CASE STUDIES IN THE ICU: SEIZURES AND EPILEPSY

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Summary
Seizures, both clinical and subclinical, are commonly encountered in the critical care setting due to a number of factors – including cerebral structural injury, systemic diseases, and toxic-metabolic derangements, not to mention preexisting epilepsy. The evaluation of a patient with suspected or known seizures necessitates a thorough search for underlying etiology, which is closely tied with prognosis and oftentimes specific treatment. Nonconvulsive seizures (NCS) are an under-recognized phenomenon in the ICU. While the diagnosis of convulsive status epilepticus (CSE) is clinical and treatment algorithmic, the diagnosis and management of nonconvulsive status epilepticus (NCSE) is nuanced, requires EEG, and should be tailored to the individual case. Continuous EEG (cEEG) monitoring in the ICU is useful when readily available, but may be prone to diagnostic pitfalls, among them the uncertainty of specific EEG patterns.

Definitions
Seizures are defined as the clinical sequelae of abnormally firing cortical neurons, which have become hyperexcitable and hypersynchronous.[1] Excessive depolarization causes increased calcium permeability and subsequent influx at the NMDA (glutamate) receptor, leading to neuronal damage, a process known as excitotoxicity. Recurrent and prolonged seizures can also lead to acidosis, hypoxia, hemodynamic changes, and transient increases in intracranial pressure. **Status epilepticus** (SE) is defined as ongoing seizure activity or seizures without return to baseline lasting more than 30 minutes, although many experts have proposed 5 minutes[2] as the cutoff to fulfill the definition – a scenario currently known as "impending SE."

Seizures are typically identified by scalp EEG, and forms of SE are named for the seizure types they represent. For example, generalized convulsive status epilepticus – which one can envision as a nonstop tonic-clonic seizure – is both clinically obvious and has an electrographic correlate on EEG. **Focal status epilepticus** (FSE) may not appear on scalp EEG when not accompanied by mental status change, due to the relatively small pool of neurons involved (if <4-6 cm^2), and so FSE remains a clinical rather than electrographic diagnosis. Other forms of status epilepticus are named for the seizure type they represent (tonic, clonic, atonic, absence, myoclonic), or the area of brain involved (generalized, partial or focal, multifocal, and either "complex" – with loss of consciousness/awareness – or "simple" – with no alteration. A recent classification system proposed by the International League Against Epilepsy (ILAE) breaks status epilepticus into categories based on semiology, etiology, EEG findings, and patient age.[3] While updated classification systems for seizure and status epilepticus are released periodically, for the purposes of this syllabus, we will refer to two major categories of SE: **convulsive status epilepticus (CSE)**, which involves ongoing motor activity (either generalized or focal), which is *obvious to the naked eye*, and **nonconvulsive status epilepticus (NCSE)**, a broad category that includes numerous subtypes, but the hallmark of which is that consciousness has been affected, hypersynchronous activity is identified on EEG *without obvious clinical signs*.

NCSE can present with a spectrum of mental status findings, though usually divided into two major groups based on level of alertness at presentation. The "**wandering confused**" represent a group with a more favorable prognosis and response to treatment, whereas **presentation in coma** oftentimes does not bode well. Especially in NCSE presenting as coma, subtle clinical findings can be seen, though often only in retrospect: ocular findings (nystagmoid movements, gaze deviation or hippus) and motor findings (subtle twitching in the face or a limb) are most common.[4] NCSE or this form of "subtle status epilepticus" can follow CSE. In one prospective study of 146 patients,[5] 14% were found to have converted from CSE to NCSE by cEEG, and rhythmic, epileptiform activity was identified in the remaining 34%. Mortality was highest (51%) in the group that had converted from CSE to NCSE, and lowest in the group without rhythmic discharges (13%). Serial clinical examination is important, in order to differentiate postictal states from NCSE; however, in many cases this clinical distinction is impossible and cEEG is warranted.

The Importance of Etiology

Although status epilepticus or recurrent seizure in the ICU represents to many clinicians a variant of uncontrolled epilepsy, in fact the etiology of the seizures is the major determinant of both treatment and prognosis.[6] Status epilepticus arising from known epilepsy is usually easier to treat and less likely to become refractory to antiepileptic drugs (AEDs). In contrast, SE due to global cerebral anoxia is notoriously pharmacoresistant, and furthermore may represent an electrical pattern on EEG suggestive of an irreversible cerebral "end state" rather than a dynamic and treatable process – in other words, a marker of severe disease rather than the cause of neurological impairment.

Most studies examining neurological injury due to SE involve CSE rather than NCSE. Treatment for NCS and NCSE is traditionally based on the approach to CSE – "time is brain." However, CSE is a clinical diagnosis whereas the diagnosis of NCSE must be suspected then confirmed with cEEG. A delay to diagnosis (typically hours to days, based on availability of cEEG) inevitably precedes initial treatment of NCSE in nearly all cases. After hours of SE, neuronal and vascular changes likely contribute to pharmacoresistance, including the internalization of GABA receptors and overexpression of glutamate receptors – suggesting that first line treatments for NCSE be reevaluated.[2] The intravenous drugs typically used to manage SE bear their own risks (including but not limited to ileus, cardiopulmonary depression, cardiac arrhythmias, metabolic acidosis, hyperammonemia, among others), and therefore the risks of treatment must be weighed carefully against the goals of therapy. Predictors of poor outcome following SE include: presentation in coma, older age, etiology (especially global cerebral anoxia), and to a lesser extent, medical comorbidities.[7] [8] In refractory SE, which represents 20% of cases, duration of SE after 10 hours is of uncertain clinical significance. These factors should be considered in determining treatment.

In the medical/surgical ICU, a number of elements serve as additional risks and provoking factors for SE. Patients with sepsis and ventilated patients are at risk for end organ (and by extension, brain) damage due to hypoperfusion and hypoxemia, resulting from cardiopulmonary and hemodynamic instability. Circulating toxins, both endogenous and iatrogenic (medications), as well as altered metabolic pathways are common in the critically ill. The cerebral effects of medical illness and its treatment in the ICU setting may typically manifest with "ICU delirium;" however, seizure and SE are additional manifestations of cortical dysfunction. Acute neuronal injuries, such as stroke, intracranial hemorrhage, neoplasm or mass lesion, CNS infection, and autoimmune processes such as limbic encephalitis, may additionally require an ICU setting for management. Remote neurological injuries can become a seizure focus in the setting of medical illness. Finally, seizures may be the presenting symptom for which a patient (either a known epileptic or new onset SE) may be hospitalized in the ICU; presentation in CSE or NCSE may be initially managed in the ER, but refractory cases of SE warrant additional treatment and cEEG. Antibiotics that lower the seizure threshold (specifically the beta-lactams, which bind to and block GABA receptors) warrant special mention given their widespread use in the management of sepsis and febrile neutropenia in the ICU. They may include penicillin-based antibiotics like nafcillin and piperacillin-tazobactam; 3rd/4th generation cephalosporins like cefazolin and cefepime; and carbapenem-based antibiotics like imipenem and meropenem.[9] [10] [11] Causes of seizure and SE in the ICU are listed in **Table 1**, below. An important emerging concept is that patients who present in new onset refractory status epilepticus (called "NORSE"), workup for etiology should include an exploration of potential autoimmune encephalitides.[12]

Given the notions that seizures cause harm, and that etiology influences outcome and treatment, the major diagnostic and treatment challenge of seizures in the ICU setting lies with differentiating cases in which seizures are the *cause* of cerebral dysfunction rather than the *effect* whenever possible.

Continuous EEG (cEEG) Monitoring in the ICU

Since the advent of digital continuous EEG (cEEG) a higher than expected percentage of critically ill patients have been identified as having NCS and NCSE, including those with underlying neurological[13] [14] and medical[15] conditions (including 8-20% of comatose patients in the ICU setting). Particularly advantageous has been the use of digital video EEG (vEEG), in correlating uncertain clinical activities with EEG patterns. In one study by Hirsch[16] (2004), among 110 patients in the ICU setting found to be in NCSE, only 13% of noncomatose and 17% of comatose patients had seizures that could be identified at the start of the cEEG; within 1 hour, the percentages had risen to 61% and 50% respectively, and continued to rise thereafter. Over 48 hours of cEEG were necessary for detection of 96-100% seizures in comatose patients. These numbers imply that critically ill patients are a moving target, and systemic issues and metabolic demands change day to day. While SE in the critical care setting can be associated with poor clinical outcomes, data on outcomes following treatment with anticonvulsants

are still lacking. Furthermore, patient selection for such studies has not been randomized, and most studies are retrospective. The EEG patterns themselves can contribute to diagnostic and treatment pitfalls. Although some EEG patterns represent definite seizure, there remain patterns of unclear clinical significance, especially in an ICU setting. **Table 2** lists findings typically seen in patients with suspected NCSE.

Treatment of Seizures and Status Epilepticus.

An algorithmic approach is appropriate for treatment of CSE, but for management of NCS and NCSE, deviations from the algorithm may be necessary in an ICU setting in which medical comorbidities may prohibit the use of certain medications, or alter the pharmacokinetics of others. A *typical* treatment algorithm for CSE in the ER and ICU is illustrated below.

1) ABCs, IV, Oxygen, blood glucose, head CT
2) ER: thiamine with D50, draw labs; *A trial of pyridoxine 100-200mg IV is typically given to children under 18 months.
3) Benzodiazepines (IV lorazepam or IM midazolam, for example)[17]
4) Phenytoin 20mg/kg or Fosphenytoin 20 PE/kg (preferred, when available); alternatives: valproic acid, levetiracetam, lacosamide
5) Repeat benzos, repeat doses of phenytoin/fosphenytoin (up to 10mg/kg) or add valproic acid, levetiracetam, lacosamide
6) Phenobarbital 20mg/kg, intubation
7) IV infusions (midazolam, propofol, pentobarbital) with cEEG, goal of generalized (drug-induced) burst-suppression pattern for 24 hours after the last seizure, with wean over 12-24 hours if possible

Note that there is a paucity of evidence differentiating secondary treatment with phenytoin from valproic acid, levetiracetam, or other agents; furthermore, *emergent* treatment with phenobarbital is effective but risky.[18] [19]Medicines typically used in the treatment of status epilepticus are by definition off label, and therefore treatment algorithms vary by institution and by clinician preference. Treatment of NCSE is nuanced and case-based. EEG patterns of uncertain significance, for example, may be amenable to “challenge” with an antiepileptic drug (AED), often at a lower dose than may be used to treat CSE. Alternative treatment options for **NCSE**, and **refractory SE** are listed in **Table 3**, which details treatment considerations, advantages and risks. Most important to remember in selecting therapy is determining the treatment goal. In underlying epilepsy, for example, one should not expect to abolish every spike on EEG. Similarly, in patients with severe underlying systemic and neurological disease, treatment effect may be difficult to detect on cEEG, as the test is unlikely to suddenly “normalize.” Treatment of “end-stage” patterns including burst suppression with identical (spiky) bursts following cardiac arrest, may be futile; these patterns must be differentiated from treatable EEG patterns by skilled electroencephalographers. Milder cases of repetitive seizures and non-comatose patients should be treated with a ginger approach, while comatose patients warrant aggressive therapy and a more thorough search for etiology. Studies are underway currently to determine the best management strategies for NCSE, particularly in the ICU setting.[20] [21] [22] Among treatment options currently or recently explored include higher doses of conventional anticonvulsant therapies, allopregnanolone, therapeutic hypothermia, and ketogenic diet.[23]

Table 1: Etiology of Seizures and Status Epilepticus in the Intensive Care Unit	
Cerebral	**Systemic:**
Vascular Ischemic stroke (arterial, venous; acute or chronic) Hemorrhagic stroke Hypertensive encephalopathy, posterior reversible encephalopathy syndrome (PRES) Global anoxic injury Traumatic Subdural hematoma Subarachnoid hemorrhage Contusion Infectious and inflammatory Meningitis Encephalitis (infectious) Autoimmune encephalitis Multiple sclerosis and demyelinating diseases Brain abscess Underlying cerebral structural lesion Brain tumor Demyelinating disease Gliosis or prior injury Postoperative – neurosurgical procedure Underlying epilepsy	Metabolic Hyponatremia, hypernatremia Hypocalcemia, hypercalcemia Hypophosphatemia Hypomagnesemia Hypoglycemia, hyperglycemia Uremia, renal failure Post-dialysis (dialysis disequilibrium syndrome) Hyperthyroidism Hyperammonemia, liver failure Inborn errors of metabolism and genetic disorders Systemic States Fever Acidosis Systemic infections (sepsis) Toxins Alcohol and benzodiazepine withdrawal Antiepileptic drug withdrawal, rarely severe toxicity Psychiatric drugs (lithium, clozaril, buproprion) Antibiotics: Beta lactams, including carbapenem-based, cefepime Drugs of abuse: cocaine and sympathomimetics (ecstacy, bath salts, others)

Table 2: EEG Findings and Clinical Significance in the ICU	
Most suggestive of seizure:	*Obvious clinical seizure – with or without EEG *Focal or generalized epileptiform discharges (spike, sharp wave, sharp and slow wave complex), rhythmic, and at frequencies >3Hz, particularly with waxing/waning frequency and/or amplitude, WITH OR WITHOUT a clinical change (vEEG) *Any rhythmic *and stereotyped* activity (0.5 to <3Hz) WITH clinical change (vEEG) seen with the above finding, OR a combination of clinical and EEG improvement after a trial of anticonvulsant/benzodiazepine.
Less typical, but *may* represent seizure:	*Any rhythmic activity (0.5 to <3Hz) *without* clinical change (vEEG), particularly with abrupt onset and offset (lacking the above "waxing/waning" quality) *Focal or generalized epileptiform discharges (spike, sharp wave, sharp and slow wave complex) in clusters – arrhythmic, with no clinical change. The more stereotyped the activity, and the greater the difference from the usual background, the higher the likelihood of seizure. *Example: burst of spikes or fast activity, followed by global suppression lasting seconds, differing from the usual background*
Unclear or controversial clinical significance:	*Periodic discharges – either lateralized, bilateral, or generalized *Triphasic waves (classically a marker of acute toxic-metabolic encephalopathy, but with significant similarity to and characteristics of slow, generalized periodic discharges) *Stimulus-induced rhythmic periodic or ictal discharges (SIRPIDs) *Epileptiform potentials, including generalized period discharges, following cardiac arrest or with known cerebral anoxic injury – particularly in the setting of a discontinuous or nonreactive background. *Example: burst suppression pattern with identical bursts, which contain spikes* *Patterns of rhythmic delta activity (frontal: FIRDA, temporal: TIRDA, for example)
Common seizure mimics on EEG:	*Muscle artifact (usually frontal and temporal) overlying a well-formed background rhythm (8-13Hz). *Arousal pattern can appear faster or slower, sometimes rhythmic with overlying muscle. *Artifact from ventilator, EKG, IV drips can appear rhythmic or periodic. Correlation with vEEG or bedside testing useful. *Sleep morphologies such as spindles, vertex and K-complexes can also be confused for ictal patterns but can be differentiated by a skilled EEG reader.

Table 3: Treatment of Seizures and Status Epilepticus in the ICU Setting		
Medication	**Advantages/Considerations**	**Risks**
Lorazepam (0.1mg/kg to 10mg max IV), OR **Midazolam** (0.05 mg/kg IV) OR **Diazepam** (0.1 mg/kg to 20mg max IV) can be administered.	-Intravenous, intramuscular, intranasal (midazolam) administration. Buccal and rectal administration are alternatives. -Lower doses can be used for AED challenge in NCSE	Hypotension; respiratory depression; tachyphylaxis with continued use
Phenytoin (20mg/kg IV at 50mg/min) or **fosphenytoin** (20 PE/kg IV at 150mg/min)	-Fosphenytoin reduces risk of "purple glove" syndrome -CYP450 effects, protein binding -Level readily available	Hypotension; cardiac arrhythmia; allergy
Phenobarbital (20mg/kg at 50mg/min)	-Long acting -For NCSE, can give sequential smaller boluses (5mg/kg) 4-6 hours apart to reduce risks -Level readily available	-Hypotension; respiratory depression (consider intubation); intestinal complications (ileus); allergy
Valproic acid (valproate sodium) (20-40mg/kg)	-Broad spectrum AED, hepatic metabolism -CYP450 effects -Level readily available	Hyperammonemia, Pancreatitis, Thrombocytopenia, Hepatotoxicity; allergy
Levetiracetam (1000-4500mg IV)	-Broad spectrum AED with no medication interactions, renal excretion	No known
Lacosamide (200-400mg IV)	-Newer AED, less sedating, few interactions and renal excretion	Hypotension, sedation, AV nodal blockade and prolonged PR interval at higher doses; less experience in SE
Topiramate (200-1600mg/day PO, divided)	-Broad spectrum AED -No IV formulation – administered by OG/NGT	Metabolic acidosis
IV infusions: **propofol** (1-2mg/kg bolus then 20 mcg/kg/min) OR **midazolam** (0.2mg/kg bolus then 2 mg/kg/min) OR **pentobarbital** (10-15mg/kg over 1h, then <50mg/min). **Thiopental** (2-7mg/kg at <50mg/min) is used less frequently.	-Requires mechanical ventilation, cEEG	Propofol: Hypotension, Respiratory depression, propofol infusion syndrome (Rhabdomyolysis, Metabolic acidosis, Renal failure, cardiac failure, fatty liver, hyperlipidemia) Midazolam: Respiratory depression, Hypotension, tachyphylaxis w/ continued use, benzos associated with ICU delirium Pentobarbital: Hypotension, Respiratory depression, Cardiac depression, ileus Thiopental: hypotension, cardiopulmonary depression
Other IV infusion options for refractory SE: **Ketamine** (2mg/kg, then 50 mg/kg/min)	-Alternative mechanism – NMDA receptors, lower risk of cardiopulmonary depression	Hypertension, tachycardia, neuropsychiatric risks
Other options for refractory SE: -Inhaled anaesthetics (**isoflurane**); **ketogenic diet**, **vagal nerve stimulation**, **corticosteroids** or **IVIG/plasma exchange**, brain **surgery**, **hypothermia,** transcranial magnetic stimulation (**TMS**) and electroconvulsive therapy (**ECT**).	-Based on hypothesis about etiology in some cases, presence of cortical lesion (surgery, TMS); immune-related etiology (steroids, IVIG/PE)	Experimental in most cases, with limited evidence – weigh risks and benefits of each treatment

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