Curr Treat Options Neurol (2016) 18: 8
DOI 10.1007/s11940-015-0391-0

Critical Care Neurology (K Sheth, Section Editor)

Understanding and Managing the Ictal-Interictal Continuum in Neurocritical Care

Adithya Sivaraju, MD, MHA[1]
Emily J. Gilmore, MD, MS[2,*]

Address
[1]Division of Clinical Neurophysiology and Comprehensive Epilepsy Center, Department of Neurology, Yale School of Medicine, New Haven, CT, USA
[*,2]Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Yale School of Medicine, New Haven, CT, USA
Email: emily.gilmore@yale.edu

Published online: 13 February 2016

This article is part of the Topical Collection on *Critical Care Neurology*

Keywords Ictal-interictal continuum · Periodic discharges · Rhythmic delta activity · Nonconvulsive status epilepticus · Continuous electroencephalography · Neuromonitoring

Opinion statement

Continuous electroencephalographic (EEG) monitoring has become an invaluable tool for the assessment of brain function in critically ill patients. However, interpretation of EEG waveforms, especially in the intensive care unit (ICU) setting is fraught with ambiguity. The term ictal-interictal continuum encompasses EEG patterns that are potentially harmful and can cause neuronal injury. There are no clear guidelines on how to treat EEG patterns that lie on this continuum. We advocate the following approaches in a step wise manner: (1) identify and exclude clear electrographic seizures and status epilepticus (SE), i.e., generalized spike-wave discharges at 3/s or faster; and clearly evolving discharges of any type (rhythmic, periodic, fast activity), whether focal or generalized; (2) exclude clear interictal patterns, i.e., spike-wave discharges, periodic discharges, and rhythmic patterns at 1/s or slower with no evolution, unless accompanied by a clear clinical correlate, which would make them ictal regardless of the frequency; (3) consider any EEG patterns that lie in between the above two categories as being on the ictal-interictal continuum; (4) compare the electrographic pattern of the ictal-inctericta continuum to the normal background and unequivocal seizures (if present) from the same patient; (5) when available, correlate ictal-interictal continuum pattern with other markers of neuronal injury such as neuronal specific enolase (NSE) levels, brain imaging findings, depth electrode recordings, data from microdialysis, intracranial pressure fluctuations, and brain oxygen measurement; and (6) perform a diagnostic trial with preferably a nonsedating antiepileptic drug with the endpoint being both clinical and electrographic improvement. Minimize the use of anesthetics or multiple AEDs unless there is clear supporting evidence

from ancillary tests or worsening of the EEG patterns over time, which could indicate possible neuronal injury.

Introduction

In the absence of a reliable biomarker to assess neuronal damage, clinicians rely on several surrogate markers such as scalp electroencephalogram (EEG), depth EEG, cerebral microdialysis (CMD), brain oxygen measurement (PbtO2), neuron specific enolase (NSE) levels, magnetic resonance imaging (MRI), evoked potentials, single photon emission computerized tomography (SPECT) scans, and positron emission tomography (PET) scans; often in combination to assess brain function or therein neuronal injury. Several of these methods are still experimental, some invasive in nature and most only provide snapshots of cerebral activity. Scalp EEG is the only noninvasive method that facilitates continuous monitoring of brain function. However, interpretation of EEG waveforms is fraught with ambiguity and carries a great deal of subjectivity. While the American Clinical Neurophysiological Society (ACNS) Critical Care EEG terminology has helped improve this ambiguity to a large extent [1••], some questions remains unanswered. With advent of this new nomenclature, academic centers are beginning to adopt a standardized way of reporting EEG findings, thus facilitating improved communication and scope for multicenter research projects. However, the biggest challenge still remains: which of these EEG patterns warrant aggressive treatment?

The most important questions for the primary ICU team treating the patient are the following: (1) is there ongoing seizure activity on the EEG? (2) how long should we continue the EEG? and (3) how aggressive should the treatment be? The term ictal-interictal continuum (IIC) has no standard definition, includes EEG patterns that may in fact be harmful and the interpretation of what constitutes this 'continuum' varies among neurophysiologists. In our opinion, being able to effectively communicate the nature of these findings is the centerpiece of management. Even though any kind of abnormal EEG activity can be suppressed with aggressive measures, the ultimate goal is to preserve as much brain function as possible, while minimizing the side effects from treatment. The goal of this paper is to try and discuss the various EEG patterns that could potentially be included in the umbrella term of 'ictal-interictal continuum', how to communicate these findings and more importantly, develop a rational treatment approach while dealing with patients whose EEG patterns lie on the ictal-interictal continuum.

Treatment paradigm

Figure 1 illustrates a stepwise approach in the most simplistic manner when dealing with patients whose EEG patterns lie on the ictal-interictal continuum. We shall now discuss each step in detail.

1. **Identify and treat clear seizures/nonconvulsive status epilepticus (NCSE)**

Nonconvulsive seizure (NCS)

In general, there must be clear and unequivocal evolution in frequency, morphology, or location of an ongoing EEG pattern to be classified as a seizure [2]. The presence of a clinical correlate makes it easier to identify an ongoing pattern as seizure activity, however, approximately 90 % of critically ill patients in an intensive care unit setting have purely nonconvulsive seizures, which are unrecognized at bedside and can only be diagnosed by continuous EEG (cEEG) monitoring [3, 4]. Subtle clinical manifestations may include myoclonic limb, facial, or ocular movements, psychosis, nausea/vomiting, etc.… among several others

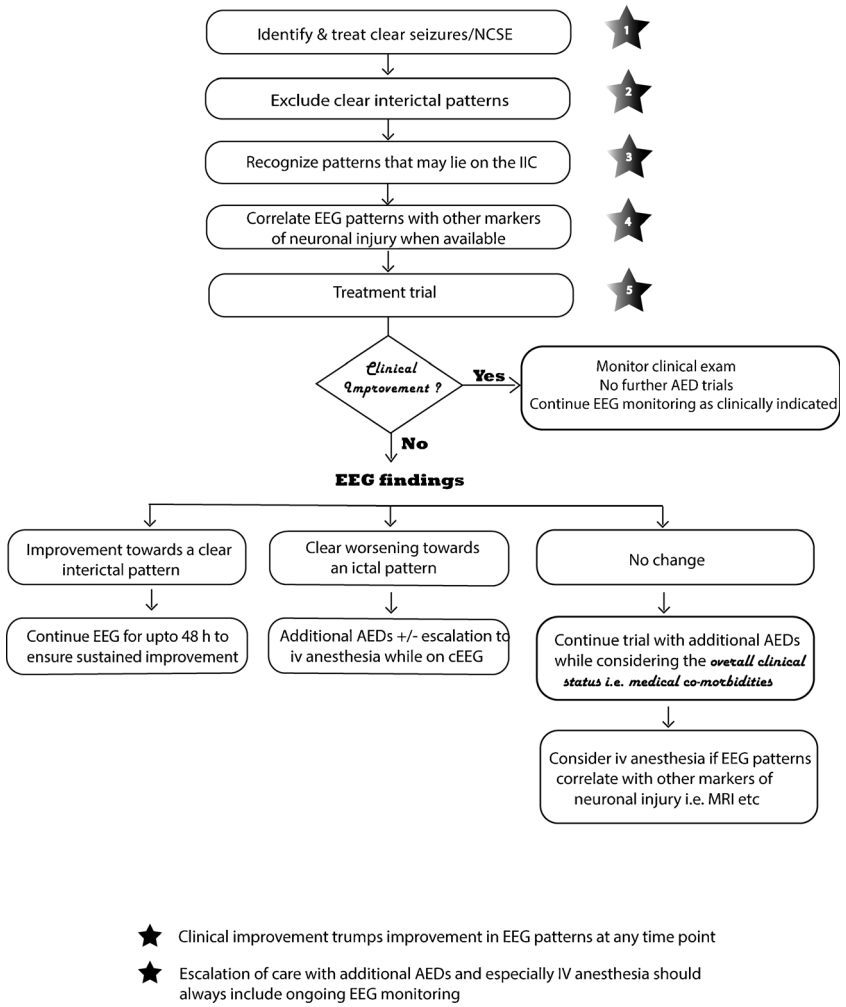


Fig. 1. NCSE: nonconvulsive status epilepticus, IIC: interictal ictal continuum, AED: antiepileptic drug, cEEG: continuous electroencephalographic monitoring.

[5]. American clinical neurophysiological society (ACNS) defines unequivocal electrographic seizures as "generalized spike-wave discharges at 3/s or faster; and clearly evolving discharges of any type that reach a frequency >4 s, whether focal or generalized [1••]."

While the criteria for defining nonconvulsive seizures (NCS) are evolving towards uniformity, most electroencephalographers agree with the original criteria of Young et al. [2], which were later modified by Chong and Hirsch [6] as shown in Table 1.

Nonconvulsive status epilepticus (NCSE)

As with nonconvulsive seizures, clinical signs are subtle or even absent in NCSE and EEG is indispensable in the diagnosis and management of these patients. While brief nonconvulsive seizures are easier to identify, prolonged nonconvulsive seizures leading to NCSE can be more difficult to recognize due to subtle or even lack of evolution of EEG patterns and the absence of interictal background for contrast. Most

Table 1. Criteria for nonconclusive seizure

Any pattern lasting at least 10 s satisfying any one of the following three primary criteria

Primary criteria:

1 Repetitive generalized or focal spikes, sharp-waves, spike-and-wave, or sharp-and-slow wave complexes at ≥3/s.

2 Repetitive generalized or focal spikes, sharp-waves, spike-and-wave or sharp-and-slow wave complexes at ≥3/s and the secondary criterion.

3 Sequential rhythmic, periodic, or quasi-periodic waves at ≥1/s and unequivocal evolution in frequency (gradually increasing or decreasing by at least 1/s, e.g., from 2 to 3/s), morphology, or location (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone is not sufficient. Change in sharpness without other change in morphology is not adequate to satisfy evolution in morphology.

Secondary criterion:

Significant improvement in clinical state or appearance of previously absent normal EEG patterns (such as a posterior dominant rhythm) temporally coupled to acute administration of a rapidly acting AED.

Resolution of the "epileptiform" discharges leaving diffuse slowing without clinical improvement and without appearance of previously absent normal EEG patterns would not satisfy the secondary criterion.

Reproduced with permission from Chong and Hirch, 2005 [6]

electroencephalographers agree that NCSE typically includes patients with >30 min of ictal EEG activity in any given hour of recording (i.e., >50 % of the record) [7–9, 10••], at least one society has recommended shortening this to 5 min [11]. What constitutes ictal activity, especially in the critically ill with prolonged nonconvulsive seizures, is anything but straightforward, often depends on many variables and is best summarized in Table 2, which is an effort towards the development of a unified terminology and classification system for NCSE [10••].

2. **Exclude clear interictal patterns**
With the advent of new ICU EEG nomenclature [1••], most academic centers have now adopted a standardized method of quantifying interictal discharges—see Fig. 2. Despite this, most electroencephalographers agree that the division between interictal and ictal patterns, especially in the critically ill population is ambiguous.

   We propose the following arbitrary criteria for a pattern to be considered interictal: (a) frequency <1.5 Hz; (b) static (NON-evolving and NON-fluctuating); and (c) absence of a clinical correlate. When EEG patterns start extending beyond this conceptual divide, we enter the zone where we struggle to define "which patterns are possibly ictal?" i.e., the ictal-interictal continuum.

3. **Recognize patterns that may lie on the ictal-interictal continuum**
Jirsch and Hirsch in 2007 [12] probably provided the best definition of 'continuum': "large centers that review abundant EEG monitoring records in the critically ill recognize that a clear division of EEG patterns as either ictal or interictal is elusive or nonexistent, and interpretation varies considerably among different electroencephalographers." Indeed, 8 years later, this line of thought still holds value. Prior to the advent of the standardized ACNS Critical Care EEG nomenclature [1••], the '3 Hz' criteria were used to differentiate interictal and ictal patterns. This was

Table 2. Working criteria for nonconvulsive status epilepticus

Patients without known epileptic encephalopathy
EDs > 2.5 Hz, or (EDs include GSW, GPD, LPD, BiPD, LRDA, polyspikes)
EDs or rhymic delta/theta activity at 0.5–2.5 Hz AND one of the following
EEG and clinical improvement after IV AED[a], or
Subtle clinical ictal phenomena during the EEG patterns mentioned above, or
Typical spatiotemporal evolution[b]
Patients with known epileptic encephalopathy
Increase in prominence of frequency of the features mentioned above, when compared to baseline with observable clinical change
Improvement of clinical and EEG[a] features with IV AEDs

EDs epileptiform discharges, *GSW* generalized spike waves, *GPD* generalized periodic discharges, *LPD* lateralized periodic discharges, *BiPD* bilaterally independent periodic discharges, *LRDA* lateralized rhythmic delta activity

[a]If EEG improvement occurs without clinical improvement, or if fluctuation without definite evolution, this should be considered possible NCSE

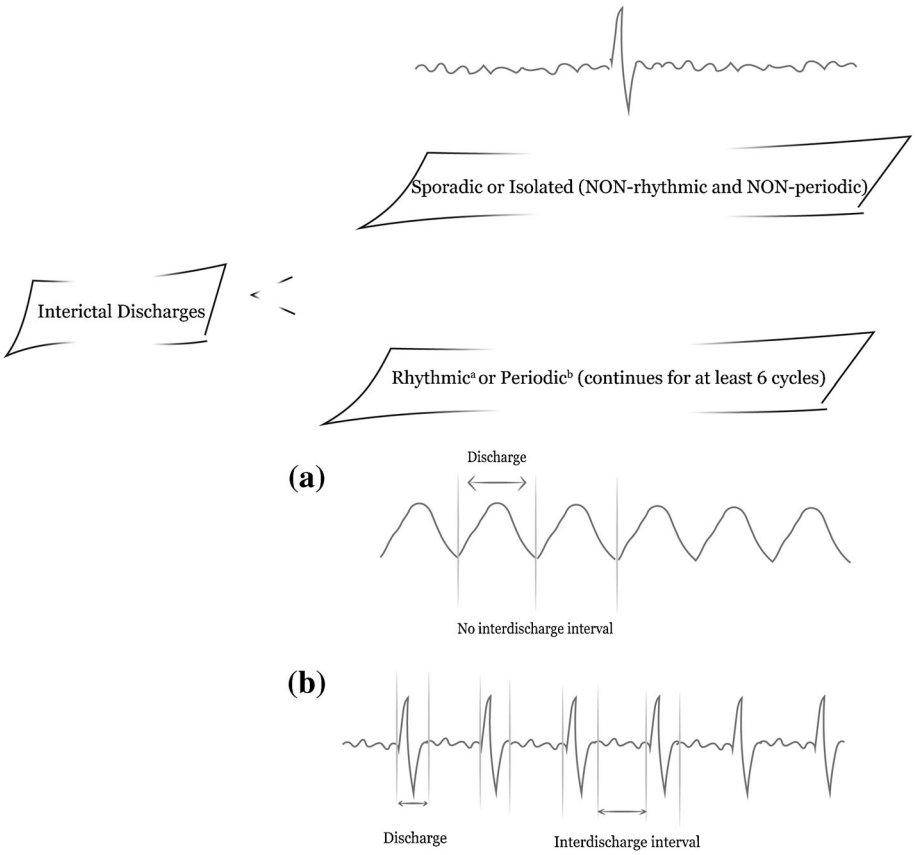
[b]Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency > 1 Hz or change in location), or decrementing termination (voltage or frequency)

Modified with permission from Beniczky et al. [10••] who modified the criteria by Kaplan [7]

arbitrary and left a gaping hole that comprised of patterns of uncertain clinical significance. This 'gap' over time evolved into what is now considered the 'ictal-interictal continuum.'

First and foremost, the most important challenge in understanding the clinical significance of this 'continuum' was to develop a common language to define the patterns, and thus facilitate communication across academic centers utilizing a high volume of continuous EEG monitoring in the critically ill. There have been some prior attempts to subclassify EEG patterns that may constitute the continuum but these were limited by moderate interrater agreement and lack of generalizability across different centers [13]. Great strides have been made in this direction with the introduction of the standardized Critical Care EEG terminology [1••]. The interrater agreement (IRA) for this terminology has been recently validated by Gaspard et al. [14••], and they found nearly perfect (90–100 %) IRA values for identification of seizures, pattern location (generalized/lateralized/bilaterally independent/multifocal), pattern type (rhythmic/periodic/spike wave), sharpness, amplitude, frequency, and numbers of phases. However, IRA dropped to 21 % for identifying 'evolution' of EEG patterns. Our experience has been similar with regard to reaching a consensus on 'evolution' of EEG patterns.

To this date, there is no standard definition for the 'ictal-interictal continuum', and this is not part of the most current version of the ACNS Critical Care EEG terminology. However, this is a work in progress and has been limited by the paucity of large studies demonstrating that one particular EEG pattern is unequivocally more harmful than others. This is starting to change with emerging evidence from recent studies, such as the one by Gaspard et al. 2013 [15•] who found that lateralized rhythmic delta activity (LRDA) has a similar clinical significance as



[a] Rhythmic = repetition of a waveform with relatively uniform morphology and duration, and without an interval in between consecutive waveforms.
[b] Periodic = repetition of a waveform with relatively uniform morphology and duration with a quantifiable inter-discharge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals.

Fig. 2. A simplified classification of interictal discharges, modified from Hirsch et al. 2013 [1••]

lateralized periodic discharges (LPDs, formerly PLEDS) and is associated with a high risk (80–90 %) of acute seizures, especially nonconvulsive.

At our institution, we arbitrarily classify the 'ictal-interictal continuum' as illustrated in Fig. 3. Given our inability to correlate a particular EEG pattern with its potential for neuronal injury, we resort to ancillary testing (when readily available) and response to medications as surrogate markers. This will be discussed in detail in the next section.

4. **Correlate EEG patterns with other markers of neuronal injury when available**

Surrogate markers for neuronal injury broadly include (a) imaging and (b) serum markers. Of all imaging modalities, the best described is peri-ictal diffusion weighted MRI (DWI) changes in generalized and more frequently in complex partial status epilepticus [16–23]. The most

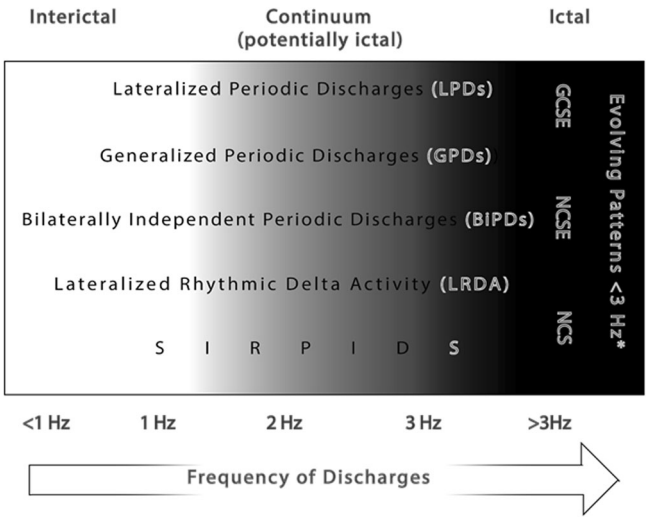


Fig. 3. This figure demonstrates various EEG patterns, primarily based on frequency depicted along the ictal-interictal continuum. The frequency of discharges is shown on the *x*-axis, which has traditionally been the benchmark guiding the aggressiveness of treatment. This frequency based division between intertical, continuum and ictal is arbitrary, conceptual, and does not take evolution of patterns into account. From our experience evolution of EEG patterns can be subtle, especially when observing long epochs in critically ill patients, and if often difficult to reach a consensus. However, the presence of even subtly evolving patterns increases the possibility of them being ictal. If clinical correlate is present with any of these patterns, it has to be considered ictal by definition, regardless of the frequency.*At least 1 Hz with clear (unequivocal) evolution in frequency, morphology, or location is considered to be ictal—see Table 1. *GCSE* generalized convulsive status epilepticus, *NCSE* nonconvulsive status epilepticus, *NCS* nonconvulsive seizure, *SIRPIDs* stimulus-induced rythmic periodic or ictal discharges

common reported locations are the hippocampus and pulvinar region of thalamus. The DWI changes are hypothesized to result from increased energy metabolism, hyperperfusion, and possible neuronal swelling secondary to ictal activity [17]. In addition to DWI changes, increased MR perfusion may be more indicative of ictal activity [19]. Of serum markers, elevated neuron specific enolase levels are associated with neuronal injury [24–26]. More invasive and serial assessment of the several other metabolic biomarkers can be measured through microdialysis and depth electrode recordings, which may prove to be helpful to clarify the ictal nature of scalp EEG findings [27, 28]. However, to date, this approach remains investigational.

Despite the above, albeit limited evidence, there is little to no information on imaging or serum markers in relation to EEG patterns of uncertain significance, i.e., the ictal-interical continuum. It is important to realize that most studies reporting imaging or serum biomarker changes were in patients with well-documented convulsive status epilepticus and epilepsia partialis continua, this evidence becomes even less robust for NCS and NCSE.

The most studied and well-described EEG pattern associated with markers of neuronal injury is periodic lateralized epileptiform discharges (PLEDs; now referred to as LPDs [lateralized periodic discharges]). LPDs most commonly occur in the setting of acute cerebral

injury (e.g., stroke, tumor, infection) with patients often presenting with a focal neurological deficit, contralateral to the location of LPDs [29]. It is well known that LPDs are highly associated with seizures and thus, should be treated accordingly [29]. In the setting where LPDs exist without associated seizures, it remains highly controversial as to the degree to which they should be "treated" as no studies have shown that treatment impacts outcome. For example, benign clinical courses with long standing chronic PLEDs have been reported, connoting a non-ictal state or one that possibly does not cause further neuronal injury [30, 31]. Clinically, the general consensus among electroencephalographers is that the presence of LPDs warrants prophylactic dosing of antiepileptics to prevent bona fide seizures. In certain clinical situations, LPDs may actually represent an ictal phenomenon [32]. Anecdotally, from our experience, we see confusional states reversed with antiepileptics often leading us to conclude that their associated EEG patterns could represent a form of NCSE. Indeed, the literature is peppered with convincing and significant evidence that LPDs are at times ictal. Terzano et al. (1986) reported on seven elderly patients with LPDs that were associated with a reversible confusional state and could possibly represent an ictal state [33]. Handforth et al. (1994) demonstrated increased local cerebral glucose metabolism on positron emission tomography during LPDs; since this is also seen during seizures, the authors surmised that this supported LPD's ictal nature [34]. Case series and case reports of single photon emission computerized tomography have shown increased regional blood flow in the area of the LPDs that disappears with the resolution of the LPDs, invoking seizure as the most likely explanation for this transient, focal hyperperfusion [27, 35, 36] and thus may warrant more aggressive treatment. At our institution, we have found DWI and perfusion changes to be most helpful in guiding treatment decisions in selected patients. However, as Claassen noted [27] these findings need to interpreted cautiously. For example, in traumatic brain injury, such imaging changes could represent either dynamic blood flow changes secondary to the underlying injury or a healthy, compensatory response of increased blood flow in the region generating the LPDs (e.g., neurovascular coupling). This leads us to the last section; synthesizing all the ancillary information in relation to EEG patterns and formulating a treatment approach.

5. **Consider a treatment trial with a sedating or nonsedating AED**
When considering management of EEG patterns felt to lie on the continuum, we recommend the following triangular approach that includes investigating the underlying cause, initiating or escalating AEDs and continuing EEG monitoring not only to assess response to treatment but also detect the development of NCSE. Figure 1 illustrates this approach in a simplified stepwise manner.

   When treatment is initiated, there are several options. Historically, a benzodiazepine trial had been the standard approach [12], however given the potential sedative effect, few centers have moved towards a nonsedating AED trial, especially in those with hepatic and renal

dysfunction, to maximize the opportunity to discern quantifiable clinical improvement [37•]. Currently, there are several IV antiepileptic medications that can be used; the choice should be weighed against the concomitant medical comorbidities or pharmacological interactions inherent to the individual patient. A 'loading' dose of an AED can be administered relatively quickly and correlated with clinical and EEG changes at the bedside. In some patients, there will be EEG improvement without clinical improvement and in others, EEG improvement with clinical improvement, the latter of which is the gold standard for defining a successful treatment trial. However, it is important to realize that clinical improvement may not be immediate, though it can be, and can often take a couple days to emerge [38]. If neither clinical nor EEG improvement occur, then the options are to continue trialing additional AEDs or escalate to an IV anesthetic if the EEG pattern can be correlated with other markers of neuronal injury as discussed above (e.g., DWI or perfusion changes on MRI, NSE levels etc.…). If there is clear EEG worsening towards an ictal pattern then additional AEDs or IV anesthetics should be considered and EEG monitoring should be continued to assess responsiveness to treatment with clearly defined EEG endpoints (e.g., decrease in frequency to less than 1 Hz, absence of 'evolution', emergence of background rhythms or sleep architecture and reactivity). Clinical improvement trumps improvement in EEG patterns at all time points.

Case

An 84-year-old woman with significant cardiac disease including atrial fibrillation, congestive heart failure, and a recent right middle cerebral artery stroke for which she underwent mechanical thrombectomy at an outside hospital. Her hospital course was complicated by septic shock with multiorgan failure requiring dialysis, tracheostomy and a feeding tube as well as unequivocal nonconvulsive status epilepticus. She was discharged to rehab, awake and able to follow simple commands, but bedbound on the ventilator. Soon after arriving in rehab, she became less interactive and it was felt that AED was the culprit so it was quickly weaned off. When she did not improve, she was transferred to Yale University for further evaluation. Immediately, she was placed back on her prior AED regimen, but her cEEG revealed generalized periodic discharges fluctuating between 0.5 and 2.5 Hz (see Fig. 4). Given concern for NCSE and her concomitant medical issues, she was treated with 2 mg IV lorazepam, after which her EEG background immediately improved with resolution of the periodic pattern. We continued EEG monitoring for the next 24–48 h to ensure that the response was sustained and also introduced a very low dose long acting benzodiazepine (clobazam 5 mg twice a day). However, clinically, she did not wake up and begin following commands until 48 h after the trial with lorazepam. Sustained improvement of EEG patterns despite a lag in clinical improvement helped prevent escalation to IV anesthetics in this particular case (see Fig. 4).

It is not uncommon to encounter cases where the EEG pattern is on the continuum, but may be attributable to an underlying infectious or metabolic derangement (e.g., severe sepsis, renal failure, liver failure). In such cases, it may

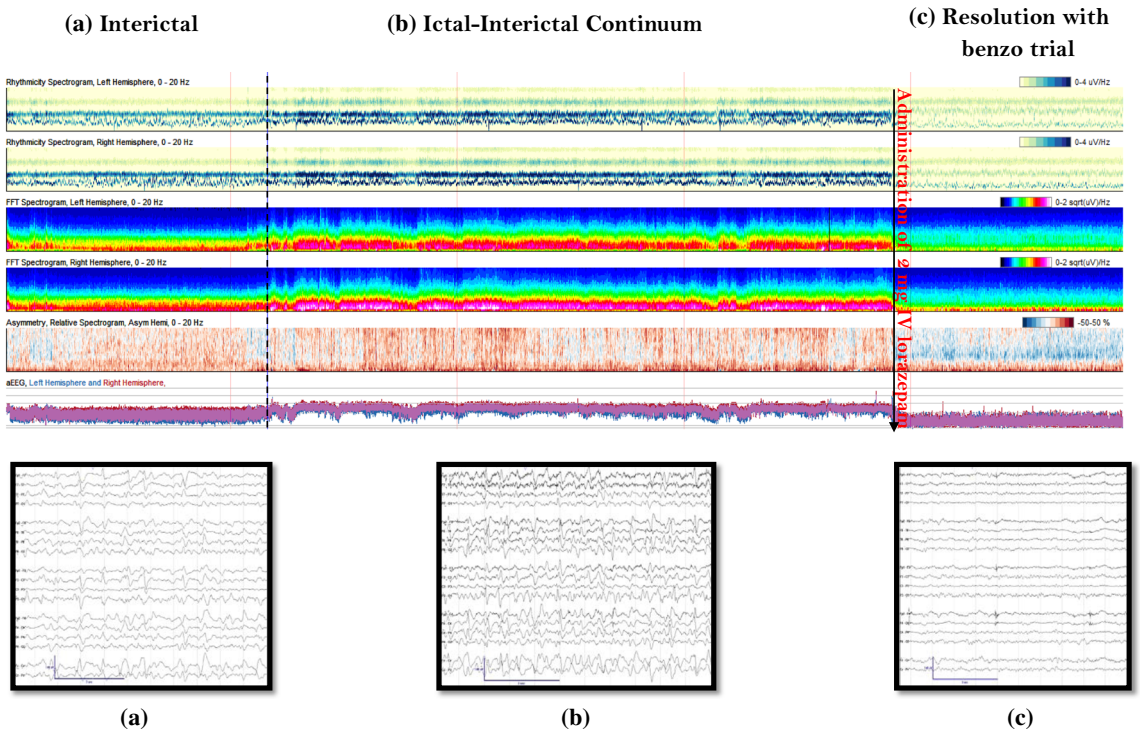


Fig. 4. Illustrates a 6-h epoch of cEEG. The top portion is a snapshot of the quantitative EEG (qEEG) as seen on Persyst 12. The bottom portion shows three separate raw EEG snap shots, 10 seconds each, with sensitivity: 7 uV; low-frequency filter: 1 Hz; high-frequency filter: 70 Hz; and notch filter turned off: (**a**) the interictal portion with poorly demarcated generalized periodic discharges (GPDs) at approximately 1 Hz; (**b**) worsening of EEG background with clear increase in frequency (up to 2.5 Hz) and amplitude of the GPDs. This information can also be obtained from the qEEG, where there is a clear increase in rhythmicity (top 2 rows), power (on color density spectral array (CSDA); middle 2 rows), and amplitude (on amplitude integrated EEG (aEEG); bottom row); (**c**) resolution of GPDs with appearance of rudimentary sleep architecture after administration of lorazepam. qEEG shows a decrease in the previously seen rhythmicity, power, and amplitude.

be reasonable to initiate conventional AED prophylaxis without escalation to treatment dosing and continue to monitor the patient with cEEG. If the medical conditions are being actively treated (e.g., antibiotics, dialysis) and have the potential to be reversed, then there will be clinical and/or EEG improvement to help guide further management. Should the pattern worsen or become clearly ictal, despite medical optimization, then a more aggressive treatment path, as outlined Fig. 1, may be considered.

Compared to GCSE, evidence supporting an aggressive treatment approach is less robust in the setting of NCS or NCSE and almost nonexistent when it comes to ictal-interictal continuum. Adopting an aggressive approach in these cases should involve a discussion with the patient's family so as to set realistic expectations as well as potentially prepare for complications relating to intubation, and the potential for a prolonged hospital course. More importantly, there should be a clear line of communication between the electroencephalographers interpreting the EEG and the ICU team responsible for making treatment decisions. Interpreting cEEG reports can be daunting and fraught with

ambiguity, especially when terms such as 'ictal-interictal continuum' are used. At our institution, we have found it extremely beneficial for teams to have a visual discussion of the overnight EEG findings, much like reviewing imaging with a radiologist, rather than just relying on the technical jargon in the report. For example, a single glance at the quantitative portion of Fig. 4 and concurrent raw EEG paints a clearer portrait for the ICU team.

With an astronomical increase in cEEG monitoring and the use of ICU EEG terminology being adopted nationally and internationally, we are now able to better define the EEG patterns which may lie on the continuum, i.e., potentially ictal. This is a crucial step, as it facilitates communication across centers, which in turn will hopefully drive the next decade of research in this field. However, the true clinical implications of the ictal-interictal continuum may not fully unravel until we can identify a reliable biomarker for neuronal injury. Until that point, less may be more, with individualizing care based on clinical context and ancillary information.

Compliance with Ethical Standards

Conflict of Interest

Adithya Sivaraju reports no conflicts of interest.

Emily J. Gilmore is supported by Yale's Center for Clinical Investigation CTSA Grant (ULTR000142), Yale's Claude D. Pepper Older Americans Independence Center (P30AG021342 NIH/NIA), American Brain Foundation, and the National Institute of Health.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol. 2013;30:1–27.

This study laid the basis for standardized critical care EEG terminology and thereby providing the opportunity for collaborative research.

2. Young G, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variable associated with mortality. Neurology. 1996;47:83–9.
3. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62:1743–8.
4. Pandian JD, Cascino GD, So EL, Manno E, Fulgham JR. Digital video-electroencephalographic monitoring in the neurological-neurosurgical intensive care unit: clinical features and outcome. Arch Neurol. 2004;61:1090–4.
5. Kaplan PW. Nonconvulsive status epilepticus in the emergency room. Epilepsia. 1996;37:643–50.
6. Chong DJ, Hirsch LJ. Which EEG patterns warrant treatment in the critically ill? Reviewing the evidence for treatment of periodic epileptiform discharges and related patterns. J Clin Neurophysiol. 2005;22:79–91.

7. Kaplan PW. EEG criteria for nonconvulsive status epilepticus. Epilepsia. 2007;48 Suppl 8:39–41.
8. Bauer G, Trinka E. Nonconvulsive status epilepticus and coma. Epilepsia. 2010;51:177–90.
9. Sutter R, Kaplan PW. Electroencephalographic criteria for nonconvulsive status epilepticus: synopsis and comprehensive survey. Epilepsia. 2012;53 Suppl 3:1–51.
10.•• Beniczky S, Hirsch LJ, Kaplan PW, Pressler R, Bauer G, Aurlien H, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. Epilepsia. 2013;54 Suppl 6:28–9.

First effort towards the development of a unified terminology for non convulsive status epilepticus.

11. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17:3–23.
12. Jirsch J, Hirsch LJ. Nonconvulsive seizures: developing a rational approach to the diagnosis and management in the critically ill population. Clin Neurophysiol. 2007;118:1660–70.
13. Gerber PA, Chapman KE, Chung SS, Drees C, Maganti RK, Ng YT, et al. Interobserver agreement in the interpretation of EEG patterns in critically ill adults. J Clin Neurophysiol. 2008;25:241–9.
14.•• Gaspard N, Hirsch LJ, LaRoche SM, Hahn CD, Westover MB, Critical Care EEGMRC. Interrater agreement for critical care EEG terminology. Epilepsia. 2014;55:1366–73.

This study validated the critical care EEG terminology, which in turn has helped better identify and understand certain EEG patterns of uncertain significance.

15.• Gaspard N, Manganas L, Rampal N, Petroff OA, Hirsch LJ. Similarity of lateralized rhythmic delta activity to periodic lateralized epileptiform discharges in critically ill patients. JAMA Neurol. 2013;70:1288–95.

This study showed that lateralized rhythmic delta activity in critically ill is associated with high risk of acute seizures.

16. Lansberg MG, O'Brien MW, Norbash AM, Moseley ME, Morrell M, Albers GW. MRI abnormalities associated with partial status epilepticus. Neurology. 1999;52:1021–7.
17. Chu K, Kang DW, Kim JY, Chang KH, Lee SK. Diffusion-weighted magnetic resonance imaging in nonconvulsive status epilepticus. Arch Neurol. 2001;58:993–8.
18. Kavuk I, Koeppen S, Agelink M, Dorfler A, Limmroth V, Diener HC. Transient MRI abnormalities associated with partial status epilepticus. J Neurol. 2004;251:1156–7.
19. Szabo K, Poepel A, Pohlmann-Eden B, Hirsch J, Back T, Sedlaczek O, et al. Diffusion-weighted and perfusion MRI demonstrates parenchymal changes in complex partial status epilepticus. Brain. 2005;128:1369–76.
20. Di Bonaventura C, Bonini F, Fattouch J, Mari F, Petrucci S, Carni M, et al. Diffusion-weighted magnetic resonance imaging in patients with partial status epilepticus. Epilepsia. 2009;50 Suppl 1:45–52.
21. Katramados AM, Burdette D, Patel SC, Schultz LR, Gaddam S, Mitsias PD. Periictal diffusion abnormalities of the thalamus in partial status epilepticus. Epilepsia. 2009;50:265–75.
22. Chatzikonstantinou A, Gass A, Forster A, Hennerici MG, Szabo K. Features of acute DWI abnormalities related to status epilepticus. Epilepsy Res. 2011;97:45–51.
23. Huang YC, Weng HH, Tsai YT, Huang YC, Hsiao MC, Wu CY, et al. Periictal magnetic resonance imaging in status epilepticus. Epilepsy Res. 2009;86:72–81.
24. DeGiorgio CM, Correale JD, Gott PS, Ginsburg DL, Bracht KA, Smith T, et al. Serum neuron-specific enolase in human status epilepticus. Neurology. 1995;45:1134–7.
25. DeGiorgio CM, Gott PS, Rabinowicz AL, Heck CN, Smith TD, Correale JD. Neuron-specific enolase, a marker of acute neuronal injury, is increased in complex partial status epilepticus. Epilepsia. 1996;37:606–9.
26. DeGiorgio CM, Heck CN, Rabinowicz AL, Gott PS, Smith T, Correale J. Serum neuron-specific enolase in the major subtypes of status epilepticus. Neurology. 1999;52:746–9.
27. Claassen J. How I treat patients with EEG patterns on the ictal-interictal continuum in the neuro ICU. Neurocrit Care. 2009;11:437–44.
28. Waziri A, Claassen J, Stuart RM, Arif H, Schmidt JM, Mayer SA, et al. Intracortical electroencephalography in acute brain injury. Ann Neurol. 2009;66:366–77.
29. Pohlmann-Eden B, Hoch DB, Cochius JI, Chiappa KH. Periodic lateralized epileptiform discharges—a critical review. J Clin Neurophysiol. 1996;13:519–30.
30. Tellez-Zenteno JF, Pillai SN, Hill MD, Pillay N. Chronic PLEDs with transitional rhythmic discharges (PLEDs-plus) in remote stroke. Epileptic Disord. 2007;9:164–9.
31. Westmoreland BF, Klass DW, Sharbrough FW. Chronic periodic lateralized epileptiform discharges. Arch Neurol. 1986;43:494–6.
32. Hughes JR. Periodic lateralized epileptiform discharges: do they represent an ictal pattern requiring treatment? Epilepsy Behav. 2010;18:162–5.
33. Terzano MG, Parrino L, Mazzucchi A, Moretti G. Confusional states with periodic lateralized epileptiform discharges (PLEDs): a peculiar epileptic syndrome in the elderly. Epilepsia. 1986;27:446–57.
34. Handforth A, Cheng JT, Mandelkern MA, Treiman DM. Markedly increased mesiotemporal lobe metabolism in a case with PLEDs: further evidence that PLEDs are a manifestation of partial status epilepticus. Epilepsia. 1994;35:876–81.
35. Assal F, Papazyan JP, Slosman DO, Jallon P, Goerres GW. SPECT in periodic lateralized epileptiform discharges (PLEDs): a form of partial status epilepticus? Seizure. 2001;10:260–5.

36. Bozkurt MF, Saygi S, Erbas B. SPECT in a patient with postictal PLEDs: is hyperperfusion evidence of electrical seizure? Clin Electroencephalogr. 2002;33:171–3.
37.• O'Rourke D, Chen PM, Gaspard N, Foreman B, McClain L, Karakis I, Mahulikar A, Westover MB. Response Rates to Anticonvulsant Trials in Patients with Triphasic-Wave EEG Patterns of Uncertain Significance. Neurocrit Care. 2015.
This study discussed the significance and management of the controversial Triphasic—Wave EEG patterns.
38. Drislane FW, Lopez MR, Blum AS, Schomer DL. Detection and treatment of refractory status epilepticus in the intensive care unit. J Clin Neurophysiol. 2008;25:181–6.