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Ictal Interictal Continuum Patterns

Gamaleldin M. Osman, MD[1]
Davi F. Araújo, MD-candidate[2]
Carolina B. Maciel, MD[3,4,*]

Address
[1]Department of Neurology, Henry Ford Hospital, Detroit, Michigan, 48202, USA
[2]Federal University of Ceará School of Medicine, Fortaleza, CE, 60430-160, Brazil
[3]Department of Neurology. Neurocritical Care Division, Yale University School of Medicine, New Haven, CT, 06520, USA
[*,4]Department of Neurology, Neurocritical Care Division, McKnight Brain Institute, 1149 Newell Dr/L3-185, Gainesville, FL, 32610, USA
Email: carolina.maciel@yale.edu; carolina.maciel@ufl.edu

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Abstract

Purpose of review To present data available on the epidemiology and significance of rhythmic and periodic patterns that lie on the ictal interictal continuum and propose an algorithm for the clinical approach to patients exhibiting these patterns.
Recent findings There is accumulating evidence on the prognostic implications of various rhythmic and periodic patterns in the critically ill population. These patterns are not only associated with increased seizure risk but have also been associated with worse outcome and increased long-term risk of epilepsy in recent studies. There is emerging evidence suggesting that certain EEG features as well as ancillary studies including serum, neuroimaging, and invasive multimodality monitory can assist in the risk stratification of neuronal injury associated with these patterns, allowing for a targeted approach to these patterns.
Summary We present a case illustrating the clinical nuances of these patterns. We propose an algorithm for a personalized and targeted approach to ictal interictal patterns based on risk stratification according to clinical, EEG, imaging, and invasive monitoring markers.

Introduction

Continuous electroencephalogram (cEEG) is a non-invasive tool that provides a unique opportunity for monitoring brain activity in real-time manner. The primary indication of cEEG is the detection of nonconvulsive seizures and the evaluation of paroxysmal events; its use has now expanded to include ischemia detection in selected neurocritically ill patients and in neuroprognostication, as recognized by the American Clinical Neurophysiology Society (ACNS) [1]. The widespread use of cEEG has allowed for the recognition of the frequent occurrence of electrographic seizures and of rhythmic and periodic patterns in critically ill patients. Determining the ictal versus interictal nature of these patterns and developing the next steps in the plan of care of such patients can be quite challenging in practice.

The ACNS has proposed a unified nomenclature for describing rhythmic and periodic patterns, aiming at creating a universal language for defining those patterns and streamline research [2]. A summary of main terms and modifiers included in the most recent version of this nomenclature is displayed in Table 1. Patterns are described based on their location (main term 1) and type of recurring discharges (main term 2). The three main pattern types include recurring discharges of relatively uniform morphology and are divided into periodic discharges (PD), rhythmic delta activity (RDA), and spike-and-wave or sharp-and-wave discharge (SW). In PDs, the discharges occur at nearly regular intervals with a clearly defined inter-discharge interval, whereas in RDA and SW, there is no intervening inter-discharge interval. The SW discharges are formed of spike, polyspikes, or sharp waves, immediately followed by a slow wave in a regularly repeating and alternating manner (e.g., spike-wave, spike-wave, spike-wave). Multiple modifiers can be used to characterize other features of the pattern of interest. The interrater agreement (IRA) for describing these patterns was nearly perfect for main terms 1 and 2, moderate or substantial for most modifiers, and fair for evolution according to one recent study [3]. The fair IRA for evolution can be partially explained by the provision of short epochs in which evolution can be difficult to appreciate in this study.

There have been multiple proposed sets of criteria for defining electrographic seizures and nonconvulsive status epilepticus (NCSE). The current and most widely used criteria were initially proposed by Young et al. in 1996 and have gone through multiple revisions since the original publication [4]. The most recent revision was proposed at the 4th London-Innsbruck Colloquium on Status Epilepticus in Salzburg, 2013, and is commonly referred to as the Salzburg criteria (Table 2) [5]. Based on these criteria, epileptiform discharges occurring at a rate of more than 2.5 Hz and epileptiform or rhythmic

Table 1. Standardized critical care EEG terminology for rhythmic and periodic patterns

Main term # 1	Main term #2	Plus modifiers
Generalized (G)	Periodic discharge (PD)	+R
Lateralized (L)	Rhythmic delta activity (RDA)	+F
Bilateral independent (BI)	Spike-and-wave or sharp-and-wave (SW)	+FR +S +F +FS (Top 3 modifiers apply for PDs while bottom 3 apply for RDA)
Multifocal (Mf)		

Adapted from Hirsch LJ et al. [2]
"+F" includes PDs or RDA with superimposed fast frequency discharges. "+R" includes PDs with superimposed rhythmic activity. "+FR" includes PDs associated with both prior features. "+S" includes RDA intermixed with spikes or sharp waves as well as sharply contoured rhythmic delta activity, while "+FS" includes RDA with both "+F" and "+S" features. Other modifiers specify pattern's prevalence, frequency of discharges, duration, number of phases, sharpness, amplitude (relative to inter-discharge intervals and absolute), polarity, whether pattern display activation by stimulus, and whether there is fluctuation or evolution in patterns. Some modifiers are only applicable to some main terms, for instance, relative amplitude is only applicable to PD and not to RDA or SW.

Table 2. Salzburg criteria for electrographic seizures and nonconvulsive status epilepticus

EEG data

EEG changes fulfilling the criteria have to be continuously present for ≥ 10 s. Criteria not applicable to physiological graphoelements.

A: Patients without known epileptic encephalopathy (at least ONE of the criteria 1–3 should be fulfilled for diagnosis of NCSE)

1. EDs > 2.5 Hz (i.e., > 25 EDs in "worst" 10-s epoch)
2. Typical ictal spatiotemporal evolution of:
   - –(2a) EDs OR
   - –(2b) Rhythmic activity (> 0.5 Hz)
3. Subtle ictal clinical phenomena with:
   - –(3a) EDs OR
   - –(3b) Rhythmic activity (> 0.5 Hz)
4. If criteria 1–3 are not fulfilled, but one of the following patterns is present, apply appropriate AED(s) after careful consideration of clinical situation and document response:
   - –(4a) EDs ≤ 2.5 Hz with fluctuation OR
   - –(4b) Rhythmic activity (> 0.5 Hz) with fluctuation OR
   - –(4c) Rhythmic activity (> 0.5 Hz) without fluctuation

B: Patients with known epileptic encephalopathy

In addition to the criteria above (A), these patients have to fulfill one of the following:

- –Increase in prominence or frequency when compared to baseline *with* observable change in clinical state
- –Improvement of clinical and EEG features with IV ASDs (see A.4.)

Clinical data

Add clinical information for establishing the diagnosis of NCSE:

- –Transition from premorbid to current ill state within minutes to hours
- –Patient did not improve significantly in last minutes to hours, apart from waxing and waning.
- –No information from brain imaging sufficiently explaining EEG pattern (e.g., brain stem hemorrhage)
- –No metabolic/toxicological derangement sufficiently explaining EEG pattern (e.g., acute renal or liver failure)

ASDs anti-seizure drugs, *EDs* epileptiform discharges
Reproduced from Leitinger M et al. [5] (with permission from Elsevier)

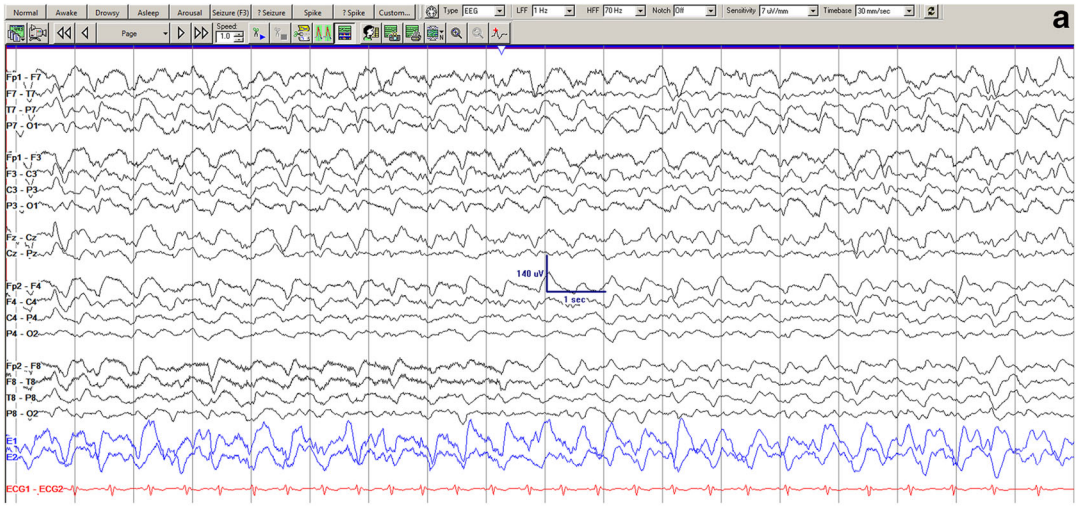
discharges associated with typical spatiotemporal evolution or subtle clinical phenomena are considered ictal patterns (i.e., NCSE). However, there are a variety of rhythmic and periodic patterns with a high degree of uncertainty regarding their ictal nature. These present a diagnostic and therapeutic dilemma to electroencephalographers, intensivists, and general neurologists taking care of these patients. The term "ictal interictal continuum" (IIC) was first introduced by Pohlmann-Eden et al. in 1996, who described periodic lateralized epileptiform discharges (formerly called PLEDs, now referred to LPDs according to the new ACNS nomenclature) as "an electrographic signature of a dynamic pathophysiological state in which unstable neurobiological processes create an ictal interictal continuum, with the nature of the underlying neuronal injury, the patient's preexisting propensity to have seizures, and the coexistence of any acute metabolic derangements all contributing to whether seizures occur or not" [6]. The use of the term has now expanded to include other rhythmic and periodic patterns that are not definitely ictal, but could still be, and that may contribute to neuronal injury in certain clinical settings. There is no consensus agreement on IIC patterns definition, but these generally include rhythmic and periodic patterns occurring at a rate of 1–2.25 Hz—particularly

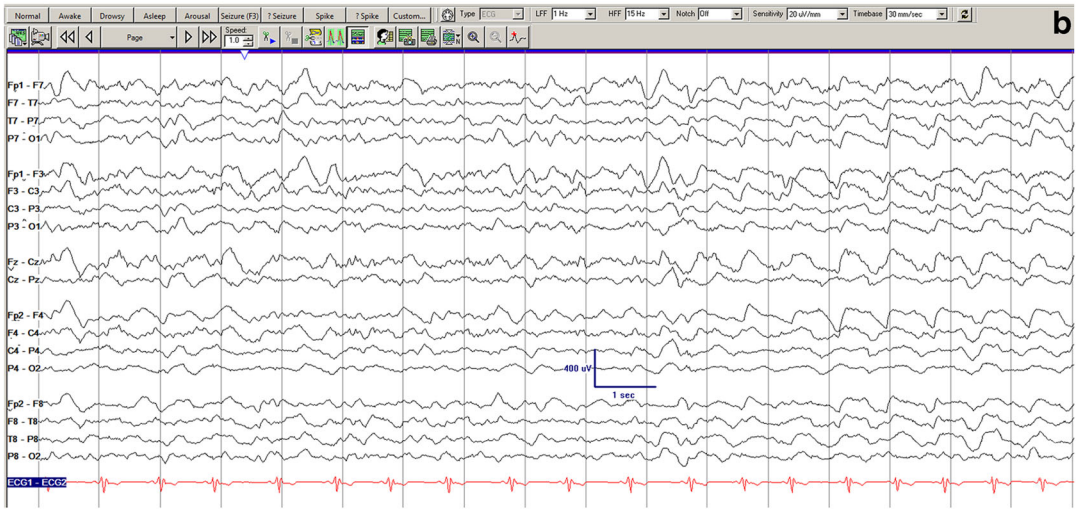
when fluctuating and including "plus modifiers" (Table 1). In this review, we shed some light on the data available on the significance of those patterns and the approach to managing patients harboring them.

Case report

A 24-year-old man was admitted to the hospital following a witnessed first lifetime generalized tonic-clonic seizure while standing in line at a restaurant. According to the family, he was experiencing forgetfulness and difficulty maintaining concentration during the preceding weeks. They denied any mouth or hand automatisms, behavior or speech arrest, or limb shaking. On admission, he received 2000 mg of levetiracetam and was started on 750 mg every 12 h as maintenance therapy. A brain magnetic resonance imaging (MRI) demonstrated a cortically based right frontal 3.1 × 2.3 × 3.0 cm mass with peripheral and internal nodular enhancing foci for which he underwent an uneventful gross total resection (pathology consistent with World Health Organization grade III anaplastic oligoastrocytoma) 2 days later. Immediately following surgery, he was noted to have mild left hemiparesis, which gradually improved. On post-operative day 1, he experienced severe nausea and was noted to be more somnolent. A repeat noncontrast head CT demonstrated expected post-surgical changes with some blood in the surgical cavity. Given the concern for subclinical seizures possibly related to post-operative irritation and edema, levetiracetam dosing was increased (received a total of 2500 mg in 12 h) and 1 g/Kg of mannitol was administered; both interventions led to no change in the exam. He subsequently developed aphasia and on the morning of post-operative day 2, he was connected to continuous EEG, which demonstrated left temporal fluctuating lateralized rhythmic delta activity, at times spreading broadly throughout the left hemisphere with embedded spikes (LRDA+S) reaching 2 Hz. Since there was no clear onset/offset to suggest unequivocal seizures, nor was the pattern sustained at > 2.5 Hz to qualify as NCSE, this pattern was on the ictal end of the IIC (Fig. 1a–c). Given the presence of this potential ictal pattern despite a

Fig. 1. Electroencephalographic evolution ictal interictal continuum following treatment. All epochs demonstrate at least 15 s of recording captured with high-pass filter at 1 Hz, low-pass filter at 70 Hz, sensitivity at 7 uV/mm, notch filter off, paper speed of 30 mm/s, and displayed in longitudinal bipolar montage. **a** Left hemispheric lateralized bilateral asymmetric rhythmic delta activity with embedded spikes sustaining 2 Hz lying on the ictal end of the ictal interictal continuum. **b** Left frontotemporal periodic discharges with associated rhythmicity at 1–1.5 Hz. These patterns waxed and waned significantly (rhythmic delta activity and periodic discharges merging into one another). **c** Comprehensive trend panel on quantitative EEG displaying 4 h of recording capturing the phenytoin load (red arrow). Gradual decrease in rhythmicity and power is seen following treatment on the rhythmicity and color density power spectra, respectively. Gradual decrease in amplitude is also seen on the bottom panel corresponding to amplitude integrated EEG (aEEG). As demonstrated by the raw EEG on Fig. 1a, b, the pattern is broadly distributed; however, left predominance of hyperexcitability is noted on the left across all trends, in particular on the relative asymmetry spectrogram with increased blue hue on theta frequencies band (red box). **d** Fragmentation of hyperexcitability is seen as waveforms lose sharp component and rhythmicity approximately 30 min after phenytoin load. **e** Continued gradual improvement is seen with increase in faster frequencies and better organization with emergence of posterior dominant rhythm (particularly on the left). Note ongoing attenuation of faster frequencies in addition to slowing on the right frontocentral region despite skull defect consistent with underlying structural cortical and subcortical dysfunction in this region.


a
Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fz - Cz
Cz - Pz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
E1
E2
ECG1 - ECG2
140 uV
1 sec


b
Fp1 - F7
F7 - T7
T7 - P7
P7 - O1
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fz - Cz
Cz - Pz
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fp2 - F8
F8 - T8
T8 - P8
P8 - O2
ECG1 - ECG2
400 uV
1 sec

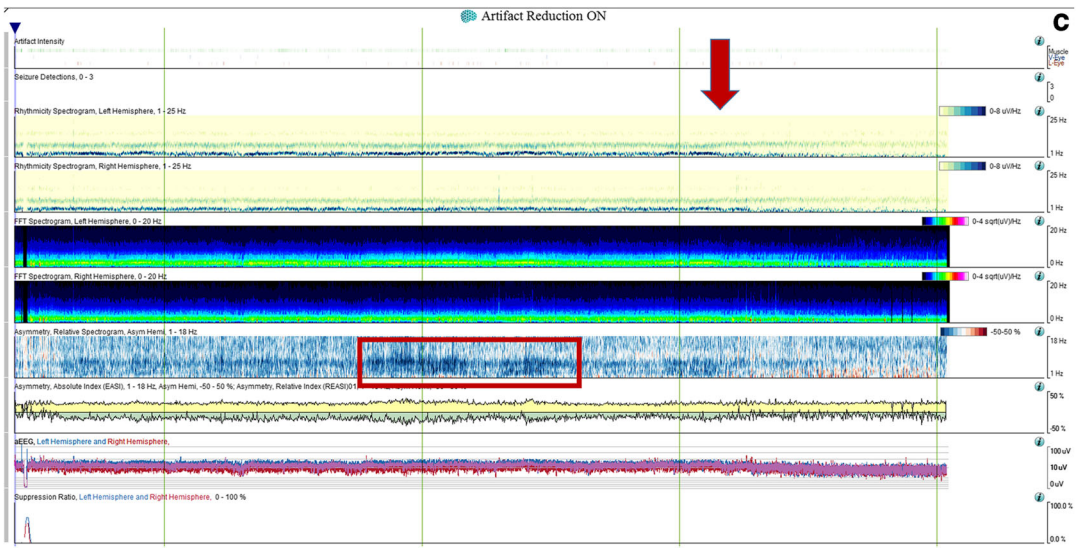
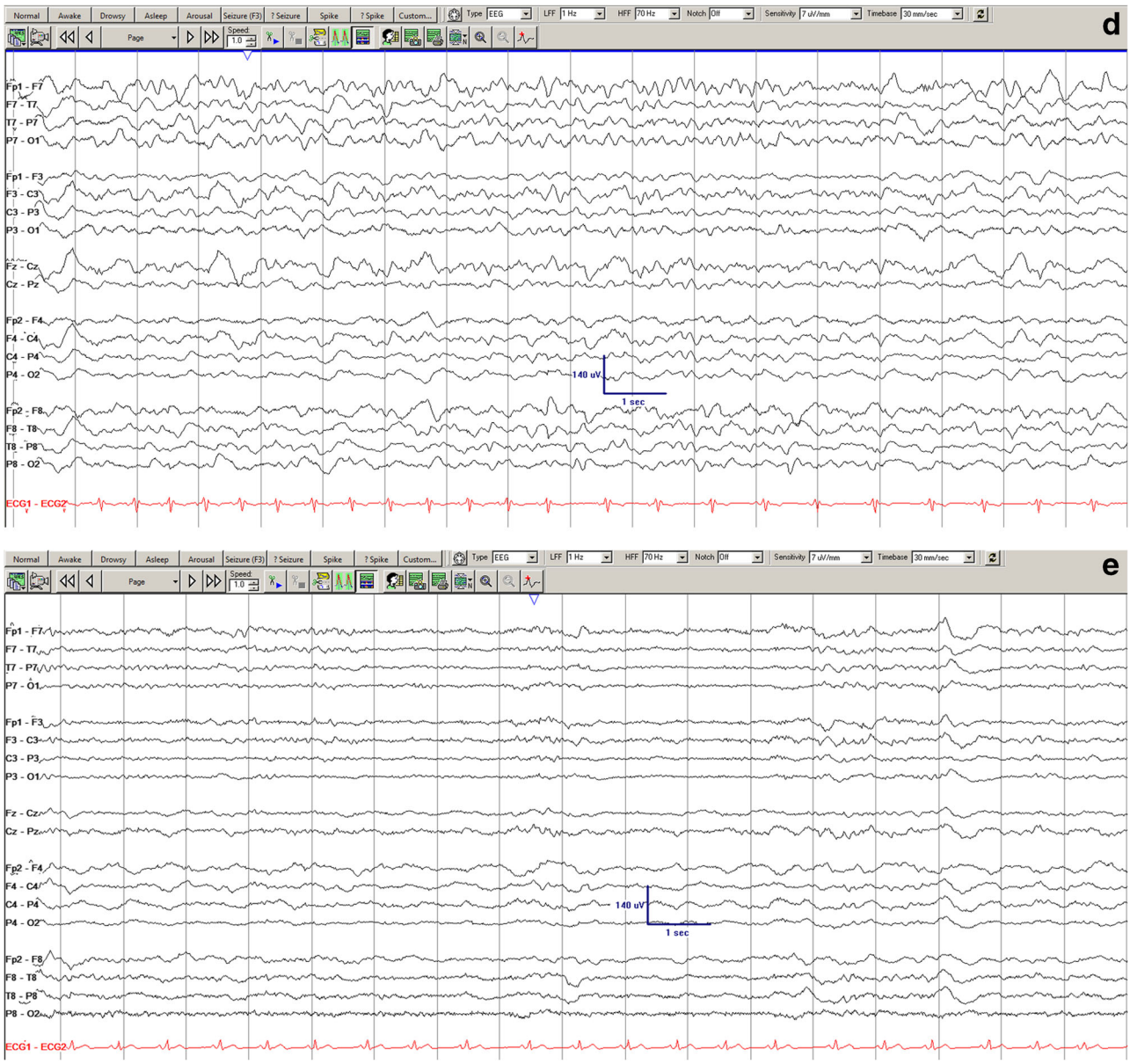

c
Artifact Reduction ON
Artifact Intensity
Seizure Detections, 0 - 3
Rhythmicity Spectrogram, Left Hemisphere, 1 - 25 Hz
Rhythmicity Spectrogram, Right Hemisphere, 1 - 25 Hz
FFT Spectrogram, Left Hemisphere, 0 - 20 Hz
FFT Spectrogram, Right Hemisphere, 0 - 20 Hz
Asymmetry, Relative Spectrogram, Asym Hemi, 1 - 18 Hz
Asymmetry, Absolute Index (EASI), 1 - 18 Hz, Asym Hemi, -50 - 50 %; Asymmetry, Relative Index (REASI)01
aEEG, Left Hemisphere and Right Hemisphere,
Suppression Ratio, Left Hemisphere and Right Hemisphere, 0 - 100 %

Fig. 1 (continued)



therapeutic dose of levetiracetam (3000 mg/24 h), a second agent was added. Approximately 45 min following a 15 mg/kg load of phenytoin, there was a significant electrographic response to treatment with a slow and gradual clinical improvement over the course of hours (Fig. 1d, e).

This case has many notable points: (a) a clinical response to anti-seizure therapeutic trial seals a diagnosis of NCSE despite the fact that the electroencephalographic pattern did not meet criteria for unequivocal NCSE (sustained discharges > 2.5 Hz); (b) the clinical, and electroencephalographic, response to a therapeutic trial may be gradual over hours; (c) the fact that the patient did not

respond to adequate doses of levetiracetam (although the patient was not monitored on EEG when this drug was given) does not rule out the potential ictal nature of his symptoms; (d) the epileptogenic focus may be remote from any obvious structural abnormality: in this case, the patient had a right frontal tumor resected (which is an obvious potential epileptogenic source); however, the epileptogenic focus was contralateral to his lesion.

Epidemiology

Rhythmic and periodic patterns have been reported to occur in 30–37% of patients undergoing cEEG monitoring [7, 8]. In these studies, patterns included lateralized periodic discharges (LPDs; previously called PLEDs), bilateral independent periodic discharges (BIPDs; previously called BIPLEDs), generalized periodic discharges (GPDs; previously GPEDs), lateralized rhythmic delta activity (LRDA), and generalized rhythmic delta activity (GRDA). Although less commonly seen, multifocal (Mf-) periodic discharges and rhythmic delta activity and any SW are also included in rhythmic and periodic patterns. LPDs are primarily seen in the setting of acute structural brain lesions, most commonly ischemic stroke [9, 10, 11], and tend to resolve over weeks following acute injury or seizure [12]. BIPDs most commonly occur in patients with structural brain injury as well, though they are more frequently seen in the setting of bilateral brain lesions [11]. On the other hand, GPDs are most frequently seen in the setting of metabolic derangements [13, 14, 15]. Other causes for GPDs include acute brain injuries [13, 14, 15], post-anoxic encephalopathy [13, 16], Creutzfeld Jacob disease (CJD) [15], subacute sclerosing panencephalitis (SSPE) [15], and toxic exposure such as cefepime [17, 18] and lithium [19]. LRDA, a recently described pattern, is seen most frequently in the setting of acute or remote brain injury [20]. Frontally predominant GRDA (GRDA; previously termed frontal intermittent rhythmic delta activity; FIRDA)—the most common form of GRDA—is considered a nonspecific pattern reflective of various degrees of encephalopathy [21]. Notably, most studies investigating this pattern predate the current ACNS terminology and the term "FIRDA" was more loosely applied to any rhythmic appearing frontally predominant delta frequency discharges; many of which would not fulfill the current ACNS criteria for GRDA. Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs)—initially described by Hirsch et al. in 2004—encompass rhythmic, periodic, or ictal-appearing discharges induced by alerting stimuli [22]. This term was replaced in the ACNS terminology by a modifier denoting whether the pattern was spontaneous or stimulus-induced (e.g., SI-LPDs, SI-GPDs, and so forth) [2]. Often, SIRPIDs are not associated with any clinical correlate, but there have been few reports of focal motor seizures induced by alerting stimuli [23] contradicting the common notion of stimulus-induced patterns being exclusively interictal in nature.

Significance

Various rhythmic and periodic patterns are associated with increased seizure risk. The incidence of seizures during the course of acute illness ranges from 45

to 85% among patients with LPDs [7–11, 20], 43–78% among patients with BIPDs [11, 24], 11–89% among patients with GPDs [7, 8, 13–15], and 35–63% among patients with LRDA on EEG [8, 20]. Meanwhile, GRDA—even when associated with a plus modifier—was not associated with increased seizure risk, based on one multi-center retrospective study including 927 patients [25••]. Thus, GRDA is usually not considered a pattern that lies on the ictal interictal continuum. In addition to their long recognized association with seizures, periodic discharges have been associated with worse short-term outcome in patients with poor-grade subarachnoid hemorrhage (SAH) [26], intracerebral hemorrhage (ICH) [27], and even in patients with no evidence of acute brain injury [28]. The significance of SIRPIDs remains controversial. SIRPIDs were not associated with in-hospital mortality after controlling for confounders in a recent multicenter study including 416 critically ill patients undergoing cEEG [29••], while another recent study reported SIRPIDs as a poor prognostic determinant in patients with post-anoxic encephalopathy, particularly when recorded during therapeutic hypothermia [30]. Of importance, one recent study demonstrated that IIC patterns were strongly associated with the development of delayed cerebral ischemia in patients with SAH [31]. Furthermore, a recent prospective study demonstrated an association of LPDs on EEG with an increased risk for long-term development of epilepsy [32]. It is important to note that a causal relationship cannot be drawn from these data, and it remains debatable whether IIC patterns represent an ictal or interictal phenomena, or merely an epiphenomena of underlying structural or functional neuronal injury. Consequently, there is no consensus on whether these patterns need to be treated as seizures or not, and how aggressive a clinician should be in treating those patterns if the decision is made to treat them at all. Further, to this date, data guiding the pharmacologic approach to patients with IIC patterns, comparing watchful monitoring with therapeutic trials, and exploring how aggressively therapeutic trials should be implemented are lacking. Treatment algorithms are largely based on experts' opinion and extrapolated from studies with NCSE.

Arguments for the ictal nature of certain IIC patterns

1- Focal clonic movements—including *epilepsia partialis continua*—can be seen time-locked to LPDs (ictal LPDs) and represent brief seizures, particularly in those with fronto-central fields [33]. The lack of clinical correlate in patients with LPDs localized to other regions could therefore be due to involvement of "silent brain regions." Negative motor and sensory phenomena including hemiparesis, aphasia, amnesia, apraxia, and cortical blindness have been reported in association with LPDs [34]; this further substantiates the evidence supporting this hypothesis. Clinical correlates in ictal LPDs are seizures and may resolve completely upon administration of anti-seizure medications [35] (although some cases may be refractory and hard to treat), denoting the ictal nature of LPDs in this setting.

2- There are multiple reports of clinical improvement coupled with EEG pattern resolution following intravenous (IV) benzodiazepine [36–39] or non-sedating anti-seizure drug [38] administration in patients with IIC

patterns associated with disturbed level of consciousness. We will further expand on medication trials later in this article.

3- IIC patterns have been reported in association with known imaging markers of status epilepticus. These include restricted diffusion on diffusion-weighted imaging (DWI) on MRI [40], increased regional cerebral flow on computed tomography (CT) [41], or MRI-perfusion studies [40, 41] as well as single-photon emission computed tomography (SPECT) imaging [40, 43], and regional hypermetabolism on fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans [44, 45]. FDG-PET hypermetabolism predicted electroclinical status epilepticus with 79% sensitivity and 100% specificity in IIC patients undergoing cEEG according to one recent study including 18 patients [45]. These changes often reversed with treatment in a similar fashion to what would be expected in the setting of unequivocal status epilepticus [40].

4- IIC patterns are frequently associated with markers of neuronal injury such as increased lactate/pyruvate ratio (LPR) and decreased glucose levels in cerebral microdialysate (a modality of invasive multimodal monitoring) [46]. Periodic discharges as well as nonconvulsive seizures were temporally associated with metabolic crisis—defined as increased LPR and concurrent focal neuroglycopenia—in patients with traumatic brain injury according to one recent study [46]. These findings raise the question whether these potentially avoidable (or treatable) findings could be targeted to mitigate the development of secondary neuronal injury in traumatic brain injury.

5- Periodic discharges have been reported as an intervening pattern in patients with unequivocal status epilepticus [47].

6- IIC patterns on scalp EEG can be associated with unequivocal seizures on simultaneous intracranial recordings using depth EEG. Claassen et al. analyzed intracortical EEG with simultaneous scalp EEG and multimodality physiological monitoring recordings, and demonstrated that up to 19% of seizures detected on depth EEG were associated with IIC patterns on scalp recordings [48].

Arguments for the interictal nature of certain IIC patterns

1- Rarely, chronic LPDs may be seen in patients with longstanding epilepsy in a similar fashion to other interictal patterns [49]. However, LPDs in this setting generally occur at a frequency of < 1 Hz, which would not fulfill our definition for IIC patterns. Nonetheless, one form of LRDA (temporal intermittent rhythmic delta activity—TIRDA), is a long-recognized interictal pattern seen in patients with temporal lobe epilepsy, particularly those with mesial temporal sclerosis[50]; this raises the possibility that their LRDA counterparts seen in ICU setting may represent similar interictal phenomena.

2- Electrographic seizures often emerge from periodic discharges similar to their emergence from other interictal patterns coupled with disappearance of periodic discharges, arguing for PDs being an interictal rather than an

ictal pattern. Similarly, one study using electrocorticography concurrently with scalp cEEG demonstrated disappearance of LRDA on scalp (pseudonormalization) correlating with intracranial seizure recording [51].

3- Periodic discharges are not consistently associated with the restricted diffusion on DWI imaging that is typically seen in patients with status epilepticus. In one recent study including 10 patients with LPDs, all 5 patients with electrographic seizures in addition to LPDs had restricted diffusion in the region of LPDs, whereas all other 5 patients with isolated LPDs had no areas of restricted diffusion [52]. Apparent diffusion coefficient (ADC) changes on MRI have been strongly correlated with the degree of seizure-induced neuronal injury in animal studies [53], and therefore, the lack of diffusion restriction associated with LPDs may suggest that these are interictal findings rather than unequivocally ictal, or at least "less malignant" ictal patterns potentially warranting less aggressive management. Further, there have been few reports of patients with SIRPIDs lacking the regional cerebral hyperperfusion that is typically seen in patients with unequivocal seizure activity [54, 55].

Taken altogether, these arguments on both sides suggest that *not all rhythmic and periodic patterns should be treated in the same way* and that certain patterns are more likely to be ictal (or more harmful) and may warrant more aggressive management with pharmacologic therapy.

Suggested approach to patients with rhythmic and periodic patterns on cEEG

The following is our suggested approach to these patterns (summarized in Figure 2):

1- Exclude clear ictal or interictal patterns:

Epileptiform discharges occurring at a frequency of ≥ 2.5 Hz and periodic discharges or rhythmic activity associated with unequivocal spatiotemporal evolution or subtle ictal clinical correlate are classified as ictal patterns [56, 57], and should be treated accordingly. On the other hand, most electroencephalographers agree that PDs or RDA occurring at a frequency of less than 1 Hz as well as static RDA without *plus* features are interictal. Patterns occurring at a frequency of 1–2.5 Hz, those with *plus* features, and/or displaying fluctuation are considered to lie on the IIC.

2- Identify EEG characteristics highly associated with seizures:

Certain EEG features are strongly associated with seizures and, when present, represent patterns that lie on the IIC. These include distinctive morphological features of the pattern as well as higher pattern frequency. Reiher et al. in 1991 classified PLEDs (now called LPDs) into two main subtypes: *PLEDs proper* and *PLEDs plus* [58]. PLEDs proper included periodic patterns not associated with rhythmic discharges, whereas PLEDs plus included those with superimposed rhythmic discharges, most commonly in the form of low amplitude fast frequency discharges. Electrographic seizures were seen in 74% of PLEDs plus patients, compared to only 6% of patients with PLEDs proper [58]. In a more recent retrospective study investigating EEG characteristics associated with

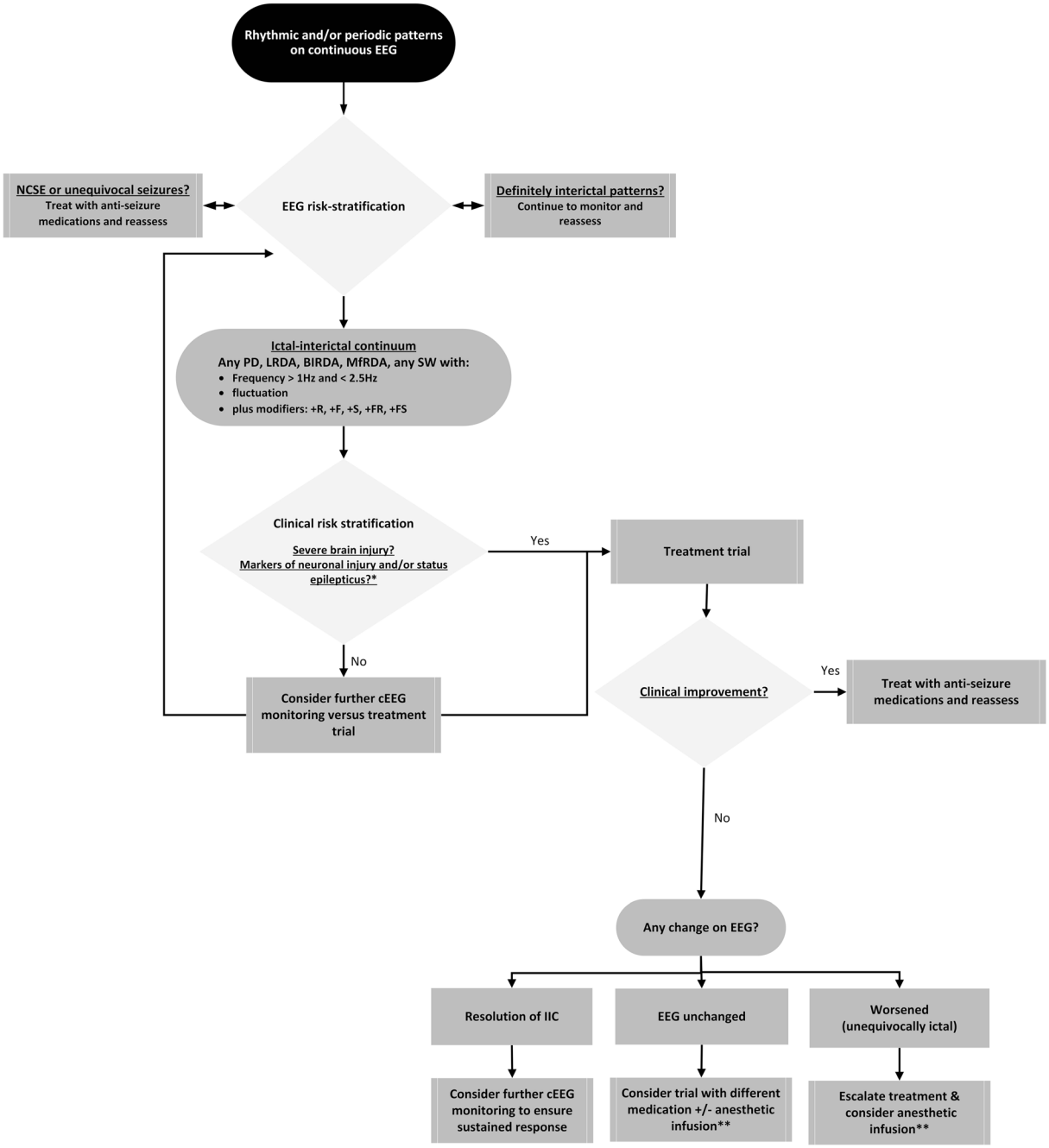


Fig. 2. Clinical approach to patients with rhythmic and periodic patterns. Single asterisk indicates the evaluation for markers of neuronal injury may include serum biochemical markers (e.g., neuron-specific enolase), neuroimaging, and/or multimodal invasive monitoring. The access to these resources varies across different institutions. Double asterisks indicate anesthetic infusions have been associated with an increased morbidity; thus, these treatments are often reserved for unequivocally ictal patterns (nonconvulsive status epilepticus). In selected cases, these may be considered if further aggressive treatment is warranted. EEG electroencephalogram (cEEG continuous electroencephalogram), IIC ictal interictal continuum, PD periodic discharges, RDA rhythmic delta activity (LRDA lateralized rhythmic delta activity, MfRDA multifocal rhythmic delta activity, BIRDA bilateral independent rhythmic delta activity), SW spike-wave.

seizures in 100 patients with LPDs on cEEG, patterns with superimposed rhythmic activity "LPD + R" were associated with the highest odds for developing status epilepticus and seizures (OR 13.91; CI 5.3–36.52; $P < 0.0001$). In the same study, patterns with associated fast activity "LPD + F" were also highly associated with unequivocal ictal activity (OR 5.16; 2.08–13.07; $P = 0.0004$), whereas LPDs bearing blunt morphology were not (OR 0.24 (CI 0.097–0.62; $P = 0.0036$) [59••]. Generalized periodic discharges (GPDs) and LRDA were associated with seizures in a frequency-dependent manner, where only frequencies > 1.5 Hz were associated with increased seizure risk in one in one multicenter retrospective study including 4772 patients undergoing cEEG monitoring [25••]. Further, LPDs, GPDs, and LRDA with *plus* features were more likely to be associated with seizures than those without [25••]. Another study demonstrated that PDs > 2 Hz in frequency were associated a decrease in the partial pressure of oxygen in interstitial brain tissue (PbtO2); this relationship was dependent on the frequency of discharges: PDs > 2 Hz were more likely to be associated with secondary neuronal injury from lower regional oxygen saturation [60]. In summary, when periodic and/or rhythmic patterns that lie on the IIC are identified on cEEG, a careful clinical risk stratification is in order: patients with high risk for secondary brain injury or those who have evidence of ongoing neuronal injury may be the ideal candidates for a therapeutic challenge.

3- Correlate pattern with ancillary studies that reflect ongoing neuronal injury and/or may represent status epilepticus:

Neuroimaging

One of the most useful approaches in investigating IIC patterns is to correlate the EEG with neuroimaging findings. Findings commonly seen in patients with status epilepticus include restricted diffusion on DWI imaging [52], increased regional perfusion on CT [41], MRI perfusion [40, 42] or SPECT imaging [40, 43], and hypermetabolism on PET scans [44, 45]. It is important, and particularly challenging, to distinguish these findings from those related to underlying illness; reversal of these changes following treatment further corroborates the hypothesis of them being a result of an ictal process.

Serum biomarkers

Elevation of serum markers of neuronal injury such as neuron-specific enolase (NSE) can often be seen in patients with SE, potentially serving as a marker of seizure-induced neuronal damage. Serum NSE levels correlated with severity of histological brain injury in a study using a rat model of status epilepticus [61]. Serum NSE levels generally peak 24–48 h after status epilepticus onset [62], regardless if nonconvulsive or convulsive, though focal status epilepticus with impaired consciousness (previously called CPSE) and subclinical status epilepticus are associated with the most significant NSE elevation [63]. Given the close association of NSE elevation with unequivocally ictal patterns, high titers in association with IIC patterns

may provide evidence to justify their management as an ictal pattern given the potential for ongoing neuronal injury.

Multimodality monitoring

Recent data have highlighted the role of invasive multimodality monitoring as an emerging tool for continuous monitoring of physiological parameters that act as markers of ongoing neuronal injury, possibly providing a window of opportunity for early intervention before irreversible neuronal injury ensues. Commonly employed modalities include intracranial EEG monitoring via intracortical mini-depth or subdural strip electrodes, intracranial pressure monitoring via intraventricular catheters or intraparenchymal probes, monitoring cerebral tissue oxygenation (PbtO2) via specialized probes, indirect cerebral oxygenation via jugular bulb oximetry, continuous cerebral blood flow monitoring via thermal diffusion probes, and monitoring regional metabolism via cerebral microdialysis. Claassen et al. demonstrated that only 19% of intracranial seizures were associated with IIC patterns on scalp EEG [48]; these were also associated with increases in heart rate, respiratory rate, and mean arterial pressure (MAP), as well as trends towards higher intracranial pressure and cerebral perfusion pressure [48]. In addition, PDs can be associated with metabolic crisis, and PDs > 2 Hz can be associated with regional hypoxia (see above) [60]. This suggests that high-frequency (> 2 Hz) periodic discharges place an increased metabolic demand, which in turn may lead to bioenergetic mismatch in the setting of acute brain injuries and may lead to secondary neuronal injury. These markers when detected in association with IIC patterns may provide evidence for these patterns being on the ictal end of the IIC, thus warranting aggressive management in selected cases. It is important to remark that the use of these modalities remains largely investigational, and a causal relationship between IIC patterns and neuronal injury cannot be drawn from available evidence at this point.

Treatment approach

There is no consensus agreement on how to treat IIC patterns given the paucity of available evidence comparing the performance of different therapeutic modalities. Our suggested approach includes a careful consideration of the potential risk of secondary neuronal injury from increased metabolic demand based on the primary acute brain injury; thus, this is a case-by-case risk stratification. Often, we recommend primary seizure prophylaxis with a non-sedating antiseizure medication using a standard maintenance regimen without a loading dose (e.g., levetiracetam 750 mg every 12 h). The escalation of pharmacologic therapy, including loading doses of the initial agent and the addition of a benzodiazepine trial, largely depends on the perceived ictal potential of the pattern characterized on EEG and its evolution over time, guided by the previously discussed risk factors and ictal correlates. Given the paucity of available data guiding management of those patterns, patterns thought to be

Table 3. Medications used in nonconvulsive status epilepticus

Drug	Initial or loading dose	Maintenance therapy	Caution/adverse effects
Lorazepam	IV abortive therapy 0.1 mg/kg in divided doses (max dose 4 mg per dose)	Most commonly used as abortive therapy	Hypotension, respiratory depression IV formulation contains propylene glycol which can lead to anion-gap metabolic acidosis
Diazepam	IV abortive therapy 0.15–0.25 mg/kg (max dose 10 mg per dose)	Most commonly used as abortive therapy	Hypotension, respiratory depression IV formulation contains propylene glycol which can lead to anion-gap metabolic acidosis PR route acceptable if no IV available
Phenobarbital	IV load 20 mg/kg (max rate 60 mg/min)	Adjust dosing by desired level 1–3 mg/kg/day in 2–3 divided dose	Hypotension, respiratory depression prolonged half-life (53–140 h) IV formulation contains propylene glycol which can lead to anion-gap metabolic acidosis Potent CYP inducer ➔ multiple drug interactions avoid in porphyria, hepatic disease, and renal impairment
Phenytoin	IV load 20 mg/kg (max rate 50 mg/min); can give extra 5–10 mg/kg after 10 min Check level 1 h after completion of infusion	Adjust dosing by desired level: 0.8 × weight in kg × (desired – measured total level) Start at 100 mg every 8 h	Hypotension, heart block, and asystole SJS/TEN, purple glove syndrome; avoid in porphyria and hepatic disease Potent CYP inducer ➔ multiple drug interactions Zero order kinetics ➔ high toxicity potential Highly protein bound
Fosphenytoin	IV load 20 mg PE/kg (max rate 150 mg PE/min); can give additional 5 mg/kg after 10 min Check level 2 h after completion of infusion	Similar as phenytoin	Favored over phenytoin for loading doses given decreased risk of cardiac toxicity Hypotension, heart block, and asystole SJS/TEN Potent CYP inducer ➔ multiple drug interactions Zero order kinetics ➔ high toxicity potential Highly protein bound avoid in porphyria
Valproic acid	IV load 40 mg/kg (max rate 6 mg/kg/min); can give extra 20 mg/kg after 10 min	Adjust dosing by desired level: 0.4 × weight in kg × (desired – measured total level) Start at 15-30 mg/kg/day divided as every 6 h	Hepatotoxicity, pancreatitis, thrombocytopenia, hyperammonemia, aplastic anemia (rare), SJS (rare); avoid in bleeding diathesis Enzyme inhibitor ➔ multiple drug interactions Highly protein bound

Table 3. (Continued)

Drug	Initial or loading dose	Maintenance therapy	Caution/adverse effects
Levetiracetam	IV load 60 mg/kg or 3000–4500 mg*	1000–4000 mg/day in divided doses (every 12 or every 6 h) HD 50% removed; dose every 12 h and add 50% of am dose to pm dose CRRT Consider 50% ↑ in total daily dose in 4 divided doses	Leukopenia and/or thrombocytopenia (rare)
Lacosamide	IV load 200 mg–400 mg over 15 min	100–600 mg/day in divided doses (every 12 or every 6 h)	Tachy- or bradyarrhythmias. Monitor PR interval with EKGs when using high doses
Anesthetic infusions**			
Midazolam	IV load 0.1–0.2 mg/kg over 5 min; may repeat every 5 min until seizure cessation (up to total of 2 mg/kg) May be administered via alternate routes: 0.2 mg/kg (up to 10 mg) IM, intranasal, or buccal	0.05–2.9 mg/kg/h	Hypotension, respiratory depression
Ketamine	IV load 1.5 mg/kg IV over 3–5 min (max 150 mg); may repeat every 5 min until seizure cessation (up to total of 4.5 mg/kg)	0.2–7.5 mg/kg/h	Non-GABA mediated activity provides a different mechanism of action. Sympathomimetic properties ➔ vasopressor sparing effects High doses require high volumes of infusion, use with caution in patients with volume overload
Pentobarbital	IV load 5 mg/kg (max rate: 50 mg/min); can give extra 5 mg/kg	0.5–5 mg/kg/h*	Hypotension, cardiorespiratory depression, paralytic ileus, immunosuppression Contains propylene glycol which can lead to anion-gap metabolic acidosis
Propofol	IV load 2–5 mg/kg; can repeat once	30–200 mcg/kg/min (some indicate 5–10 mg/kg/h, later reduced to 1–3 mg/kg/h)	Hypotension, cardiac failure, respiratory depression, acute pancreatitis, rhabdomyolysis, metabolic acidosis, renal failure (PRIS); contraindicated in young children; caution when using doses higher than 80 mcg/kg/min for periods > 48 h

This table contains commonly used drugs in clinical practice. Dose ranges vary widely in clinical practice and the choice of agents should be tailored to individual cases. Adapted from Brophy G et al. [77], Trinka E et al. [78], Glauser et al. [79], and from the Yale's treatment algorithm for status epilepticus

CRRT continuous renal replacement therapy, *HD* hemodialysis, *IV* intravenous, *PE* phenytoin equivalents, *PRIS* propofol related infusion syndrome, *SJS* Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis

*Some institutions use much higher doses, particularly in critically ill patients with an increased metabolism

**Use in refractory status epilepticus

on the ictal end of the IIC (see above) are usually managed in the same manner as NCSE. Table 3 provides a list of non-sedating and sedating anti-seizure medications used in NCSE, commonly used dosage ranges, and commonly encountered adverse events.

A therapeutic trial is a simple, yet underutilized, diagnostic and therapeutic test that involves administering sequential small doses of short-acting benzodiazepines (e.g., 1 mg of midazolam), or alternatively, non-sedating anti-seizure medication (e.g., loading with fosphenytoin, levetiracetam, or valproic acid) to patients harboring IIC patterns, and monitoring for an electroclinical response. Resolution of the potentially ictal (IIC) EEG pattern coupled with clinical improvement or recovery of EEG background rhythms defines a positive response [64]. It is important to note that, at times, improvement may be delayed, which adds a level of complexity to these trials. Improvement of EEG alone is often termed "possible NCSE" [56]. Hopp et al. retrospectively analyzed EEG and clinical response to IV benzodiazepine trials in 62 patients with suspected NCSE and demonstrated positive clinical response in 35% of patients [36]. Positive clinical response correlated strongly with recovery of consciousness, survival, and with achieving a favorable functional outcome [36]. We often use non-sedating medications as IV phenytoin or fosphenytoin, levetiracetam, valproate, or lacosamide to avoid the confounding sedating effect of benzodiazepines, and appreciate a subtle clinical improvement. Recent data support the role of anti-seizure medication trial in diagnosing NCSE in patients with patterns on EEG that have triphasic morphology [38]. This is important, as these patterns have been historically considered as interictal in nature and reflective of metabolic encephalopathy, and their ictal potential is increasingly being recognized [63]. O'Rouke et al. investigated the clinical response to a therapeutic trial among 64 patients with TW pattern and demonstrated a positive clinical response in 10/53 (18.9%) patients treated with benzodiazepines and 19/45 (42.2%) patients treated with non-sedating drugs [38]. These data underscore the utility of IV therapeutic trial as a simple and inexpensive tool for diagnosing NCSE (an IIC pattern with a clinical response to medication trial). However, it is worth mentioning that there is no negative result to this test, as lack of EEG and clinical response does not completely exclude an ictal connotation (NCSE). The refractoriness of a potentially ictal pattern remains a possibility; thus, we recommend close monitoring and reassessments with either further diagnostic testing supporting neuronal injury or considering a trial with a different agent in these cases.

Non-sedating agents

Phenytoin is probably one of the most studied and frequently used medication for seizure prophylaxis in patients with acute brain injury, and in convulsive and nonconvulsive status epilepticus. In one of the largest prospective randomized placebo-controlled trials of seizure prophylaxis in severe traumatic brain injury, phenytoin prophylaxis was associated with a significant decrease in early seizures (within 7 days) but failed to demonstrate a decreased risk of late seizures (within 2 years) in this population [65]. On the other hand, data from animal [66] and human studies [67] linking phenytoin exposure to decreased functional and cognitive outcomes in stroke and subarachnoid hemorrhage have led to a decrease in its use. Furthermore, phenytoin's unpredictable zero-order kinetics and unfavorable drug interaction profile hampering the efficacy

of oral anticoagulants, antibiotics, and chemotherapeutic agents in addition to the associated risk of serious cardiovascular adverse events have limited its use in critically ill patients [68–70]. Nowadays, medications with more favorable pharmacokinetic profile (e.g., levetiracetam, lacosamide, brivaracetam) are being used more frequently. Valproic acid is another commonly used drug, but its associated risk of coagulopathy, hepatic dysfunction, and hyperammonemia [71] limits its use in certain circumstances. Other alternative therapies include carbamazepine, oxcarbazepine, topiramate, gabapentin, pregabalin, phenobarbital, brivaracetam, perampanel, clobazam, and vigabatrin.

Benzodiazepine trial

While sequential low doses of IV benzodiazepines (e.g., midazolam 1 mg in sequential doses up to a maximum dose of 0.2 mg/kg) have been utilized as a therapeutic bedside test to diagnose and potentially treat NCSE (see above), the role of continuous IV infusions in the management of IIC patterns resistant to first and seconds lines of therapy is less clear. The benefit of pattern suppression must be carefully balanced against the potential risk of iatrogenesis, and in the light of scarce evidence guiding therapeutic decisions in patients with IIC patterns, the risk/benefit ratio is largely extrapolated from status epilepticus studies. One study from 20 years ago demonstrated that IV benzodiazepine administration was associated with increased short-term mortality in critically ill elderly population with NCSE [72]. More recent studies have demonstrated that anesthetic use was associated with a poor outcome in patients with status epilepticus [73–75]. This association seemed to be stronger in patients with focal status epilepticus with impaired awareness [73]. However, none of these studies fully accounted for the severity and refractoriness of NCSE, nor did they assess long-term functional and cognitive outcomes in survivors, limiting the generalizability of these data. On the other hand, one retrospective study compared two cohorts of refractory status epilepticus treated with IV midazolam at different maximum doses. The first group (historical control) received up to a maximum dose of 0.4 mg/kg/h while the second group reached up to 2.9 mg/kg/h. Lower seizure risk and short-term mortality were seen in the second group, questioning the association of aggressive seizure management with poor outcome [76]. Randomized prospective studies are needed to solve this dilemma arising from conflicting evidence, but these studies are expensive and very difficult to conduct. Therefore, we favor the use of non-sedating anti-seizure medications as trials before resorting to anesthetic infusions, particularly in patients without a secured airway and with preserved consciousness, and in those with brief and intermittent focal seizures.

Conclusion

Ictal interictal continuum patterns present a diagnostic and therapeutic challenge to practitioners dealing with patients with acute brain injuries and critically ill patients. The presence of electrographic features suggesting a more likely ictal pattern or a positive response to a therapeutic trial can assist in the identification of those that lie on the ictal end of the continuum, and potentially carry a higher propensity for association with neuronal injury. Serum biomarkers, ancillary neuroimaging, and data from multimodality monitoring can provide further evidence for ongoing neuronal injury associated with IIC

patterns, and may guide an individualized approach to patients harboring such patterns. Further research is needed to guide the clinical approach to patients harboring these patterns. Studies exploring not only the overall impact of therapeutic trials, but targeting the identification of which patients benefit the most from pattern suppression and at what cost (non-sedating drugs versus sedation) are warranted. There are currently ongoing studies investigating the role of pattern suppression with anti-seizure medications, which will soon shed light in the therapeutic management of patients harboring IIC patterns.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

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.

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