

REVIEW

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# Ictal-interictal continuum: a review of recent advancements



James X. Tao<sup>1\*</sup>, Xiaoxiao Qin<sup>2,3</sup> and Qun Wang<sup>2,3</sup>

## Abstract

Continuous electroencephalogram (cEEG) has become an indispensable technique in the management of critically ill patients for early detection and treatment of non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE). It has also brought about a renaissance in a wide range of rhythmic and periodic patterns with heterogeneous frequency and morphology. These patterns share the rhythmic and sharp appearances of electrographic seizures, but often lack the necessary frequency, spatiotemporal evolution and clinical accompaniments to meet the definitive criteria for ictal patterns. They may be associated with cerebral metabolic crisis and neuronal injury, therefore not clearly interictal either, but lie along an intervening spectrum referred to as ictal-interictal continuum (IIC). Generally speaking, rhythmic and periodic patterns are categorized as interictal patterns when occurring at a rate of <1Hz, and are categorized as NCS and NCSE when occurring at a rate of >2.5 Hz with spatiotemporal evolution. As such, IIC commonly includes the rhythmic and periodic patterns occurring at a rate of 1–2.5 Hz without spatiotemporal evolution and clinical correlates. Currently there are no evidence-based guidelines on when and if to treat patients with IIC patterns, and particularly how aggressively to treat, presenting a challenging electrophysiological and clinical conundrum. In practice, a diagnostic trial with preferably a non-sedative anti-seizure medication (ASM) can be considered with the end point being both clinical and electrographic improvement. When available and necessary, correlation of IIC with biomarkers of neuronal injury, such as neuronal specific enolase (NSE), neuroimaging, depth electrode recording, cerebral microdialysis and oxygen measurement, can be assessed for the consideration of ASM treatment. Here we review the recent advancements in their clinical significance, risk stratification and treatment algorithm.

**Keywords:** Periodic discharges, Critical care, Continuous EEG, Ictal-interictal continuum, Nonconvulsive seizures

## Background

Periodic discharges were initially described by Cobb and Hill in patients with subacute progressive encephalitis in 1950 [1]. Chatrian and colleagues later described periodic lateralized epileptiform discharges (PLEDs) in patients with acute focal brain lesions in 1964 [2]. In the light of widespread use of continuous EEG monitoring for critically ill patients in the last several decades, a spectrum of rhythmic and periodic patterns have been described. The American Clinical Neurophysiology Society (ACNS) has created a uniform EEG terminology for

describing these EEG patterns in critically ill patients, aiming to classify these patterns with a universal nomenclature, improve interrater reliability and facilitate research [3, 4]. Under the ACNS standardized critical care EEG terminology, rhythmic and periodic patterns are classified into three different subcategories: 1) periodic discharges (PDs), 2) rhythmic delta activity (RDA), and 3) spike or sharp wave discharges (SW). These patterns can be further classified as generalized, lateralized, bilateral independent and multifocal, such as generalized periodic discharges (GPDs), generalized rhythmic delta activity (GRDA), lateralized periodic discharges (LPDs), lateralized rhythmic delta activity (LRDA), and bilateral independent periodic discharges (BIPDs) [5].

\* Correspondence: [jtao@neurology.bsd.uchicago.edu](mailto:jtao@neurology.bsd.uchicago.edu)

<sup>1</sup>Department of Neurology, The University of Chicago, 5841 South Maryland Ave. MC2030, Chicago, IL 60637, U.S.A.

Full list of author information is available at the end of the article



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The concept of IIC was first coined by Pohlmann-Eden et al. in 1996, who described PLEDs 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 current use of ictal-interictal continuum has been expanded to include other rhythmic and periodic patterns (i.e. LPDs, GPDs, BIPDs, LRDA and GRDA) [7, 8]. Nevertheless, there is no consensus agreement on the definition of IIC. IIC commonly includes the rhythmic and periodic patterns occurring at a rate of 1–2.5 Hz without spatiotemporal evolution and clinical correlates [9]. Brief potentially ictal rhythmic discharges are > 4 Hz and < 10 s. They do not meet the criteria for an ictal pattern [10], and thus can be considered IIC patterns.

## EEG patterns of ictal-interictal continuum

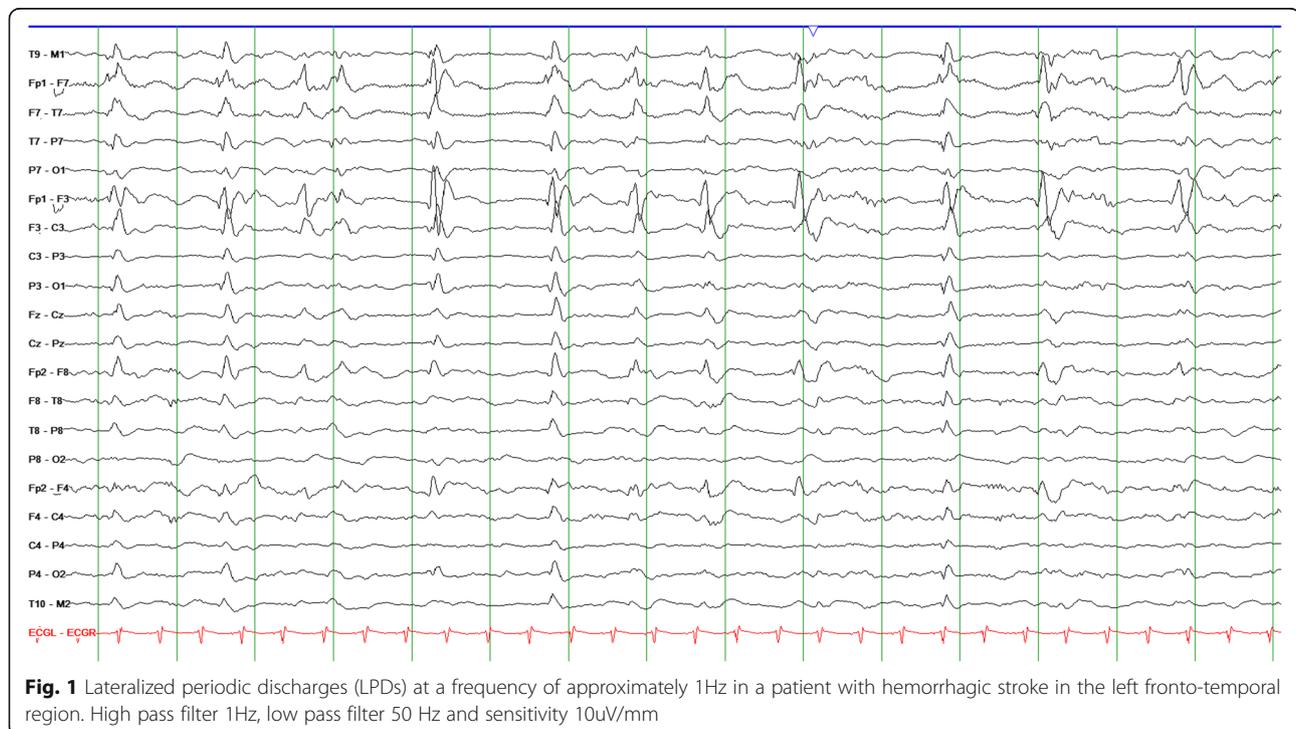
### Lateralized periodic discharges

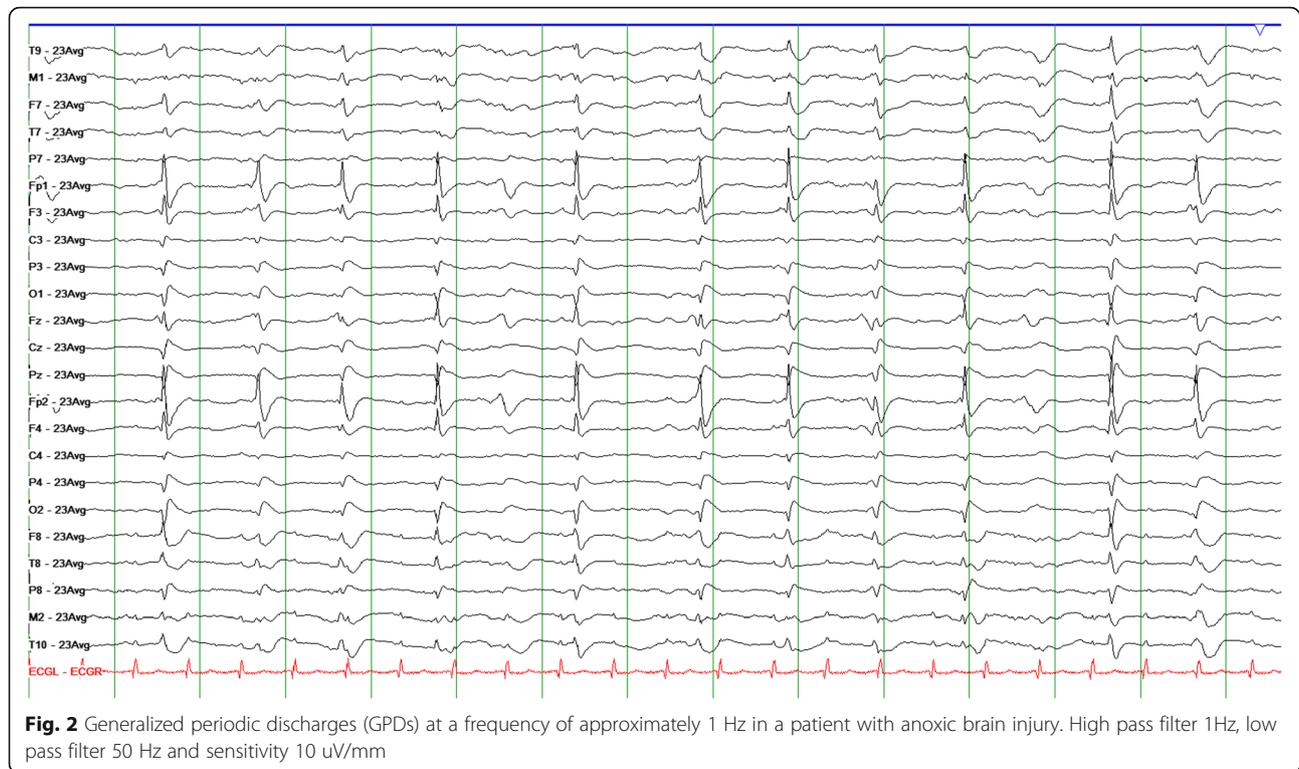
LPDs are formerly referred to as PLEDs. They are the most commonly observed periodic pattern, seen in 4.7 to 8.6% of critically ill patients [9, 11–14]. These discharges have a sharp or spiky morphology, and are typically 100–300  $\mu$ V in amplitude (Fig. 1) [4]. LPDs are commonly seen in patients with structural brain injuries, including acute stroke, traumatic brain injury,

encephalitis, and tumors [11, 12, 15–18]. Acute stroke is by far the most common etiology [11, 19]. Data from rats with focal ischemia suggested that LPDs were originated specifically from the ischemic penumbra rather than the infarcted core tissue [20]. LPDs may also occur in the setting of epilepsy, systemic infection, metabolic, and toxic insults as well as in the absence of structural lesions [15]. LPDs are significantly associated with an increased risk of seizures in 40–90% of patients during cEEG monitoring [11, 13, 16, 21]. When associated with plus features, LPDs were more likely to be correlated with seizures [12, 22]. A greater risk of seizures was also associated with LPDs > 2 Hz [22]. They are also independently associated with increased rates of severe disability, vegetative state, and death, with mortality rates ranging from 25 to 41% [12, 13, 17, 19, 23, 24].

### Generalized periodic discharges

GPDs are generalized waveforms that have relatively uniform morphology and duration with a quantifiable inter-discharge interval between consecutive waveforms at nearly regular intervals (Fig. 2) [4, 25]. Historically, GPDs were referred to as GPEDs. Triphasic waves (TW) are included in the GPDs, and often described as GPDs with triphasic morphology [4, 26]. The prevalence of GPDs varied from 0.8 to 4.5% in critically ill patients. Common etiologies include toxic–metabolic encephalopathy, anoxic brain injury, acute brain injury, infections and epilepsy [25, 27]. GPDs are often associated with





seizures, particularly NCS and NCSE. In a retrospective case–control study of 200 patients, 27% of patients with GPDs had NCS, and 22% had NCSE, compared with 8% with NCS and 7% with NCSE among 200 matched controls [25]. In a more recent retrospective study of 4 772 patients undergoing cEEG monitoring, high-frequency (> 1.5 Hz) GPDs were more likely to be associated with seizures [22]. Whether GPDs predict worse clinical outcomes remains controversial. In one study, only 36% of patients with GPDs were alive at the time of discharge [28]. However, a more recent study showed that after controlling for age, etiology, and the level of consciousness, GPDs were not an independent marker for poor prognosis [25].

#### Bilateral independent periodic discharges

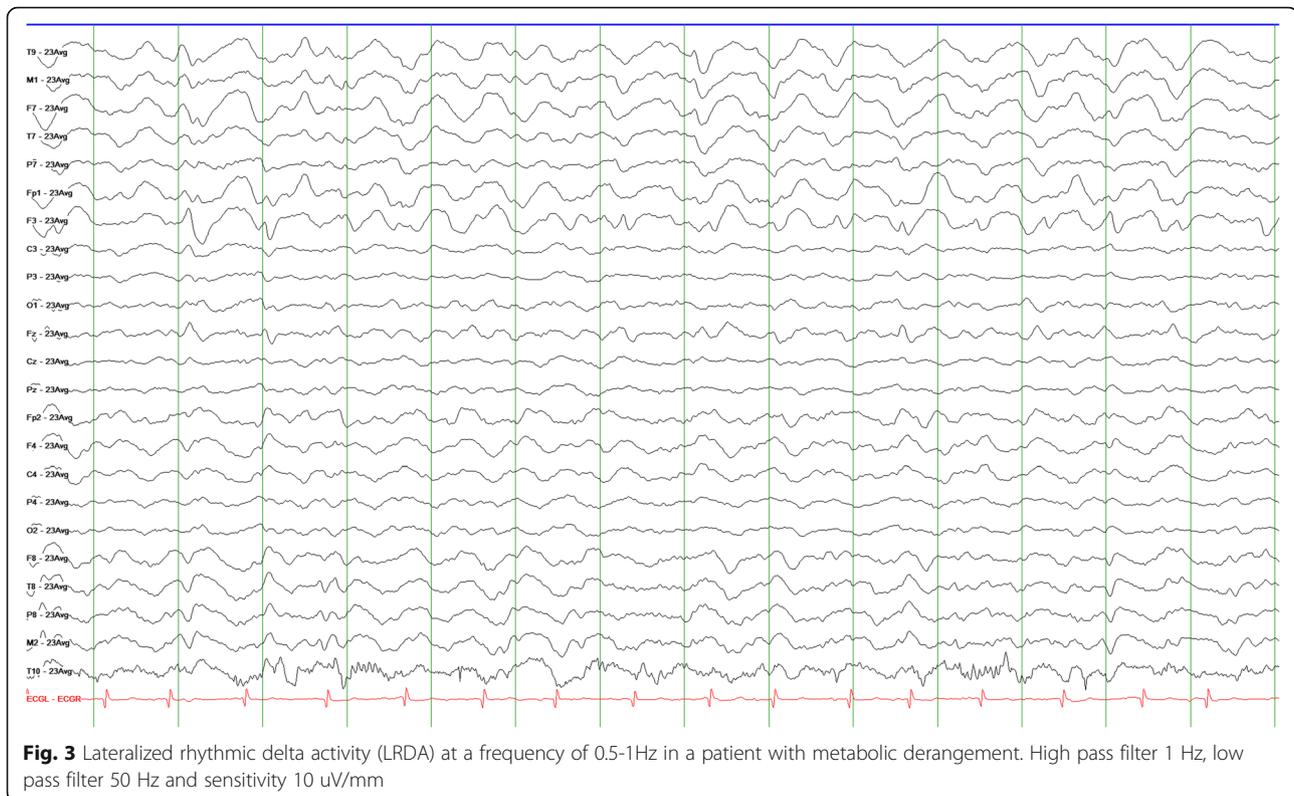
BIPDs are the lateralized periodic discharges that occur independently over each hemisphere [4]. BIPDs are previously known as bilateral independent periodic lateralized epileptiform discharges (BI-PLEDs). The prevalence of BIPDs is much less frequent than LPDs, approximately 0.5–1% in critically ill patients undergoing CEEG monitoring [29]. They typically occur with acute bilateral or diffuse cerebral injury such as traumatic brain injury, stroke, infections and anoxic encephalopathy [2, 12, 13, 30]. The high risk

of electrographic seizures associated with BIPDs has been reported in several studies [2, 12, 13, 29, 31].

#### Lateralized rhythmic delta activity

LRDA is characterized by rhythmic delta activity predominantly involving one hemisphere (Fig. 3). The prevalence of this pattern is seen in 4.7 to 7.1% of critically ill subjects undergoing continuous EEG [21, 22, 32]. The most common causes of LRDA in critically ill patients were intracerebral hemorrhage and subarachnoid hemorrhage. LRDA has a similar clinical significance as lateralized periodic discharges in critically ill patients, and is associated with a high risk of acute seizures, especially nonconvulsive seizures [21]. It was found that seizures developed in 28–63% patients with LRDA, and seizures were significantly more likely with LRDA greater than 2 Hz or with a “plus” modifier (i. e. LRDA + R or LRDA + S) [21, 22].

LRDA is also commonly found in patients with temporal lobe epilepsy without focal structural abnormalities and is formerly referred to as temporal intermittent rhythmic delta activity (TIRDA) [33, 34]. LRDA is strongly associated with the presence of temporal lobe spikes or sharp waves [35]. LRDA has also been proposed as a marker for mesial temporal atrophy. Seventy-five percent of patients with TIRDA have



evidence of signal abnormalities in the mesial temporal structures and 86% of cases of pathologically determined mesial temporal sclerosis show TIRDA on EEG [35].

#### Generalized rhythmic delta activity

GRDA is defined as 1–4 Hz generalized delta activity that is relatively uniform in morphology and duration without interval between consecutive waveforms (Fig. 4) [4]. GRDA is formerly referred to as frontal intermittent rhythmic delta activity (FIRDA) or occipital intermittent rhythmic delta activity (OIRDA). GRDA has been reported in a wide variety of cerebral lesions and metabolic disturbances [32]. Unlike most other rhythmic and periodic patterns, GRDA does not appear to be associated with seizures [22, 36, 37]. However, in a study of 665 critically ill patients, electrographic seizures were observed in 4 of 40 (10%) patients with GRDA [29]. GRDA is commonly not associated with poor clinical outcomes at the time of hospital discharge [38–40].

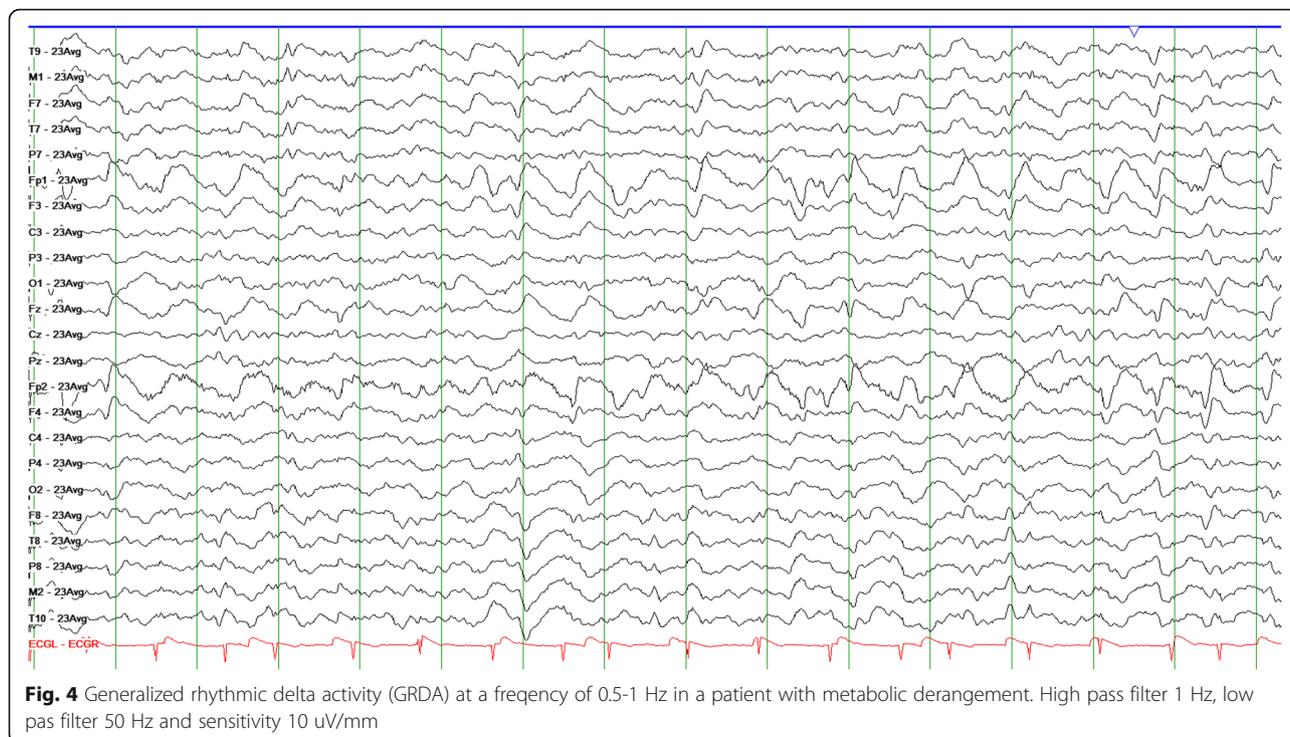
#### Stimulus-induced rhythmic, periodic or ictal discharges

Stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs) are hyperexcitable discharges commonly seen during continuous EEG recordings of critically ill patients, and are elicited by stimulation (e.g., suctioning, turning, bed-side nursing care) [41]. SIRPIDs can be lateralized or generalized periodic patterns. They are present in 10 to

34% of hospitalized patients being monitored on cEEG [41–43]. Common causes of SIRPIDs include anoxic brain injury, metabolic encephalopathy, subarachnoid hemorrhage, CNS infections, and creutzfeld-Jacob disease [44]. The clinical implication of SIRPIDs remains uncertain. Some studies suggest a strong association between SIRPIDs and seizures in critically ill patients, and particularly in those with acute brain injury [4, 41]. However, in a large, multicenter study of 4 772 patients undergoing cEEG monitoring, LPDs, LRDA, and GPDs were significantly associated with seizures, but whether the underlying pattern was stimulus-induced or not had no effect on the association with seizures [22].

#### Brief potentially ictal rhythmic discharges

Brief potentially ictal rhythmic discharges or B(I) RDs are defined as lateralized rhythmic discharges of > 4 Hz in theta, alpha and beta frequency and lasting < 10 s with or without evolution [10]. The prevalence of B(I) RDs ranges from 17 to 20% in neonates [45–47], and in 2% critically ill patients who received urgent cEEG [10]. This pattern is commonly seen patients with acute brain injury and anti-NMDA encephalitis, and is associated with an increased risk of acute seizures in up to 75% critically ill patients [10, 48]. B(I) RDs were also found in 15 of 1 230 patients (1.2%) with epilepsy undergoing long-term EEG monitoring, particularly in patients with



mediation resistant epilepsy [49]. B(I) RDs were collateralized with focal cerebral lesion and morphologically similar to EEG seizure onset pattern. Patients with B(I) RDs tended to have a worse outcome than controls, however, this finding was not statistically significant [10].

#### Risk stratification of IIC patterns associated with seizures

The seizure risk associated with IIC patterns can be stratified in the several different perspectives including: (1) segregate IIC patterns from NCS and NCSE; (2) assess the risk of seizures associated with IIC patterns; (3) determine the ictal nature of IIC patterns; (4) assess the long term risk of developing chronic epilepsy.

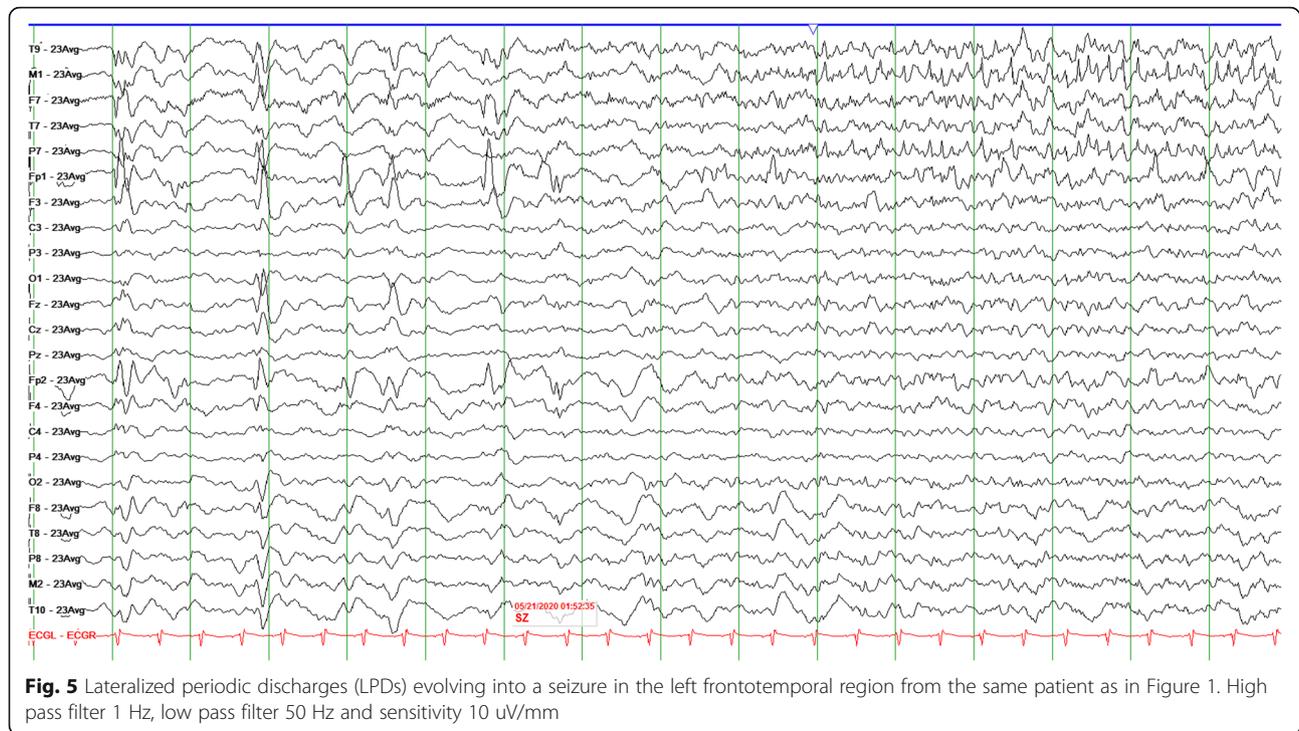
#### Differentiate IIC patterns from electrographic seizures

The first step is to differentiate IIC patterns from NCS or NCSE. Salzburg criteria have been widely adopted to identify NCS or NCSE based on EEG patterns. In order to be considered NCS or NCSE, at least one of the following criteria must be met and be continuously present for at least 10 s for NCS and 30 min for NCSE: (1) epileptiform patterns occurring at  $> 2.5$  Hz; (2) concurrent subtle clinical accompaniments; or (3) spatiotemporal evolution [50]. Periodic and rhythmic patterns occurring at a frequency of  $< 1$  Hz without plus features and displaying fluctuation are generally considered interictal patterns. Patterns occurring at a frequency of 1–2.5 Hz are considered ictal-interictal continuum. ACNS defines electrographic seizures as “repetitive generalized or focal

spikes, sharp waves, spike and wave or sharp-and-slow wave complexes at  $\geq 3$  Hz, or sequential rhythmic, periodic, or quasi-periodic waves at  $\geq 1$  Hz and unequivocal evolution (gradual increase or decrease  $\geq 1$  Hz) [4, 7]. Both Salzburg and ACNS criteria have been used to define the electrographic seizures in clinical practice.

#### Risk of electrographic seizures associated with IIC

The increased risk of seizures associated with IIC patterns has been well-described. Morphology, duration and frequency of IIC patterns are highly predictive of the seizure risk [51]. Overall, the incidence of seizures in critically ill patients range from 45 to 95% in patients with LPDs (Fig. 5) [11–13, 21, 29], 43–78% in patients with BIPDs [13, 31], 11–89% in patients with GPDs [11, 25, 28, 29, 52], and 35–63% in patients with LRDA [21, 29]. GRDA was commonly not associated with an increased seizure risk [22]. However, in a study of 665 critically ill patients, electrographic seizures were observed in 4 of 40 (10%) patients with GRDA [29]. Additionally, IIC patterns with plus features were more likely to be associated with seizures. “LPD+ R” was associated with the highest odds for developing seizures and status epilepticus. “LPD+ F” were also highly associated with ictal activity, whereas LPDs bearing blunt morphology were not associated with ictal activity [16]. In generally, GRDA lies at the interictal end of IIC spectrum, whereas LPDs lay at the ictal end of IIC spectrum. Patterns including GPDs, LRDA and B(I) RDs are in the middle range of



IIC spectrum for the seizure risk [51, 53]. IIC patterns with frequencies  $> 1.5$  Hz were associated with an increased seizure risk [22].

#### IIC patterns being potentially ictal patterns

It is highly controversial whether IIC patterns are potentially ictal patterns and if they cause neuronal injury. There are several lines of evidence suggesting that IIC patterns might be ictal in nature.

- 1) LPDs with negative clinical correlates are potentially ictal [54]. When LPDs are correlated with time-locked motor symptoms; LPDs are typically localized to lesions in the motor cortex and are considered ictal. However, when LPDs are correlated with negative clinical symptoms such as aphasia, amnesia, apraxia, and cortical blindness, LPDs are localized to brain regions that do not produce positive clinical symptoms, and are often considered non-ictal. Sen-Gupta and colleagues contended that the difference between ictal and non-ictal LPDs appears to reflect the difference in underlying anatomical locations of the periodic discharges rather than in providing distinction between ictal and non-ictal states [54].
- 2) IIC patterns may be associated with known imaging markers of electrographic seizures. In several small case studies, IIC patterns were found to be

associated with restricted diffusion on diffusion weighted imaging (DWI) on MRI [55], increased regional cerebral flow on computed tomography (CT) perfusion [56], or single-photon emission computed tomography (SPECT) imaging [57], and increased glucose uptake on fluorodeoxyglucose (FDG)-positron emission tomography (PET) [58, 59]. These changes often reversed with the resolution of IIC patterns [55, 58].

- 3) IIC patterns may be associated with metabolic biomarkers of neuronal injury. Periodic discharges as well as nonconvulsive seizures were temporally associated with metabolic crisis such as increased lactate/pyruvate ratio (LPR) and decreased glucose levels during cerebral microdialysis in patients with traumatic brain injury [60]. PDs  $> 2$  Hz in frequency were associated a decrease in the partial pressure of oxygen in interstitial brain tissue, and were more likely to be associated with secondary neuronal injury from lower regional oxygen saturation [61].
- 4) IIC patterns on scalp EEG can be associated with intracranial seizures on intracranial recordings using depth EEG. Intracranial EEG with simultaneous scalp EEG recording demonstrated that up to 19% of intracranial seizures detected on depth EEG were associated with IIC patterns on scalp recordings [62].

### Risk of IIC patterns associated with epilepsy

The risk of epilepsy associated with IIC patterns has been reported in several small case studies. Epilepsy was developed in 48.5% of patients with LPDs and electrographic seizures during a mean follow-up duration of 11.9 months [63]. Patients with LPDs had a hazard ratio of 7.7(95% CI = 2.9–20.7) of developing epilepsy in comparison of patients without periodic patterns [64, 65] LPDs superimposed with rhythmic activity and electrographic seizures have a higher risk of developing epilepsy [27, 65]. Among the different acute brain injury subtypes, IIC patterns with acute TBI were highly associated with posttraumatic epilepsy [66]. In patients with ischemic stroke, LPDs and sporadic epileptiform discharges are associated with higher risk of stroke-related epilepsy [67–70]. Overall 10 to 60% patients with LPDs go on to develop chronic epilepsy after hospital discharge [15, 19, 65].

### Treatment algorithms

There are no evidence-based guidelines on how to treat patients with IIC patterns, particularly on how aggressively to treat. A number of treatment algorithms have been proposed in the literature, which can be summarized in several different approaches [9, 51, 53, 71–74]. Treatment decision should be guided by the previously discussed risk stratification on a case by case basis.

### Treat non-convulsive seizures

The first step is to differentiate NCS from IIC patterns. Periodic discharges and rhythmic patterns occurring at frequency of  $>2.5$  Hz, associated with spatiotemporal evolution and subtle ictal clinical accompaniments are classified as seizures and should be treated accordingly [4].

### Mitigate the seizure risk associated with IIC patterns

Most of IIC patterns (other than GRDA) are highly associated with increased risk of seizures, particularly when they are  $>2.0$  Hz and associated with “plus” features. It is critical that patients with IIC patterns should be monitored with continuous EEG for the surveillance of NCS and NCSE. Prophylactic treatment with non-sedating anti-seizure medications (ASM) such as Levetiracetam and Lacosamide may be considered [51]. The therapeutic goal of prophylaxis is to prevent IIC patterns from evolving into seizures as seen in Fig. 5, and is not intend to suppress IIC patterns.

### Treat IIC patterns as potential ictal patterns

Given the paucity of the available evidence, it is highly controversial whether IIC patterns should be treated as potentially ictal patterns. When the treatment decision is uncertain, a trial of benzodiazepine or a loading dose of

ASM may be empirically performed [8, 75]. If there are both immediate electrographic and clinical improvements, the trial is considered positive and further ASM treatment is warranted for pattern suppression. If there is an immediate electrographic improvement without clinical improvement, the trial is considered equivocal and patients should be further followed for the possible delayed clinical response. Neuronal injury using neuroimaging and biochemical markers may be further assessed for the consideration of treatment. During clinical practice, a positive trial of benzodiazepine or ASM is often not observed, because many critically ill patients have underlying altered mental status and encephalopathy, which may confound the clinical improvement in these patients.

Once treatment is initiated, the next step is to decide how aggressively to treat and endpoints. To prevent the potential neuronal injury associated with IIC patterns, the endpoint is to achieve pattern suppression. Conventional ASM with less sedation and few drug-drug interactions should be quickly titrated [68]. Based on EEG response, a second ASM can be added if clinical or electrographic improvement is not seen. More aggressively, intravenous anesthetics such as midazolam and propofol can be further considered if conventional ASM are not effective [74]. Nevertheless, several studies suggested that intravenous anesthetic uses may increase the poor outcomes and mortality in the patients with non-convulsive status epilepticus [76–78], which should service as a caution for the use of anesthetics to treat patients with IIC patterns. Moreover, some IIC patterns such as LPDs in patients with acute stroke and GPDs in patients with anoxic brain injury are highly refractory to the treatment of ASM and anesthetics. Therefore, the benefits of pattern suppression must be individualized and carefully weighed against the risk of iatrogenic complications such as cardiorespiratory depression [79]. Continuous EEG monitoring is essential to guide effective treatment and limit unnecessarily iatrogenic complications of ASM and anesthetic treatments.

### Chronic treatment of IIC related epilepsy

Once patients are discharged from intensive care unit, the question is whether to continue to treat the patients with ASM. Some authors suggested that for patients with IIC patterns and without seizures during ICU admission, it is not unreasonable to discontinue the prophylactic ASM treatment at the time of hospital discharge. For patients with IIC patterns and seizures during ICU admission, ASM may be continued for 6–12 months [71]. For IIC patients with preexisting epilepsy and late onset seizures, long-term ASM treatment are often necessary.

## Conclusion

Ictal-interictal continuum presents a challenging electrophysiological and clinical conundrum in the management of critically ill patients. IIC patterns are neither ictal nor interictal, and their clinical significance remains uncertain. There are no evidence-based guidelines on how to treat the patients with IIC patterns. Treatment should be based on the patient's overall clinical picture and the seizure risk associated with IIC patterns. Prophylactic treatment with non-sedating ASM may be considered to mitigate the seizure risk for IIC patterns. When the treatment decision is uncertain, benzodiazepine trial or a loading dose of ASM can be empirically performed. If there are both electrographic and clinical improvements, further ASM treatment is warranted. Anesthetic agents may be considered when conventional ASM are not effective. If there is an immediate electrographic improvement without clinical improvement, patients should be further followed for the possible delayed clinical response. Neuronal injury using neuroimaging and biochemical markers may be further assessed for the consideration of treatment. Treatment decision should weigh the potential neuronal injury of IIC patterns against the iatrogenic complications of ASM. Regardless, treatment of underlying etiology is paramount in critically ill patients with IIC patterns.

## Abbreviations

ACNS: American Clinical Neurophysiology Society; ASM: Anti-seizure medications; BIPDs: Bilateral independent periodic discharges; BIPLEDs: Bilateral independent periodic lateralized epileptiform discharges; B(I)RDs: Brief potentially ictal rhythmic discharges; cEEG: continuous electroencephalogram; CT: Computed tomography; DWI: Diffusion weighted imaging; FDG: Fluorodeoxyglucose; FIRDA: Frontal intermittent rhythmic delta activity; GPEDs: Generalized periodic epileptiform discharges; GPDs: Generalized periodic discharges; GRDA: Generalized rhythmic delta activity; IIC: Ictal-interictal continuum; LPDs: Lateralized periodic discharges; LPR: Lactate/pyruvate ratio; LRDA: Lateralized rhythmic delta activity; NCS: Non-convulsive seizures; NCSE: Non-convulsive status epilepticus; OIRDA: Occipital intermittent rhythmic delta activity; PD: Periodic discharges; PET: Positron emission tomography; PLEDs: Periodic lateralized epileptiform discharges; RDA: Rhythmic delta activity; SIRPIDs: Stimulus-induced rhythmic, periodic or ictal discharges; SPECT: Single-photon emission computed tomography

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## Authors' contributions

JXT: Conceived the study, reviewed literature and wrote the manuscript. XXO: Reviewed literature and the manuscript for intellectual context; QW: Reviewed literature and the manuscript for intellectual context. The author(s) read and approved the final manuscript.

## Authors' information

James Tao, MD, PhD. Associate Professor in the Department of Neurology, the University of Chicago, IL, USA.  
XiaoXiao Qin, MD. Epileptologist in the Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, P. R. China, and China National Clinical Research Center for Neurological Diseases, Beijing, P. R. China.

Qun Wang, MD, PhD. Professor of Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, P. R. China, and China National Clinical Research Center for Neurological Diseases, Beijing, P. R. China.

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## Ethics approval and consent to participate

N/A, this is systematic review of literature.

## Consent for publication

All the authors are consent for the publication of this article.

## Competing interests

Authors have no competing interests.

## Author details

<sup>1</sup>Department of Neurology, The University of Chicago, 5841 South Maryland Ave. MC2030, Chicago, IL 6063, U.S.A. <sup>2</sup>Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, P. R. China. <sup>3</sup>China National Clinical Research Center for Neurological Diseases, Beijing, P. R. China.

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