy, delirium, or septic schock [4-6]. The role of cEEG mostly resides in identifying epileptic seizures and status epilepticus (SE), which often do not show specific clinical correlates in this setting [7] and may induce secondary brain injury [8], or to monitor treatment in patients with SE requiring general anesthesia [9]. Furthermore, EEG is a cornerstone of multimodal outcome prognostication after cardiac arrest [10, 11], and can also detect changes heralding vasospasms following subarachnoid hemorrhage [12, 13]. The American Clinical Neurophysiology Society (ACNS) has updated recommendations for reporting EEG features in ICU[14], contributing to a uniform nomenclature that will certainly improve generalizability and inter-institutional comparability; they have been recently validated [15, 16].

In the last few years, the European Society of Intensive Care Medicine (ESICM) [4] and the ACNS [5, 6] published consensus statements for the use of EEG in ICUs. cEEG is recommended for most patients with altered consciousness, to assist SE treatment management in forms requiring pharmacological coma, and to detect nonconvulsive seizures in brain-injured or comatose patients with unexplained altered consciousness. The American guidelines further suggest its use in subjects with reduced level of consciousness under sedation or pharmacologically induced coma. cEEG should be recorded at least for 24 hours and interpreted at least twice daily [6]. However, especially in the European publication, the authors recognize that supporting evidence is low, and that additional data are required [4].

Compared to routine EEG (rEEG, typically lasting 20-30 minutes), cEEG has a clearly superior sensitivity in uncovering seizures and SE: a seminal retrospective study showed that the detection rate increases from 50% after one hour recording to 95% after 48 hours [7]. Further evidence revealed an increased detection rate of nonconvulsive SE after introduction of cEEG as compared to historic controls undergoing rEEG (monthly detection rates: cEEG 5.44 ±1.33; rEEG 2.17 ±1.89, p=0.002) [17]. It has also been shown that cEEG influences clinical practice by inducing treatment changes in adults [18] and children[19]. Furthermore, recent data suggests that the amount of time spent in the ICU having electrographic seizures, in other words the seizure “load”, may correlate with prognosis, also both in children [20] and adults [21].

On the other hand, cEEG is relatively time- and resource consuming, requiring skilled technical personnel, regular assessments by electroencephalographers, and ideally constant availability of dedicated, portable video-EEG recording machines connected to the hospital network for out-of-site

review [22]. In an attempt to rationalize resources, it has been suggested that in comatose patients after cardiac arrest the prognostic yield of cEEG information seems comparable to that of repeated rEEG [23]. Also, prolonged EEG does not appear to correlate with better outcome in elderly patients with non-convulsive SE, as compared to those managed with repeated rEEG[24] .

Practical considerations have recently emerged. For example, it seems that a refined analysis of the first part of cEEG may allow stratifying the risk of encountering seizures in the subsequent recording: if no epileptiform discharge is detected within the first 30 minutes, the likelihood would be below 5% [25, 26]. Also, the use of automated softwares allowing interpretation of compressed EEG seems to improve efficacy, reducing the time to analyze a cEEG by 78%, with minimal loss of sensitivity [27]. While large, mostly academic centers in North America have been using cEEG increasingly since the turning of the century, the vast majority of European hospitals still do not have the resources to apply cEEG to all patients with altered consciousness in- or outside the ICUs, and therefore, disturbingly, are not complying with current guidelines [4].

To the best of our knowledge no trial has clearly determined whether increased seizure detection simply reflects a more severe brain damage / dysfunction by the underlying etiology, or it is directly and causally related to outcome. In particular, it remains unclear if cEEG leads to better prognosis; this represents a central unanswered clinical question. To date, only a retrospective population-based study, relying on US discharge diagnoses and therefore probably challenged by considerable imprecision, has suggested that cEEG does improve outcome significantly[1]. A recent study matching 234 patients receiving cEEG to controls without EEG found an association of the former with longer hospitalization and more frequent anticonvulsant prescription modifications, but not with clinical outcome [28]. Financial considerations could act, at least in part, as an incentive to perform cEEG in selected settings due to higher reimbursement for cEEG as opposed to rEEG. These incentives do not exist in most European countries, where reimbursement is typically calculated through diagnosis related groups. In children, it has been estimated that if successful management of electrographic SE would improve the outcome by 3-6%, a cEEG lasting 24-48 hours would prove cost-effective[29], but no such calculations are available for adults.

Given the preceding considerations, it seems reasonable to consider that there is currently equipoise between cEEG and rEEG in terms of prognostic impact.

A study to improve current evidence

Design: The hypothesis that cEEG, leading to refined clinical care, will improve patients' prognosis has thus not been formally verified to date. We therefore designed a multicenter randomized controlled trial to evaluate the prognostic yield of cEEG (NCT03129438: Continuous EEG Randomized Trial in Adults, CERTA), carried out in four Swiss hospitals (three of the five university centers: CHUV Lausanne, Inselspital Bern, Universitätsspital Basel; one large regional center: Hôpital de Sion), located both in the German- and the French-speaking part of the country. As of September 2017, IRB has being obtained at all sites; the study was initiated between April and August 2017 in all centers; 63 patients have been recruited.

Adult in-patients presenting with consciousness disorders of any etiology defined below a quantitative threshold (of note, in the most recent guidelines only the vague term of "altered mental status" is reported [4, 6]) are randomized to receive cEEG or rEEG. Patients with already detected seizures or SE (but not interictal EEG discharges) are excluded from inclusion, as cEEG for the monitoring of SE treatment is a widely recognized indication. Since most cEEG (70-90%) performed in large skilled centers are ordered to detect non-convulsive seizures or SE in patient with disorders of consciousness and only 4-10% to monitor SE [30], this criterion should not greatly impact inclusion rate.

Inclusion and exclusion criteria: are found in Tables 1 and 2, respectively.

Randomization: Through an online program accessible 24/7, site-stratified 1:1 randomization will be performed between cEEG and rEEG.

Procedures (intervention period, see **Figure 1**): Patients randomized to cEEG will be recorded with at least 21 electrodes placed according to the international 10-20 system; reduced montages will be allowed in patients with extensive neurosurgical scars, according to common practice. Electrodes type and the use of automated, quantitative EEG interpretation softwares will be at the discretion of the centers, but will have to follow minimal technical requirements for EEG recordings in patients with consciousness impairment [31]. Continuous recordings will last between 30 and 48 hours to avoid definitive removal of electrodes during the night. During this time, interruptions for diagnostic purposes (e.g., neuroimaging) will be allowed. Reactivity testing using auditory and nociceptive stimuli will be performed at least twice during the recording time. Recordings will be visually (raw traces) interpreted by certified electroencephalographers (i.e., exclusive interpretation of automated algorithm won't be allowed) at least 3x during working days, and 2x during weekends and bank holidays, using the 2013 ACNS nomenclature [14]; all investigators being ACNS certified. Interpretations will be communicated within two hours of their completion to the treating team. Patients randomized to rEEG will be recorded using the same technical and analytical approach. Two recordings will take place over a period of 24-

48 hours, lasting each between 20 and 30 minutes, in accordance with current practice in the vast majority of Swiss (and European) hospitals.

During the intervention period of up to 48 hours, patients who will be diagnosed with clinical or electrical seizures or SE (10-15% expected [32]) will exit intervention and managed according to best clinical practice; this will allow converting to cEEG from rEEG if needed. A uniform operational definition of electographic seizures (minimum time >10 seconds) and SE (minimum time >5 minutes) will be used: repetitive, rhythmic or periodic discharges or spike-waves at a frequency of <3 Hz together with evolution in frequency, location, or with electroclinical response to antiseizure drugs; or occurring at >3 Hz [7, 14, 33, 34].

Several variables will be collected during the hospital stay, including but not limited to: demographics, body weight, reason for admission, presumed modified Rankin scale before admission, neuroimaging results (if available), history of epileptic seizures, indication for EEG, Glasgow Coma Score/Four score immediately before EEG, full medication (including doses and timing) administered during EEG recordings, medical comorbidities assessed through the Charlson Comorbidity Index (CCI) [35], use of commercial, automated EEG interpretation algorithms, use of cEEG or rEEG, within four weeks following the intervention period and serious adverse events related to the intervention.

Outcomes: Mortality at six months will represent the primary outcome, a robust, non-debatable variable that will be assessed through blinded phone interview with the patient, relatives, or treating physician. Secondary outcomes (**Table 3**) will be assessed through collection of clinical data during the hospital stay and semi-structured phone interviews, as recently suggested [36], at four weeks and six months (blinded interview for the latter).

Statistical analysis: According to the only existing study addressing this issue [1], patients with consciousness disorders and cEEG have a 75% survival rate, and those without cEEG 61%. Considering a power of 0.8, an alpha error of 0.05, and applying a 2-sided test, 2x174 patients (348 in total) are needed to detect this difference (χ^2 test for independent samples, Stata version 12, College station, TX). This represents a reasonable difference of non-debatable clinical relevance. An interim analysis of the primary outcome will be performed on the first 100 recruited patients: if the difference of 14% in survival at six months between the two arms will be met, the study will be interrupted.
At study completion, the two interventional groups will be compared regarding survival at six months as “intention to monitor” (predefined analysis for the primary endpoint including all patients receiving at least 5 minutes of EEG recording) and “per protocol”, adjusted for potential confounders (logistic regressions). Analysis of each secondary endpoint will also be conducted as per the two approaches using univariable and multivariable approaches.

For univariable analyses, frequency tables (χ^2 or Fisher exact tests, as needed), t-, Mann-Whitney U, and Kaplan-Meier tests will be applied, as needed. For multivariable approaches, stepwise logistic regression models will be performed to identify independent outcome predictors among those with a p <0.1 on univariable analyses. "Goodness-of-fit" of the models will be evaluated with a Hosmer-Lemeshow test. Solid predictors will be used to predict survival and functional outcome in a model. To evaluate performance of these models, sensitivity, specificity, positive predictive value, negative predictive value, unweighted accuracy (using exact binomial 95% CI), and the area under the Receiver Operating Characteristic (ROC) curves will be calculated.

Feasibility: In any given ICU in a participating hospital, whose size is between 15 – 44 beds, at least half of the patients exhibit impaired consciousness. Conservatively, it may be postulated that 1/4 of patients have unexplained altered mental state with a GCS≤11 or FOUR score ≤12 at any given time. Taking into account that patients remain in the ICU for a mean of two weeks (generous estimation), that some patients will not be eligible for randomization, and liberally assuming a missed rate of 50% (failed screening over week-ends, transient unavailability of local investigators, informed consent refusals), two to six patients may undergo randomization every second week (50-150 pts/year and institution) (**Figure 2**).

Taking into account the capability of the EEG units, which will represent the most important limiting factor on the one side, and the fact that several patients with unexplained altered mental state will be found outside the ICU on the other side (which will, conversely, increase recruitment), we conservatively foresee that the CHUV should randomize at least 80 patients/year, the Inselspital 60, the Universitätsspital Basel 30, and the Hôpital de Sion 25. Over the planned enrolling period of two years, this would allow to enroll at least 390 patients. This conservative estimation is already 12% larger than the target sample size of 348.

Discussion

Impact and limitations: This study should help clarifying whether cEEG monitoring has a measurable impact on mortality and functional outcome, and define its cost effectiveness. It is likely that it will have a considerable potential to influence clinical practice in this difficult to manage population, by improving patients' care and rationalizing hospital resources. To the best of our knowledge, such a study has not yet be performed, despite the acknowledgment of the authors of the American recommendations that the relationship between cEEG and improved outcome has not been proven [37], mirroring the reported estimate of "low evidence" in the European recommendations [4]. Ultimately, this study will allow answering the almost philosophical question whether "more is really better". If the study results would indicate that cEEG significantly improves outcome, this will eventually call for the propagation

of cEEG and lead to a broad implementation of cEEG on ICUs, as suggested in the current guidelines and with substantial impact on health care spending and resource allocation in larger European hospitals. If conversely the study will not show a significant outcome difference, pending further possible larger trials addressing a smaller cEEG effect, it will offer some rationale -at least for smaller and medium-size centers- not to implement widespread cEEG, with obvious savings in personnel and device costs.

We decided to exclude patients having seizures or SE shortly before possible enrollment, as prolonged EEG monitoring in this population represents a standard of care in participating centers. A recent publication analyzing recording longer than 24 hours in adults pointed out that the seizure risk is still remarkable (13%, 95% CI: 8-17%) in ICU patients with severely altered consciousness and with no previous seizures, whose clinical situation corresponds to the vast majority of the studied patients in this trial [38]. The seizure definition using 10 seconds aims at a uniformity of reports across centers, but may reflect clinical practice (especially guiding treatment) in a limited way.

The sample size is somewhat limited to an estimation based upon the only available data in this context [1], and admittedly aims at identifying a relatively large cEEG effect. Given the current stand of recruitment, we expect that the minimal sample size could be surpassed by at least 10-15%. One may argue that a difference in mortality of 5% would still represent a valuable result, if detected; this would however require about 1250 patients in each arm (2500 totally); it seems obvious that such a study lies far beyond the capability of an investigator-initiated trial. Nevertheless, if we will end with a negative result with a tendency towards improved outcome in one arm, the study may serve as a solid rationale to estimate how many patients should be tested in a larger study (for example, the present sample has 0.7 power to address a survival difference of 10% with an alpha error of 0.15). Moreover, the large palette of secondary outcomes will likely enhance our current understanding in terms of impact on clinical care, resources and costs, and ultimately improve patients' care. This trial will not however be applicable to children

Risks: Since the EEG is a noninvasive procedure, there are no known significant risks that will be associated with either rEEG or cEEG, apart from skin reactions under electrodes in patients undergoing cEEG, an extremely uncommon occurrence before ten days of uninterrupted recording [31]. All files and records will be coded; therefore, there will be no risk of disseminating patients' identities. All study members will be submitted to strict confidentiality, according to Swiss laws. There will be no blinding of the procedure to treating physicians and electroencephalographers. Blinding in this particular clinical setting would imply having two separate teams of clinical neurophysiologists in each center, which seems highly unpractical. Furthermore, withdrawing EEG information to the treating team would not only raise ethical questions, but also potentially impact on the clinical outcome at six months, therefore biasing the study. Importantly, in order to minimize confounding by EEG allocation (information bias),

the primary and several secondary endpoints will be blindly assessed using a recently proposed structured interview for the functional outcome [36].

Ethical considerations: We believe that there is equipoise regarding the prognostic impact of cEEG. Furthermore, the interim analysis and the careful follow-up would prevent a futile continuation of the study if results were to be very clear early. Since no Swiss hospital (along with the vast majority of European centers) has the capability of complying with the European guidelines [4] suggesting to perform cEEG of at least 24-48 hours in every patient with unexplained altered mental status, we firmly believe that the question on cEEG relationship with outcome deserves an answer. The study will be carried out in accordance to the protocol and principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice issued by ICH and the Swiss Law. Given its emergency nature, intervention is started after approval by a physician unrelated to patient care or the study, then informed proxy consent is obtained at seven +/- three days; finally, patient's consent is sought in survivors who regain awareness and intellectual capability.

Figure 1*: illustration of the study flow. cEEG=continuous EEG; rEEG=routine EEG.*

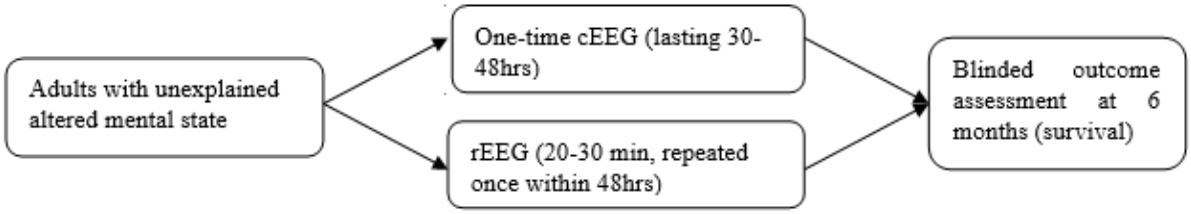

Figure 2: *yearly eligibility assessment <u>per center</u> (smallest to largest), for details see text.*

Table 1: *Inclusion criteria.*

Table 2: *Exclusion criteria.*

Table 3: *Secondary endpoints.*

Table 1: *Inclusion criteria.*

- In-patients aged above 18 years, treated in an ICU or intermediate care unit.
- Alteration of mental state of any etiology, with Glasgow-coma scale ≤11 or FOUR score ≤ 12 [37, 38].
- Need of an EEG to detect seizures or SE, or to evaluate prognosis, as per the treating physician or consulting neurologist.
- Informed consent obtained for research in emergency situation at the time of inclusion.

Table 2: *Exclusion criteria.*

- Clinical or electrographic seizures or SE already diagnosed within 36 hours, respectively 96 hours, before randomization (in order to allow cEEG as per current clinical practice).
- Palliative care situation (detection of SE or seizures would lack any impact on patient's care).
- High likelihood of needing a surgical intervention or an invasive diagnostic procedure within the next 48 hrs according to the treating physician (this would require cEEG removal).

Table 3: *Secondary endpoints.*

- Functional outcome at four weeks and at six months (modified Rankin Scale, Cerebral Performance Categories [39], ordinal),
- Back to work if previously working at four weeks and at six months (proportion),
- Seizure/SE detection rate, time to detection after the start of EEG intervention, and presence of concomitant clinical signs of seizures (proportions, resp. continuous)
- Detection of interictal, potentially epileptiform features (spikes, spike and waves, sharp waves, isolated or repeated at <3Hz without any evolution; lateralized rhythmic delta activity [40]; proportion),
- Rate of in-hospital infections requiring antibiotic treatment at four weeks after the first EEG (proportion),
- Need and duration of mechanical ventilation at four weeks after the first EEG, (proportion, resp. continuous),
- Duration if ICU and hospital stay (continuous),
- Patient destination after acute facility (home, rehabilitation center, nursing home; categorical)
- Change in clinical patient management (i.e., antiseizure drug introduced or stopped, increased or decreased, brain imaging procedure order) occurring during the 60 hours following the start of the EEG intervention (categorical).
- Hospitalization costs, intended as amount billed for each patient's acute hospital stay, assessed through the billing department of each hospital (continuous).

References

1. Ney, J.P., et al., *Continuous and routine EEG in intensive care: utilization and outcomes, United States 2005-2009.* Neurology, 2013. **81**(23): p. 2002-8.
2. Friedman, D., J. Claassen, and L.J. Hirsch, *Continuous electroencephalogram monitoring in the intensive care unit.* Anesth Analg, 2009. **109**(2): p. 506-23.
3. Gavvala, J., et al., *Continuous EEG monitoring: a survey of neurophysiologists and neurointensivists.* Epilepsia, 2014. **55**(11): p. 1864-71.
4. Claassen, J., et al., *Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM.* Intensive Care Med, 2013. **39**(8): p. 1337-51.
5. Herman, S.T., et al., *Consensus statement on continuous EEG in critically ill adults and children, part II: personnel, technical specifications, and clinical practice.* J Clin Neurophysiol, 2015. **32**(2): p. 96-108.
6. Herman, S.T., et al., *Consensus statement on continuous EEG in critically ill adults and children, part I: indications.* J Clin Neurophysiol, 2015. **32**(2): p. 87-95.
7. Claassen, J., et al., *Detection of electrographic seizures with continuous EEG monitoring in critically ill patients.* Neurology, 2004. **62**(10): p. 1743-8.
8. Vespa, P., et al., *Metabolic Crisis occurs with Seizures and Periodic Discharges after Brain Trauma.* Ann Neurol, 2016.
9. Rossetti, A.O. and D.H. Lowenstein, *Management of refractory status epilepticus in adults: still more questions than answers.* Lancet Neurol, 2011. **10**(10): p. 922-30.
10. Horn, J., T. Cronberg, and F.S. Taccone, *Prognostication after cardiac arrest.* Curr Opin Crit Care, 2014. **20**(3): p. 280-6.
11. Rossetti, A.O., A.A. Rabinstein, and M. Oddo, *Neurological prognostication of outcome in patients in coma after cardiac arrest.* Lancet Neurol, 2016. **15**: p. 597-609.
12. Gollwitzer, S., et al., *Early prediction of delayed cerebral ischemia in subarachnoid hemorrhage based on quantitative EEG: A prospective study in adults.* Clin Neurophysiol, 2015. **126**(8): p. 1514-23.
13. Claassen, J., et al., *Nonconvulsive seizures after subarachnoid hemorrhage: Multimodal detection and outcomes.* Ann Neurol, 2013.
14. Hirsch, L.J., et al., *American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version.* J Clin Neurophysiol, 2013. **30**(1): p. 1-27.
15. Gaspard, N., et al., *Interrater agreement for Critical Care EEG Terminology.* Epilepsia, 2014. **55**(9): p. 1366-73.
16. Westhall, E., et al., *Interrater variability of EEG interpretation in comatose cardiac arrest patients.* Clin Neurophysiol, 2015. **126**(12): p. 2397-404.
17. Sutter, R., et al., *Continuous video-EEG monitoring increases detection rate of nonconvulsive status epilepticus in the ICU.* Epilepsia, 2011. **52**(3): p. 453-7.
18. Kilbride, R.D., D.J. Costello, and K.H. Chiappa, *How seizure detection by continuous electroencephalographic monitoring affects the prescribing of antiepileptic medications.* Arch Neurol, 2009. **66**(6): p. 723-8.
19. Williams, R.P., et al., *Impact of an ICU EEG monitoring pathway on timeliness of therapeutic intervention and electrographic seizure termination.* Epilepsia, 2016. **57**(5): p. 786-95.
20. Payne, E.T., et al., *Seizure burden is independently associated with short term outcome in critically ill children.* Brain, 2014. **137**(Pt 5): p. 1429-38.
21. De Marchis, G.M., et al., *Seizure burden in subarachnoid hemorrhage associated with functional and cognitive outcome.* Neurology, 2016. **86**(3): p. 253-60.
22. Vulliemoz, S., et al., *Imaging compatible electrodes for continuous electroencephalogram monitoring in the intensive care unit.* J Clin Neurophysiol, 2009. **26**(4): p. 236-43.
23. Alvarez, V., et al., *Yield of intermittent versus continuous EEG in comatose survivors of cardiac arrest treated with hypothermia.* Critical care, 2013. **17**(5): p. R190.

24. Eskioglou, E., et al., *Extended EEG and non-convulsive status epilepticus: Benefit over routine EEG?* Acta Neurol Scand, 2016.
25. Shafi, M.M., et al., *Absence of early epileptiform abnormalities predicts lack of seizures on continuous EEG.* Neurology, 2012. **79**(17): p. 1796-801.
26. Westover, M.B., et al., *The probability of seizures during EEG monitoring in critically ill adults.* Clin Neurophysiol, 2015. **126**(3): p. 463-71.
27. Moura, L.M., et al., *Spectrogram screening of adult EEGs is sensitive and efficient.* Neurology, 2014. **83**(1): p. 56-64.
28. Khawaja, A.M., et al., *Continuous Electroencephalography (cEEG) Monitoring and Outcomes of Critically Ill Patients.* Med Sci Monit, 2017. **23**: p. 649-658.
29. Abend, N.S., A.A. Topjian, and S. Williams, *Could EEG Monitoring in Critically Ill Children Be a Cost-effective Neuroprotective Strategy?* J Clin Neurophysiol, 2015. **32**(6): p. 486-94.
30. Alvarez, V., et al., *The use and yield of continuous EEG in critically ill patients: A comparative study of three centers.* Clin Neurophysiol, 2017. **128**(4): p. 570-578.
31. Alvarez, V. and A.O. Rossetti, *Clinical Use of EEG in the ICU: Technical Setting.* J Clin Neurophysiol, 2015. **32**(6): p. 481-5.
32. Sutter, R., *Are We Prepared to Detect Subtle and Nonconvulsive Status Epilepticus in Critically Ill Patients?* J Clin Neurophysiol, 2016. **33**(1): p. 25-31.
33. Beniczky, S., et al., *Unified EEG terminology and criteria for nonconvulsive status epilepticus.* Epilepsia, 2013. **54 Suppl 6**: p. 28-9.
34. Sutter, R. and P.W. Kaplan, *The neurophysiologic types of nonconvulsive status epilepticus: EEG patterns of different phenotypes.* Epilepsia, 2013. **54 Suppl 6**: p. 23-7.
35. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.
36. Mak, M., et al., *Measuring outcome after cardiac arrest: construct validity of Cerebral Performance Category.* Resuscitation, 2016. **100**: p. 6-10.
37. Herman, S.T. and N.S. Abend, *Author Response: Concerns About Utility and Cost-Effectiveness of Continuous Critical-Care EEG.* J Clin Neurophysiol, 2015. **32**(5): p. 442-3.
38. Struck, A.F., et al., *Time-dependent risk of seizures in critically ill patients on continuous electroencephalogram.* Ann Neurol, 2017. **82**(2): p. 177-185.