Ictal-Interictal Continuum: When to Worry About the Continuous Electroencephalography Pattern

Justine Cormier, MD[1] Carolina B. Maciel, MD[1,2] Emily J. Gilmore, MD, MS[1,3]

[1] Department of Neurology, Yale University School of Medicine, New Haven, Connecticut
[2] Department of Neurology, UF Health Shands Hospital, University of Florida College of Medicine, Gainesville, Florida
[3] Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Yale University School of Medicine, New Haven, Connecticut

Address for correspondence Emily J. Gilmore, MD, MS, Department of Neurology, Yale University School of Medicine and Yale-New Haven Hospital, 15 York Street, Building LCI, 10th floor, Room 1000B, New Haven, CT 06520 (e-mail: emily.gilmore@yale.edu).

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Abstract

Continuous electroencephalography (cEEG) monitoring is an invaluable tool in the evaluation of encephalopathy and coma in critically ill patients. Marked increases in cEEG monitoring, coinciding with several societal guideline statements in the last decade, have allowed earlier detection and treatment of clearly harmful patterns, including nonconvulsive seizures (NCSz) and nonconvulsive status epilepticus (NCSE). However, it has also unmasked a range of EEG patterns of less clear clinical significance, with some more "malignant" than others given their potential association with increased neuronal stress and secondary brain injury. These patterns lay on a spectrum often referred to as the ictal-interictal continuum (IIC). To date, no definitive guidelines exist for the management of these potentially harmful EEG patterns, thus presenting a clinical dilemma for critical care physicians. Here, we review the various IIC patterns, their associated features, seizure risk, and outcomes and also propose a clinical approach to management based on the available data and expert opinion.

Keywords
- ictal-interictal continuum
- periodic discharges
- rhythmic delta activity
- nonconvulsive status epilepticus
- continuous electroencephalography

A 58-year-old woman with longstanding depression, anxiety, and chronic back pain on baclofen and codeine was admitted to an outside hospital with an acute change in mental status. Earlier in the day, she was noted to be confused following a fall and became unresponsive during transport to the hospital. On arrival to the emergency department, she was noted to be afebrile and hemodynamically stable, but hypoxemic to 90% on room air and comatose without lateralizing signs on examination. Her initial laboratory studies demonstrated significant metabolic derangements, which included elevated creatinine kinase (1,240 U/L), acute kidney injury (creatinine: 2.2 mg/dL, serum urea nitrogen: 59 mg/dL), transaminitis (alanine aminotransferase: 390 U/L, aspartate aminotransferase: 565 U/L), hyperammonemia (ammonia: 52 µmol/L), and leukocytosis with left shift (white blood cell: 18,800 with 23% bands). A urine toxicological screen was positive for opioids and acetaminophen. Also, she was estimated to have ingested at least 210 mg of baclofen, based on a pill count. Computed tomography without contrast of the brain demonstrated only a nasal bone fracture. She was presumed to have overdosed with opioids, acetaminophen, and baclofen, and received supportive therapy and N-acetylcysteine. However, she continued to deteriorate over 3 days with worsening multiorgan failure in the setting of severe sepsis secondary to perforated sigmoid colitis. A routine electroencephalography (EEG) reportedly demonstrated epileptiform discharges triggering a transfer to our institution for long-term monitoring and continued care. Brain magnetic resonance imaging (MRI) was motion degraded but otherwise unremarkable. Continuous EEG (cEEG)

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demonstrated nonconvulsive status epilepticus (NCSE) with generalized highly epileptiform bursts comprising greater than 50% of the recording (►**Fig. 1A, B**). Clinically, she remained comatose with intermittent, random, nonsynchronous jerks of her extremities along with stereotypic bilateral leg adduction, neither of which consistently occurred time-locked with epileptiform activity on EEG. It is important to note that the etiology of the NCSE, though likely

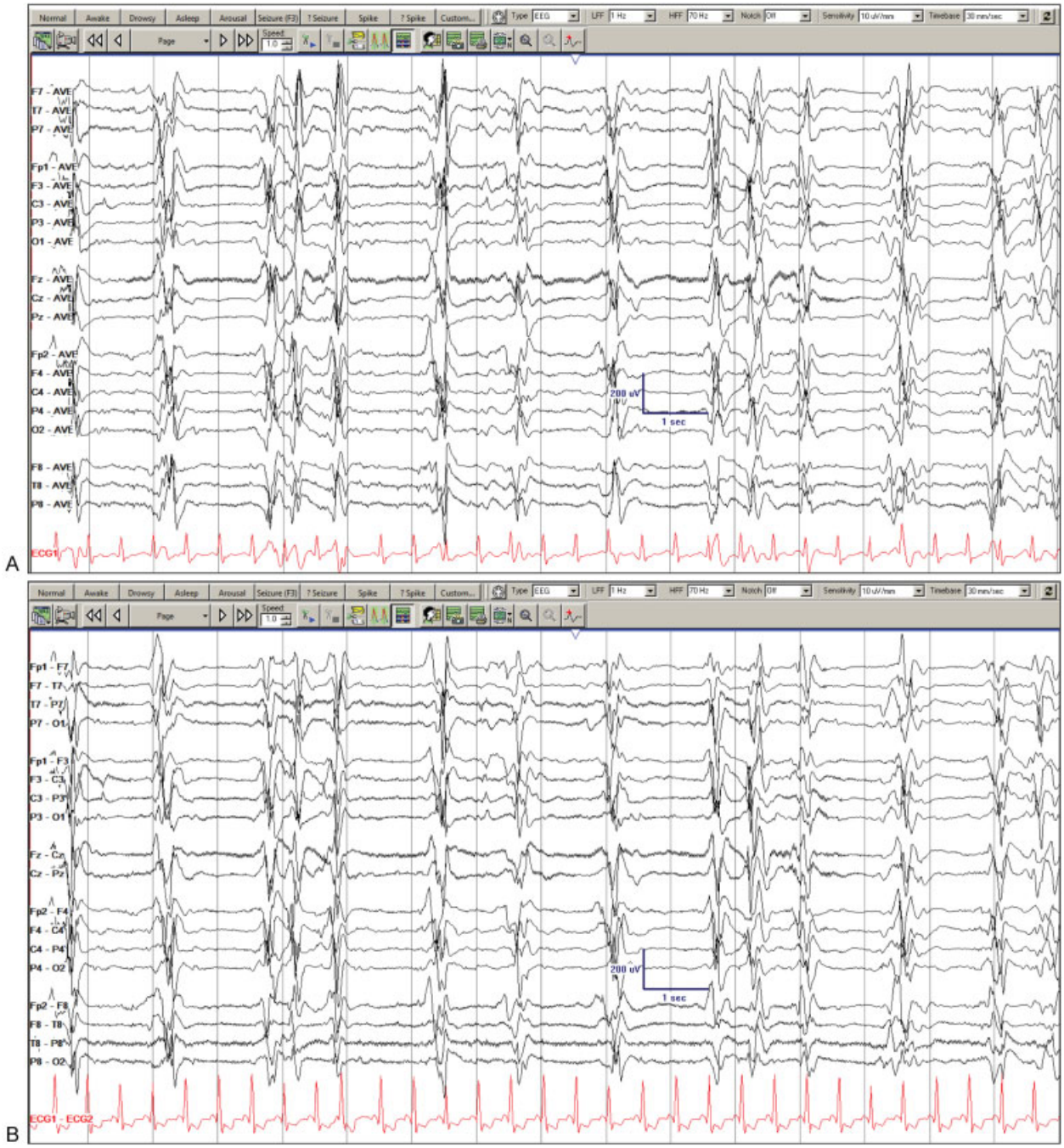

Fig. 1 Electroencephalographic evolution from nonconvulsive status epilepticus and continued diffuse hyperexcitability with ictal-interictal continuum following treatment. All epochs demonstrate at least 15 seconds of recording captured with high-pass filter at 1 Hz, low-pass filter at 70 Hz, and paper speed of 30 mm/s. Sensitivity is set at 7 μV/mm and notch filter "off," unless otherwise specified. (**A**) Common average reference montage showing generalized highly epileptiform bursts of polyspikes and spikes shifting maxima in a burst suppressed background. Note the high amplitude of epileptiform activity reaching 200 to 300 μV and the need to adjust gain (dialed down at 10 μV/mm) to allow for better characterization of morphology of discharges. (**B**) Same epoch and settings displayed on longitudinal bipolar anatomical montage. (**C**) Resolution of nonconvulsive status epilepticus and overall decrease in the ictal appearance of discharges with decreased sharpness and amplitude components of bursts. There is also improved continuity of background, now transitioned from burst suppression to a discontinuous recording. (**D**) Ictal-interictal continuum with bursts of irregular, sharply contoured, 3 to 6 Hz waveforms lasting 1 to 3 seconds admixed with fast activity displayed in longitudinal bipolar anatomical montage; Notch filter "off," note the 60 Hz artifact on midline leads. **(E)** Same epoch and montage with Notch filter "on" and resolution of 60 Hz artifact. **(F)** Continuous background consisting of rich frequencies admixed with poorly formed sharply contoured generalized discharges.

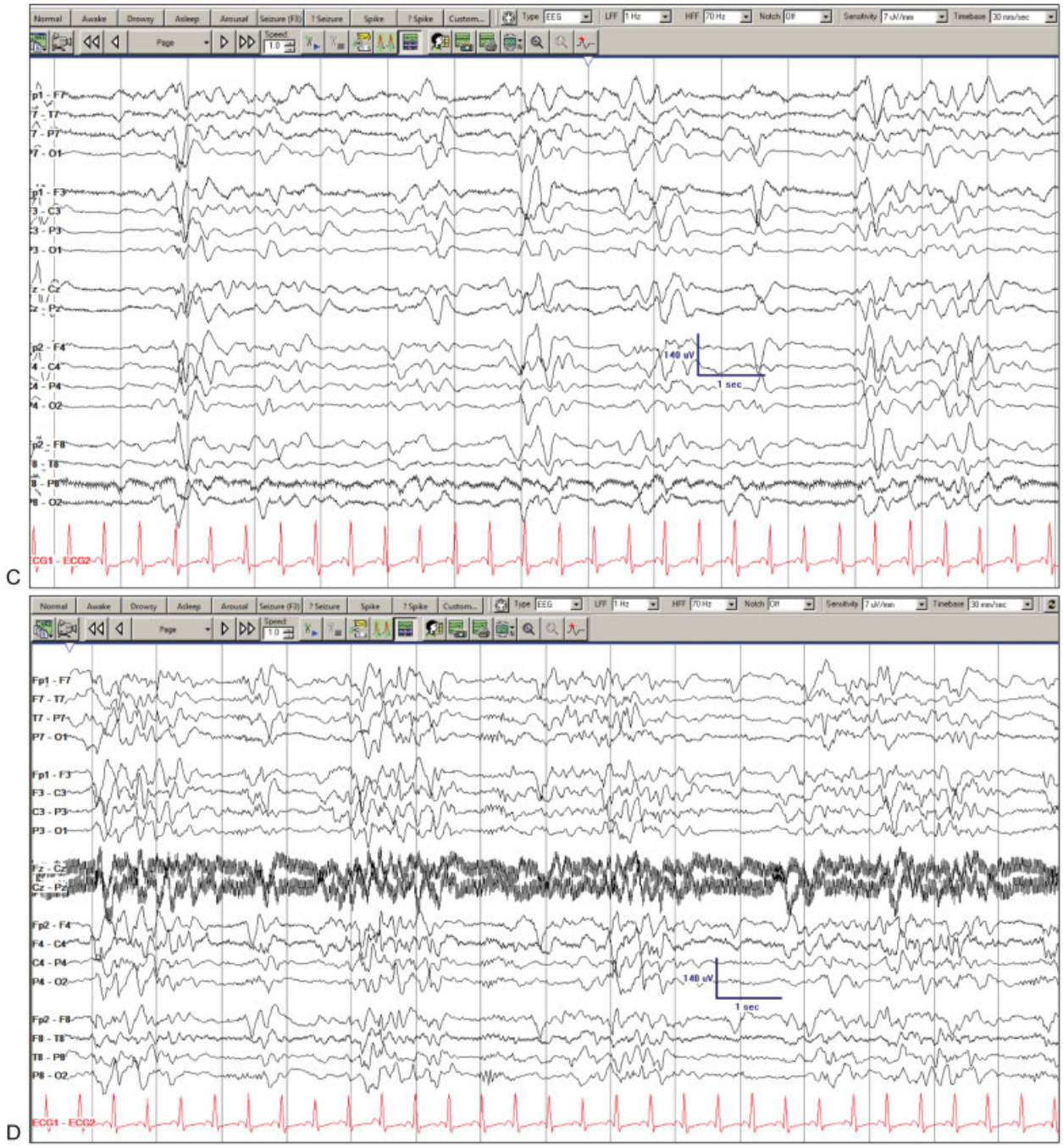

Fig. 1 (*Continued*)

multifactorial, was predominantly due to toxic-metabolic derangements in the setting of baclofen toxicity, liver and renal failure, and sepsis. While there is controversy over the most appropriate treatment of NCSE triggered by metabolic derangements, it is reasonable to follow the available guidelines for the treatment of status epilepticus. She was loaded with 2,000 mg of levetiracetam and received two 4 mg boluses of lorazepam. This resulted in a reduction of the ictal burden on EEG such that it no longer met the criteria for NCSE (< 30 min/h of recording; ►**Fig. 1C**), but there was no improvement in her neurological examination. A 20 mg/kg load of fosphenytoin failed to demonstrate further ictal burden reduction despite a free level of 3.4 µg/mL. She was then started on continuous midazolam infusion and titrated to 30 mg/h, which resulted in burst suppression with frequent generalized periodic discharges. The decision to use an anesthetic infusion was based on the refractory nature of the electrographic patterns to other antiseizure medications as well as the high likelihood of a more prolonged course and slow resolution of offending metabolic derangements given the severity of the infection, multiorgan failure, and delayed clearance of baclofen. On the following day, lacosamide (load of 300 mg followed by 75 mg every 8 hours) was added to levetiracetam (renally dosed at 500 mg every 6 hours) in

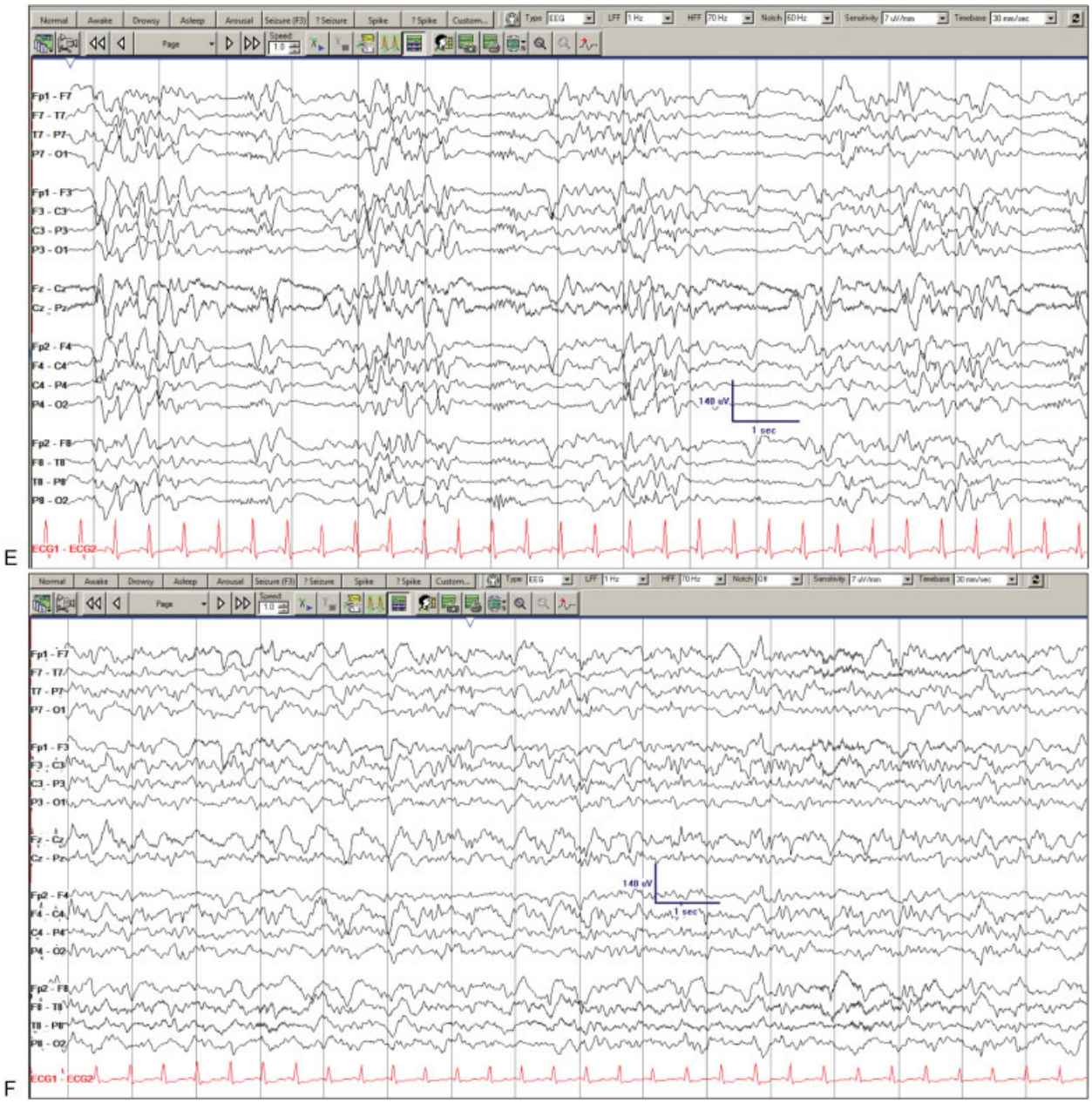

Fig. 1 (*Continued*)

anticipation of weaning midazolam, which was completed within 12 hours. In this setting, the emergence of abundant bursts of sharply contoured theta and delta discharges lasting 1 to 3 seconds were captured comprising 30% of the recording and considered to lie on the IIC (►**Fig. 1D, E**). At that point, it would have been reasonable to either pursue careful monitoring on cEEG or to continue aggressive pharmacologic treatment to decrease the IIC pattern burden further. A low-dose lorazepam taper was chosen as a bridging strategy, starting at 2 mg every 6 hours and subsequently weaned off over 4 days (►**Fig. 1F**). There was concurrent gradual electrographic and clinical improvement with resolution of the IIC pattern in the context of resolving metabolic disarray and treatment of her infection. After 10 days of the initial recording that had demonstrated NCSE, a repeat 60-minute EEG was normal (►**Fig. 2A, B**). She was discharged on lacosamide and levetiracetam, which were weaned off as an outpatient. Since her NCSE was provoked by toxic, metabolic, infectious disarray, she does not have epilepsy and does not necessarily warrant lifelong antiseizure medication.

Background

cEEG monitoring is becoming a ubiquitous tool in the evaluation, management, and prognostication of encephalopathy and coma in critically ill patients. Historically, there has been wide practice variation pertaining to indications for and duration of cEEG monitoring, in large part due to limited resources and lack of established guidelines.[1] However, in the

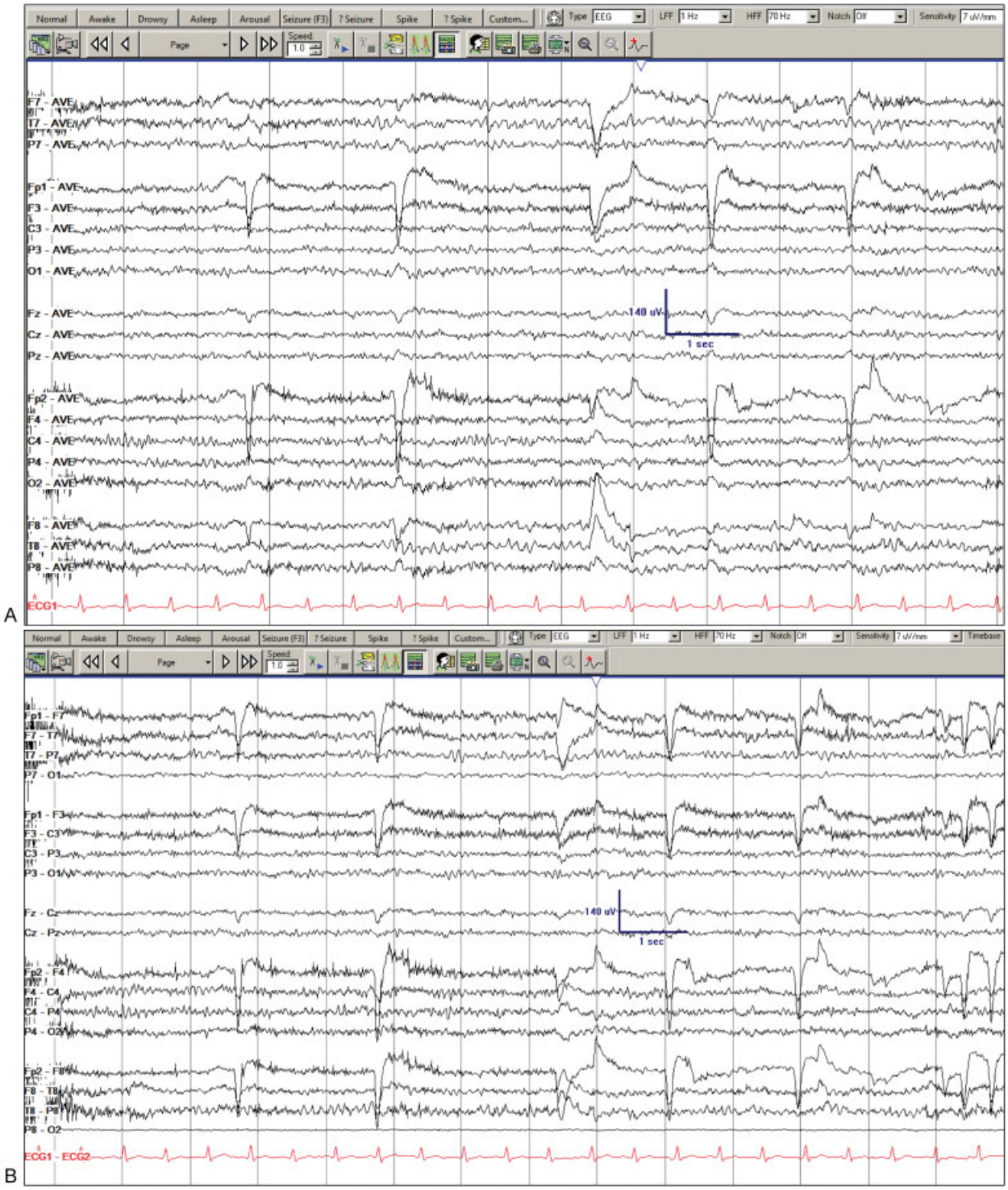

Fig. 2 Repeat 60 minutes electroencephalogram 10 days later. All epochs demonstrate at least 15 seconds of recording captured with a high-pass filter at 1 Hz, low-pass filter at 70 Hz, and paper speed of 30 mm/s. Sensitivity is set at 7 μV/mm and notch filter "off," unless otherwise specified. **(A)** Common average reference montage showing a normal awake background. **(B)** Same epoch and settings displayed on longitudinal bipolar anatomical montage. Note that the isoelectric P8–O2 channel is a result of dipole cancellation from the proximity of leads on right posterior region.

last 5 years, several national and international societies, including the Neurocritical Care Society, American Clinical Neurophysiology Society (ACNS), and the European Society of Intensive Care Medicine, have published clear guidelines for utilization of cEEG in the critical care setting.[2–4] Combined, these guidelines strongly recommend the use of cEEG to: (1) detect and aid in the management of nonconvulsive seizures (NCSz) and NCSE in the setting of persistent, unexplained alterations in mental status, (2) aid in neuroprognostication after cardiac arrest, (3) identify electrographic seizures in

patients with acute stroke, traumatic brain injury, or fluctuating mental status without known brain injury (e.g., in sepsis-associated encephalopathy); (4) determine degree of encephalopathy in patients receiving intravenous (IV) sedation or undergoing pharmacologically induced coma; and (5) assess for seizure activity in high-risk patients requiring pharmacological paralysis, such as with therapeutic hypothermia and extracorporeal membrane oxygenation (ECMO).[2,3] While the increased use of cEEG has allowed earlier detection of NCSz and NCSE, both of which have been shown to be highly associated with poor outcomes and increased mortality,[5–12] it has also led to an increased detection of epileptiform patterns—periodic discharges and rhythmic delta activity—which are of less clear clinical significance. These findings are abnormal and share some features of ictal rhythms, thus tempting clinicians treating with benzodiazepines or other antiseizure medications, which are not without risks. Although these patterns do not fully meet criteria for electrographic seizures,[13] it remains unclear not only if they cause a similar degree of neuronal injury or worse outcomes, but also whether they warrant the same degree of aggressive treatment as definitive seizures. Given this uncertainty, these patterns are felt to exist on a spectrum, with more malignant patterns at the ictal end. This is referred to as the IIC (►**Fig. 3**).[14]

The ACNS has created a standardized set of critical care EEG terminology to assist with the identification and classification of these abnormal patterns and to foster research by creating a uniform nomenclature.[13] This terminology has been widely accepted and shown to have high interrater reliability for most terms,[15] although the ability to identify triphasic wave (TW) morphology and spatiotemporal evolution of EEG patterns remains a challenge among clinicians.[15,16] In addition to the ACNS criteria, the Salzburg criteria were proposed as a standardized set of guidelines to reliably identify NCSE by EEG, with the more recent modified Salzburg criteria updated to include ACNS terminology, resulting in increased specificity.[17,18] According to these criteria, to be considered NCSE, at least one of the following criteria must be met and be continuously present for at least 10 seconds: (1) epileptiform patterns occurring at $>$ 2.5 Hz; (2) subtle concurrent clinical phenomena; or (3) typical spatiotemporal evolution.[18]

There is no such set of uniform guidelines with unequivocal recommendations addressing the management of IIC patterns, and thus the appropriate acute and long-term treatment remain a challenge for the critical care clinician. Here, we will review EEG patterns that exist on the IIC—their characteristics, typical etiologies, associated seizure risk, and outcomes—and propose a therapeutic approach based on the available data and expert opinion.

Periodic Discharges

Periodic discharges (PDs) are waveforms lasting $\leq$ 0.5 seconds, consisting of not more than three phases with a relatively uniform morphology, duration, and interdischarge interval.[13] PDs can be further classified by region of onset as lateralized, generalized, or bilateral independent. Regardless of localization, PDs found on the IIC are often between 1 and 2.9 Hz and associated with "plus" features, that is, features that render a more ictal connotation to these patterns. These features include superimposed fast (" + F") or rhythmic delta activity (" + R").[13,19] It is also possible to have both

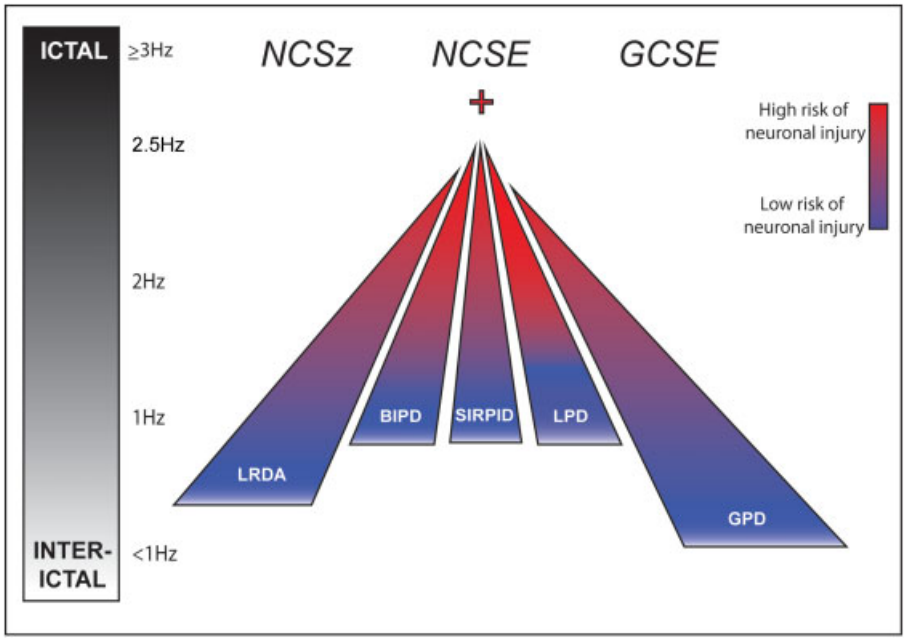

Fig. 3 This figure demonstrates the various electroencephalogram patterns felt to lay on the IIC. The frequency of discharges is shown on the y-axis. The color refers to the likelihood of causing secondary neuronal injury, with red being more harmful and blue being less harmful. Patterns on the IIC occur at frequencies $<$ 3 Hz, with patterns $\geq$ 3 Hz felt to be unequivocally ictal (including NCSE, NCSz, and GCSE). The plus sign refers to *plus* features that may render patterns closer to the ictal end of the continuum. GCSE, generalized convulsive status epilepticus; NCSE, nonconvulsive status epilepticus; NCSz, nonconvulsive seizures.

superimposed fast and rhythmic activity, denoted as " + FR."[13] When PDs are of a faster frequency and associated with *plus* features, they lay closer to the ictal end of the IIC and are associated with higher risk of seizures in patients with acute structural lesions (see ►**Fig. 3**).[20]

Lateralized Periodic Discharges

Historically referred to as periodic lateralized epileptiform discharges, the newly termed lateralized PDs (LPDs) are uniform, repetitive PDs with a clear lateral predominance. These discharges often have a sharp or spike morphology and are typically 100 to 300 μV in amplitude.[13] LPDs are uncommon in the general population, with reports ranging from 0.4 to 1% of pooled patients with a broad range of pathologies, chronicity, and indication for monitoring including those undergoing outpatient EEG.[21,22] They are, however, the most commonly observed periodic pattern in critically ill patients, seen in 6.1 to 8.6% of hospitalized patients.[23–26]

When Do We See Them?

LPDs are most often seen in structural brain injury, either acute or chronic,[27] and either cortical or subcortical.[28] Acute stroke is the most commonly reported etiology,[11,29–31] though LPDs are also seen in patients with central nervous system (CNS) tumors or mass lesions, encephalitis, CNS infection, traumatic brain injury, and hemorrhage,[11,20–22,27,31–33] reported in up to 13% of patients with intracerebral hemorrhage (ICH).[32] LPDs typically occur ipsilateral to the injury, and in acute stroke, data are suggesting that LPDs originate specifically from the ischemic penumbra rather than the infarcted core tissue.[34] These data support the hypothesis that LPDs represent an acute, partial, and transient dysfunction in a specific brain area;[33] however, LPDs have also been well described in chronic and static lesions as well as epilepsy.[35–37] Patients with LPDs often have a corresponding focal abnormality on neurological examination contralateral to the origin of the LPDs,[27,38] though it is nearly impossible to determine if this clinical correlate is attributable to LPDs or the underlying structural lesion.

LPDs can also occur in the setting of systemic infection and toxic or metabolic insults, even in the absence of a structural brain lesion.[33] There has been increasing interest in cEEG monitoring of patients in the nonneurological intensive care setting who present with sepsis and altered mental status and do not have an acute neurological injury. Multiple studies have shown that 1 in 10 septic patients admitted to the medical intensive care unit undergoing monitoring will have NCSz captured on cEEG, and up to one-quarter (17–25%) of them have PDs.[39,40] A study of patients with sepsis in the surgical intensive care unit found even higher rates of both NCSz (16%) and PDs (29%).[41] Although this cohort included patients with acute brain injury (12% of patients), there was no statistically significant association between acute brain injury and rate of NCSz or PDs.[41] Other studies, however, have suggested that the patients most at risk for LPDs are those with both a focal brain injury and concomitant toxic, metabolic, or infectious processes.[22]

Should We Worry?

LPDs are highly associated with increased risk of seizures. Numerous studies have shown this to be the case, with reports of electrographic seizures in 40 to 95% of inpatients with LPDs on cEEG.[11,20,26,27,30,31,33] As with other patterns discussed here, when LPDs are associated with *plus* features, their correlation with clinical and nonconvulsive seizures and with NCSE increases.[20,22,42] Reported rates of electrographic seizures and status epilepticus can reach 100% in patients with LPD associated with *plus* features.[22] One study demonstrating increased seizure risk in patients with LPDs plus over LPDs without associated features (odds ratio [OR] of 2) also found greater risk of seizures with higher frequency LPDs (>2 Hz).[43] Despite their correlation with seizures, LPDs can also be seen in patients who do not go on to have clinical or electrographic seizures in up to 50% of cases, and predicting which subsets of patients are at lower risk is nearly impossible.[33] In addition to the increased risk of seizures, recent work has shown that LPDs may be predictive of delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage (aSAH), although it is unclear if they are mechanistically involved, predictive markers, or merely disease bystanders.[44]

While the association between LPDs and seizure risk is well-accepted, a more controversial theory is that LPDs may themselves be an ictal phenomenon. Some groups argue that LPDs are considered ictal in cases where stereotypic focal movements—such as in focal motor seizures or epilepsia partialis continua—are time-locked to discharges.[22,30] Others have argued that even LPDs associated with nonmotor clinical signs, such as aphasia or confusional states,[45–48] can be considered ictal, particularly if there is clinical and electrographic improvement with anti seizure drug treatment.[24]

Ictal or interictal, LPDs are unequivocally associated with high morbidity and mortality. They have been shown to be independently associated with increased rates of severe disability, vegetative state, and death, with mortality rates ranging from 25 to 41%.[22,27,30,31,41,49] Studies have also shown lower likelihood of being discharged to home (OR: 0.2)[49] and poor functional outcomes at discharge, with one study reporting only 21% of 82 patients with LPDs during admission being functionally independent 1 year after hospital discharge.[30,50] Many patients with LPDs on cEEG go on to have seizures well after hospital discharge, with reports ranging from 10 to 60%.[10,30,33]

Bilateral Independent Periodic Discharges

Bilateral independent PDs (BIPDs) are much less prevalent than LPDs, typically reported in less than 1% of patients undergoing cEEG.[22,23,27] They are repetitive discharges that occur independently (asynchronously) between hemispheres, but similar to LPDs, have regular or nearly regular interdischarge intervals up to 3 Hz.[13]

When Do We See Them?

BIPDs are typically found in acute and subacute brain injury, including CNS infection,[38,51] anoxic brain injury,[38] tumors,[27] strokes,[27] and metabolic disturbances.[52] They are more rarely seen in ICH.[32]

Should We Worry?

Although less commonly seen than LPDs, BIPDs are also highly associated with seizures and carry an even worse prognosis. Seizures are recorded in 43 to 78% of patients with BIPDs,[22,27,38] although rates approached 100% in a small case series of patients with CNS infection[51] and another series of four patients with BIPDs of varying etiologies.[52] Patients with BIPDs on cEEG are more likely to have generalized seizures than focal seizures, and are more likely to be comatose on examination than those without BIPDs.[38] Mortality rates are also astonishingly high, ranging from 39 to 100%.[22,27,38,52] Similar to LPDs, patients with BIPDs who do survive to hospital discharge have poor outcomes and low likelihood of functional independence at 1 year.[27,52]

Generalized Periodic Discharges

Generalized PDs (GPDs) are repetitive, synchronous discharges occurring in both hemispheres at regular intervals with a clear interdischarge interval.[13,53] They may co-occur with LPDs, but reports of their prevalence vary, ranging from 0.8 to 1.8% in some studies,[23,25] and up to 4.5% in one review of 3,064 patients undergoing cEEG.[53]

When Do We See Them?

GPDs are most commonly associated with toxic-metabolic disturbances and sepsis, even more so than LPDs and BIPDs.[27,53–55] They are often seen in acute brain injury as well, with stroke and hypoxic-ischemic injury (HIE) being among the most common etiologies.[27,29,53,56] They are less commonly seen in ICH and traumatic brain injury (TBI).[32,53] While LPDs are more often associated with focal neurological deficits,[27,33] GPDs are often seen with severe encephalopathy or coma,[27] reflecting a more diffuse process and consistent with an increased incidence of GPDs with global insults.

Should We Worry?

Similar to LPDs and BIPDs, though to a lesser degree, GPDs have been shown to be associated with seizures and particularly so with NCSz and NCSE.[25,27,53] In a study of 3,064 patients undergoing cEEG, GPDs were associated with NCSz in 26% (vs. 7.5% in controls) and with NCSE in 21.5% (vs. 6.5% in controls). More recently, a large series of 4,772 critically ill patients demonstrated what has been seen with all PDs—that more complex discharges with "plus" features and higher frequencies (>1.5 Hz) portend an even higher risk of seizures.[43]

Many studies have reported significantly increased morbidity and mortality in patients with GPDs,[27,53] and this is particularly the case in patients with HIE or TBI.[29,56] One study showed no evidence of worse outcomes in patients with GPDs when controlling for age, etiology, and level of consciousness, suggesting that GPDs may, perhaps, be disease bystanders.[53] It has also been shown that patients with potentially reversible toxic-metabolic causes may have better outcomes.[55]

What about Triphasic Waves?

TWs are a modifier to PDs that further characterize the morphology of the waveform. They consist of three phases, each of longer duration than the preceding wave and consisting of a surface positive wave > 70 μV both preceded and followed by a negative surface wave of smaller amplitude (►**Fig. 4**).[13,57] First described by Foley et al in 1950, they were historically felt to be primarily associated with hepatic encephalopathy and not thought to portend a higher seizure risk.[16] However, since that time, TWs have been shown to be present in a wide variety of toxic-metabolic disturbances, including hyponatremia, hypothyroid states, sepsis, lithium toxicity, and hypertensive encephalopathy,[58,59] and may represent a combination of structural brain lesion and metabolic disturbance.[57,59] Furthermore, multiple studies have now shown that TW have a similar risk of seizures as other PDs.[16,57]

Rhythmic Delta Activity

Rhythmic delta activity (RDA) consists of waveforms of relatively uniform duration and morphology that occur without an interval between consecutive waveforms.[13] They can be lateralized (LRDA) or generalized (GRDA), although the RDA typically felt to lay on the IIC is lateralized, and like PDs, is often associated with increased frequency and *plus* features that signify a higher likelihood of seizures and worse outcomes (see ►**Fig. 3**). These additional features include superimposed fast activity (" + F"), frequent intermixed sharp waves or spikes (" + S"), or both (" + FS").[13,19]

Lateralized Rhythmic Delta Activity

LRDA refers to a unilateral or bilateral synchronous, but an asymmetric pattern.[13,26] In a study of 558 acutely ill patients monitored with cEEG, 4.7% had LRDA, and in 44% of these patients, LRDA co-occurred with LPDs.[26]

When Do We See It?

As with many of the epileptiform patterns described in this review, LRDA is seen in a variety of acute and remote focal CNS lesions; however, one study suggests that it is most commonly observed in intracerebral and subarachnoid hemorrhages.[26] Of note, of the 27 patients with LRDA in this study, 70% were found to have a focal abnormality on neurological examination that correlated with the laterality of the observed LRDA.[26]

Should We Worry?

Similar to LPDs, LRDA has been shown to be highly associated with seizures, and NCSz in particular.[26] Of the 4.7% of patients with LRDA in the study mentioned above, acute seizures were seen in 53% of patients with frontal LRDA and 80% of patients with nonfrontal LRDA.[26] In another extensive study of 4,772 patients undergoing cEEG, LRDA was associated with seizures in 25 to 44% of patients, and portended a much higher seizure risk when observed at a frequency of 1.5 Hz or greater or when associated with a *plus* modifier (OR: 1.8).[43]

Stimulus-Induced Rhythmic, Periodic or Ictal Discharges

Another phenomenon commonly seen on EEG recordings of critically ill patients consists of hyperexcitable discharges

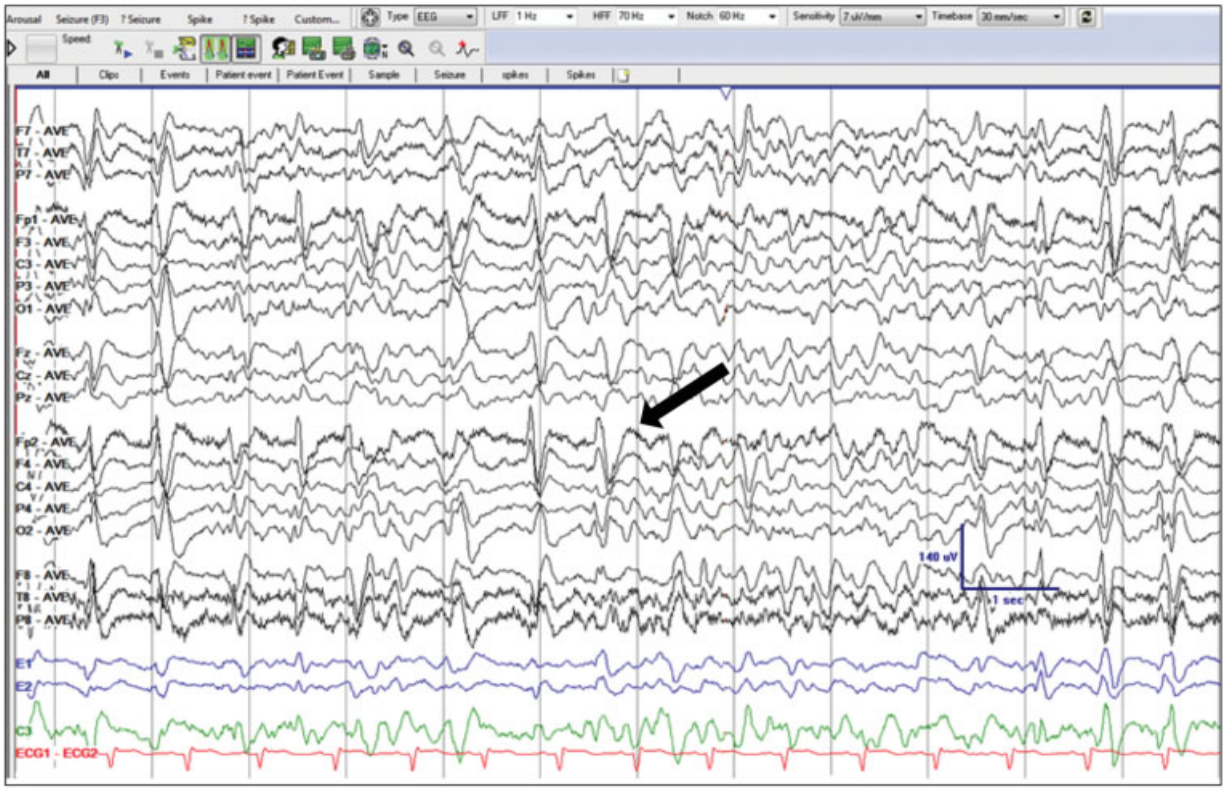

Fig. 4 Generalized periodic discharges with triphasic morphology. This epoch demonstrates 12 seconds of recording captured with a high-pass filter at 1 Hz, a low-pass filter at 70 Hz, the paper speed of 30 mm/s, sensitivity at 7 μV/mm, and notch filter "on" in a common average referential montage. The black arrow points toward a discharge with a typical triphasic morphology.

that are consistently elicited by stimulation (e.g., suctioning, turning, bedside nursing care).[19,60] Reports have shown stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs) to be present in 10 to 34% of hospitalized patients being monitored on cEEG.[60–62]

When Do We See Them?

They are most commonly seen in patients with acute brain injury; however, they have been reported in a wide range of conditions including stroke, ICH, subarachnoid hemorrhage (SAH), TBI, HIE, status epilepticus, and neurodegenerative disorders, such as Creutzfeldt–Jakob disease, as well as more systemic conditions, such as drug toxicity, hyponatremia, and other metabolic derangements.[60,63–65]

Should We Worry?

While commonly seen in critically ill patients, the significance of SIRPIDs is uncertain. Some studies seem to suggest a strong association between SIRPIDs and seizures given their frequent co-occurrence in critically ill patients, and particularly those with acute brain injury;[60,61,64] however, it would appear that this association is specific to NCSE and that there is no association between SIRPIDs and seizures out of the context of status epilepticus.[60,64] As with LPDs, there is some debate as to whether SIRPIDs may themselves be ictal phenomena. Some would suggest that this is possible given reports of both clinical and electrographic improvement with benzodiazepines.[66] Still, others argue that these patterns are not ictal given a few case reports showing absence of cerebral hyperperfusion during SIRPIDs as measured on single-photon emission computerized tomography (SPECT), a type of metabolic imaging that shows increased regional blood flow (RBF) during ictal activity.[67,68]

SIRPIDs can often be observed in patients who have poor outcomes, particularly in postcardiac arrest patients when seen during therapeutic hypothermia in a small prospective study.[69] Despite this, multiple studies have shown that SIRPIDs are not independently associated with increased in-hospital mortality or outcomes at discharge,[61,64] suggesting that any increased morbidity or mortality seen with SIRPIDs can be attributable to their underlying etiology or their association with NCSE.

When (and If) to Treat?

No clear guidelines exist regarding if, when, or how best to treat the various epileptiform patterns that lie on the IIC. Seizures, and particularly status epilepticus, have been shown to cause neuronal injury and lead to increased risk of mortality,[5–7,10] but to what degree this correlation can be extrapolated to IIC patterns is extremely difficult to determine with EEG alone. Some advocate the use of surrogate imaging, invasive multimodal monitoring, or serum markers in combination with EEG to attempt to identify the potential for neuronal injury and guide treatment decisions.[48,50,68,70] Others advocate for empirically treating with antiseizure medications, as many of these patterns themselves carry

high rates of morbidity and mortality, aside from their association with increased seizure risk.[71,72] We will discuss these approaches here and present our treatment algorithm (►**Fig. 5**).

Imaging

Perhaps the most commonly described imaging modality used for this purpose is diffusion-weighted imaging (DWI) sequence MRI. Multiple studies have shown periictal diffusion restriction, typically in the thalamus and hippocampus, and particularly with generalized and complex partial status epilepticus.[73–76] These DWI changes are hypothesized to represent increased metabolic demand and potentially neuronal swelling.[74] Some advocate for using presence or absence of DWI changes during IIC patterns to help predict neuronal injury and guide the decision to treat, but limited

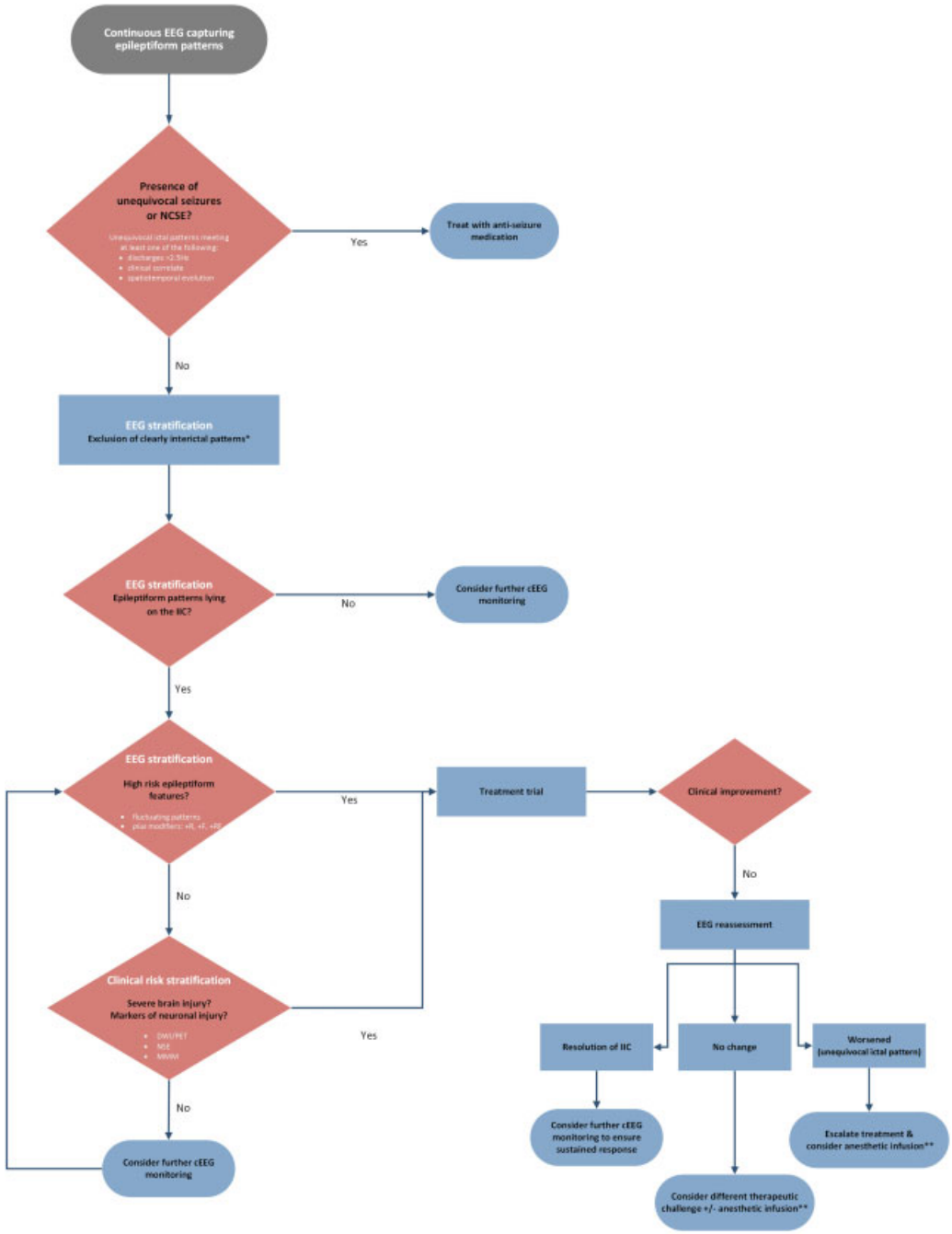

Fig. 5 A clinical approach to the ictal-interictal continuum. *If EEG findings are interictal, no need for a medication trial. The duration of monitoring is at the discretion of the treatment team, as depending on associated risk factors, such as level of consciousness and history of seizures, monitoring for > 24 hours may be of highest yield for excluding nonconvulsive seizures. **Given the potential associated morbidity of anesthetic infusions for the treatment of refractory patterns lying on the IIC, these treatments are often reserved for unequivocally ictal patterns, such as NCSE. Nonetheless, in selected cases, these may be considered as a last therapeutic resort. cEEG, continuous electroencephalography; DWI, diffusion-weighted imaging; EEG, electroencephalography; MMM, multimodal monitoring; NCSE, nonconvulsive status epilepticus; PET, positron emission tomography.

data exist on this application. Interestingly, one small observational study found that of 10 patients with LPDs, DWI changes were seen only in the 5 patients, all of whom also had seizures, suggesting that LPDs do not cause the same degree of neuronal swelling as seizures.[77] SPECT has been studied in an attempt to answer this question. Some reports have, indeed, shown increased RBF during LPDs and corresponding normalization of RBF with the resolution of LPDs.[50,78–80] ^{18}F-fluorodeoxyglucose positron emission tomography, a modality that measures glucose uptake and typically shows increased uptake during seizures, has also been studied in LPDs with similar results. Several authors have reported cases in which patients demonstrated hypermetabolism during LPDs with resolution of hypermetabolism when LPDs resolve.[78,81]

Serum Markers and Multimodal Monitoring

Emerging data suggest that various serum and cerebrospinal fluid biomarkers, as well as invasive monitoring data, may serve as valuable surrogate markers of neuronal injury. Neuron-specific enolase (NSE) is a substance contained within neurons, and thus its detection in serum can be used as a marker of neuronal injury and breakdown of the blood–brain barrier.[82] It has been shown that NSE is elevated in patients with multiple types of status epilepticus (including complex partial, absence, convulsive, and myoclonic), but more so in complex partial and myoclonic status.[70] While NSE may be helpful in guiding treatment of IIC rhythms, interpretation of elevated levels must be done with caution. NSE is also present in neuroendocrine tissues, erythrocytes,[83] and platelets,[84] potentially leading to falsely elevated levels in neuroendocrine tumors or hemolyzed samples.

Intracranial EEG (depth EEG or dEEG, and electrocorticography) and microdialysis are being increasingly used to monitor seizure activity potentially missed on scalp EEG as well as various metabolic parameters in critically ill patients. Multiple studies have shown that intracranial EEG often detects seizures and PDs that go undetected on scalp EEG, suggesting a higher sensitivity and greater potential for earlier intervention. In one study of 34 patients with severe TBI, 61% of patients had NCSz or PDs, and of these, 42.9% were captured only on dEEG.[85] In another group of 48 patients with high-grade SAH, 38% had seizures on dEEG, whereas only 8% of these were also detected on scalp EEG, and similar findings were seen in a related study of patients with high-grade SAH.[12,86] Although patients in these studies all had primary neurological injuries as the indication for invasive monitoring with intracranial EEG, it is reasonable to suspect that other critically ill patients without primary neurological injury who have unexplained coma may indeed be having NCSz or PDs occurring at a level that is not detected by scalp EEG alone.

These latter two studies in patients with aSAH also examined increases in regional cerebral blood flow (rCBF) and partial pressure of oxygen in interstitial brain tissue (Pbo_2) during seizures and PDs. In the first study, periictal increases in rCBF and decreases in Pbo_2 did not reach statistical significance.[12] In the second, however, there appeared to be a statistically significant decline in Pbo_2 time-locked to PDs with frequencies $>$ 2 Hz beginning 5 to 10 minutes after onset of discharges.[86] They also demonstrated a rise in rCBF with PDs as seen in seizures but found that at frequencies $>$ 2.5 Hz there was a relative decline in cerebral perfusion pressures (i.e., 97 mm Hg during 2 Hz PDs decreasing to 95 mm Hg for 2.5 Hz PDs and 67.8mm Hg for 3 Hz PDs).[86] These data suggest that higher frequency PDs may be associated with brain tissue hypoxia and inadequate rCBF to compensate for increased metabolic demand (e.g., neurovascular coupling and cerebral autoregulation), thus potentially arguing for the treatment of IIC patterns to prevent secondary brain injury.

Empiric Treatment

Historically, empiric treatment trials with low-dose benzodiazepines for IIC patterns were considered positive when both an electrographic and clinical improvement was observed.[14,66,71,87] Unfortunately, these trials are often equivocal with apparent electrographic improvement without corresponding clinical improvement, in part attributed to poor baseline mental status in critical illness and compounded by the sedative effect of benzodiazepines.[50,72,88] Furthermore, one retrospective study showed no clear benefit and increased mortality in elderly patients with NCSE treated with benzodiazepines.[89] Some centers have instead advocated a trial of a nonsedating ASD over a benzodiazepine as an initial choice to better assess for clinical improvement in the absence of iatrogenic sedation.[87,90] Less sedating ASDs that have been used include IV fosphenytoin, valproate, as well as both IV and oral levetiracetam[91] and oral topiramate.[92] With specific regard to SIRPIDs, it is unclear if the appropriate management involves using ASDs, minimizing stimulation or administering bolus benzodiazepines before necessary stimulation.

Conclusions

Over the last decade, the increased use of cEEG monitoring in the critical care setting has allowed detection of potentially malignant patterns that would have been otherwise missed on routine EEG,[5] facilitated earlier detection and initiation of treatment of NCSz and NCSE, and provided valuable diagnostic and prognostic information in a variety of clinical scenarios. However, the acquisition of large amounts of electrophysiological data in critically ill patients has also resulted in increased detection of EEG patterns whose clinical significance remains unclear, patterns that are neither interictal nor definitively ictal. Although there are increasing scientific efforts aimed at further characterizing these patterns, their outcomes and their potential for neuronal injury, there remain no standardized guidelines for management. There is compelling evidence that some patterns are more highly associated with seizures and may, in fact, be causing a similar degree of neuronal injury as seizures, thus warranting aggressive treatment. It is becoming more evident that these patterns differ etiologically and that the "best" treatment may not be ASDs, but rather blood pressure

augmentation or spasmolysis in SAH, antibiotics or increased cerebral perfusion pressure in sepsis, or the institution of continuous venovenous hemofiltration and ECMO, for example, in organ failure. We have proposed one possible approach to these patterns, but there is no doubt that such algorithms will continue to evolve as etiology-specific therapeutic strategies are better defined. Further prospective studies using invasive and noninvasive multimodal monitoring are needed to validate existing surrogate biomarkers of neuronal injury and their correlation with ASD trials and changes in the physiologic and serologic milieu. By tailoring our therapeutic approach to our understanding of which patterns truly warrant "treatment" and with which intervention, we can begin to deliver sophisticated, brain-focused precision medicine that will prevent not only secondary injury but also improve functional and neurological outcomes for critically ill patients.

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