Evaluation and Management of Status Epilepticus in the Neurological Intensive Care Unit

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Status epilepticus (SE) is a common and potentially life-threatening neurologic emergency characterized by prolonged seizures that are the result of primary neurologic disease or secondary to critical illness and medical management. It is associated with high rates of morbidity and mortality. Unfortunately, presentation is subclinical in many cases and requires a high index of suspicion. The authors discuss diagnostic and management schemes for SE in the neurological intensive care unit, emphasizing the importance of reducing the duration of SE through prompt recognition and aggressive treatment protocols.

Status epilepticus (SE) is a common and potentially life-threatening neurologic emergency characterized by prolonged seizures. The reported annual frequency of cases in the United States has been between 102,000 and 152,000, with roughly 55,000 of these incidents proving fatal. Because estimates of mortality range from 17% to 23% and morbidity from 10% to 23%, the impact of SE is dramatic.

Traditionally, SE was defined as continuous seizure activity lasting more than 30 minutes—or two or more sequential seizures without full neurologic recovery between episodes. However, because of the high morbidity and mortality rates associated with continuous seizures, the duration of seizure activity defining SE has been reduced to 5 minutes.

It is well known that the longer a seizure lasts, the likelihood that it will spontaneously cease diminishes. Therefore, appropriate treatment for prolonged seizures should be initiated as early as possible.

Patients who are admitted to the neurological intensive care unit (neuro-ICU) are more likely to have a primary brain disorder than patients in other critical care settings. These patients have symptomatic causes for SE and are more apt to progress to this condition.

Many hospitals worldwide now have dedicated neuro-ICUs for patients with diseases that affect the central nervous system (CNS). Specialized neurocritical care teams have been shown to improve patient outcomes, maximizing resource utilization and reducing hospital mortality. The current article specifically addresses clinical management of SE in the neuro-ICU setting.

Status epilepticus and seizures in the neuro-ICU are often the result of a primary disease of the brain. Patients who are admitted to the neuro-ICU suffer from a variety of traumatic and nontraumatic cerebral disorders that can predispose them to SE. These conditions, among others, include cerebral venous thrombosis, intracranial hemorrhage, large cerebral infarction or intracranial neoplasm, meningitis or encephalitis, postcraniotomy, and traumatic brain injury.

Both generalized convulsive (GCSE) and nonconvulsive (NCSE) forms of SE can occur in neuro-ICU patients. As the name implies, GCSE is a condition where seizures are clinically manifested as generalized tonic-clonic movements or “convulsions.” Alternatively, NCSE is generally subclinical or associated with subtle clinical findings.

Continuous electroencephalographic (EEG) monitoring is essential for the detection of seizures with subtle or no clinical manifestations. Such cases were previously described as “clinically unrecognized seizures.” These seizures are often discovered only with the assistance of EEG recording. By way of example, the incidence of seizures for patients with intracerebral hemorrhage reaches 1 in 3 cases—yet only half of these occurrences are clinically observable on bedside examination, the rest being purely electrographic.

Pathophysiology

Status epilepticus results from a combination of persistent cellular excitation and a failure of centrally mediated mechanisms to suppress sustained seizure activity.

There is evidence to suggest that in early SE, the predominant mechanism responsible is failure of γ-aminobutyric acid, or GABA, the primary inhibitory neurotransmitter of the CNS, to suppress the activated seizure focus. In later stages, the amino acid derivative N-methyl-D-aspartate, which causes...
neuronal excitation, becomes more important in sustaining seizure activity.\textsuperscript{10}

Postmortem studies indicate that the key anatomic structures involved in the pathogenesis of SE are the hippocampus and associated limbic system.\textsuperscript{11} These findings were present even for patients who did not have a preexisting diagnosis of epilepsy.

Generalized SE is also associated with several systemic physiologic changes, all of which occur as a result of a massive release of catecholamines. Early manifestations (ie, during the first 30 minutes of SE) include cardiac arrhythmia, hyperglycemia, hypertension, lactic acidosis, and tachycardia. Just beyond 30 minutes, blood pressure and glucose concentration may begin to normalize, or even reverse in abnormality.

Prolonged SE (ie, beyond 60 minutes) may be associated with hyperthermia, hypoglycemia, hypotension, pulmonary edema, renal failure, and rhabdomyolysis.\textsuperscript{12} Cerebral ischemia from hypoperfusion may even occur, the areas most susceptible being the limbic and cortical structures.\textsuperscript{13}

**Frequency and Causes**

To our knowledge, a systematic analysis of SE frequency in the neuro-ICU based on etiology has not yet been performed. Although SE prevalence in common disorders warranting admission to the neuro-ICU can be delineated, the causes are legion. A cohort study involving more than 800,000 patients reported 0.2% and 0.3% prevalence of SE in acute ischemic stroke and intracerebral hemorrhage, respectively.\textsuperscript{14} Continuous EEG monitoring has helped to elucidate cases defined with clinical and subclinical NCSE. Studies of patients with subarachnoid hemorrhage have revealed an SE rate of 8%, while a nationwide survey of patients with nontraumatic subarachnoid hemorrhage reported a rate of 0.2% for GCSE.\textsuperscript{15,16} For patients with traumatic brain injury, this rate is anywhere from 1.9% to 8%.\textsuperscript{17} In children especially, acute bacterial meningitis can cause rates of SE as high as 12%.\textsuperscript{18} The frequency of SE for other conditions that are generally managed in the neuro-ICU is unknown.

Aside from primary neurologic disease, toxic and metabolic factors may also play a role in causing seizures that progress to SE. Such factors can be the initiating cause of seizures, aggravate an underlying epileptogenic focus in the brain, or prolong a preexisting seizure (Figure 1).\textsuperscript{19}

Several medications used in the neuro-ICU may lower seizure threshold, including various antibiotics that are used for managing CNS infections. Patients with impaired renal function receiving cephalosporins or β-lactam antibiotics are especially at risk.\textsuperscript{20,21}

In addition, electrolyte imbalances may result directly from brain injury or treatment thereof. Examples are hyponatremia due to cerebral salt-wasting and hypernatremia resulting from central diabetes insipidus or aggressive, unmonitored hypertonic saline therapy for cerebral edema. Acid-base disturbances—particularly severe alkalosis caused either by aggressive alkaline therapy or inappropriate ventilator management—are also precipitating factors.

Many patients admitted to the neuro-ICU may have a preexisting history of epilepsy (due to various cerebral lesions) and may already be on an antiepileptic drug (AED). Discontinuation of these medications may lead to withdrawal and subsequently to SE.

Likewise, voluntary withdrawal from alcohol, barbiturates, or benzodiazepines is often overlooked as a cause of SE among critically ill patients.

Finally, encephalopathy from sepsis or either hepatic or renal failure can potentially lead to SE.

**Morbidity and Mortality**

The most common short-term sequelae related to SE include infection, respiratory complications, and impairment of mental status.\textsuperscript{22} Potential long-term morbidity consists of focal neurologic deficits, cognitive impairment, subsequent development of epilepsy—and recurrent SE, which has been reported at rates of 3% to 13%.\textsuperscript{23} Although the exact risk of developing these sequelae is unclear, they appear to depend largely on the underlying etiologic process.\textsuperscript{22}

Several factors can have a substantial impact on 30-day mortality, namely patient age and the etiology and duration of SE. With respect to age, there is a bimodal distribution for high mortality rates, with peak rates in neonates and elderly patients.\textsuperscript{24} Significantly increased mortality is also associated with SE duration of more than 30 minutes, which has been reported at 19% to 32%, compared to shorter duration SE being less than 3%.\textsuperscript{19,25}

![Leading causes of status epilepticus.](http://jaoa.org/pdfaccess.ashx?url=/data/journals/jaoa/932104/)
Diagnosis

As noted, prompt diagnosis of SE substantially impacts patient health, transforming a life-threatening process into a treatable and completely reversible clinical entity. Generalized convulsive SE is primarily diagnosed by its clinically recognizable presentation: consciousness is invariably impaired. An EEG is used to confirm diagnosis.

In the presence of clinical symptoms or high index of suspicion for an ongoing seizure, treatment should not be delayed to obtain EEG confirmation. Typical clinical presentations of GCSE are tonic-clonic, though this condition may also present as myoclonic or—less frequently—tonic, clonic, or mixed seizure types.

Of all three factors noted above to have a substantial impact on 30-day mortality rates, the only potentially modifiable determinant is duration. It is for this reason that the most important focus point for clinicians involved in the care of patients with SE is prompt recognition and immediate initiation of treatment.

Etiology may also be a determinant in mortality for SE. Although anoxia with SE carries the highest risk of mortality, a synergistic effect is not apparent; mortality for anoxia alone is just as high in the absence of SE. However, there is evidence to support a synergistic effect on mortality from SE in association with acute symptomatic etiologies, especially acute ischemic stroke.

In addition, multiple medical comorbidities may also contribute to increased mortality rates. Etiologies associated with low mortality rates were alcohol withdrawal and subtherapeutic levels of AEDs.

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At least one-third of all cases of SE are nonconvulsive. This condition occurs in approximately 8% of comatose patients, 22% of patients with severe head injury, and as many as 34% of patients admitted to the neuro-ICU.

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Figure 2. Continuous electroencephalographic (EEG) monitoring is an effective method for detecting nonconvulsive status epilepticus. Confused, stuporous, or comatose patients may demonstrate rapid, rhythmic epileptiform discharge on the EEG, as shown here. The diagnosis of nonconvulsive status epilepticus therefore involves a combination of abnormal mental status with diminished responsiveness, supportive EEG results, and a response to anticonvulsants.
Prolonged coma should always raise the index of suspicion for NCSE. Continuous EEG monitoring is an effective method of detection. Confused, stuporous, or comatose patients may demonstrate a rapid, rhythmic epileptiform discharge on EEG (Figure 2). The diagnosis of NCSE therefore involves a combination of abnormal mental status with diminished responsiveness, supportive EEG results—and, often, a response to anticonvulsants.33

Laboratory studies on initial diagnosis of SE include rapid evaluation of blood glucose and electrolyte panel (eg, serum magnesium and sodium), screening for drugs of abuse as well as AED levels if medical history includes epilepsy.

Management

Because SE is a life-threatening process, patients who receive this diagnosis should also receive prompt direction to treatment. The goal of therapy is rapid termination of clinical and electrical seizure activity.

Once a diagnosis has been established, treatment should follow (Figure 3):

1. Assess airway, breathing, and circulation.
2. Stop the seizure.
3. Find the underlying cause.
4. Correct it.

To minimize neural damage, resuscitation, correction of metabolic defects, and seizure termination should be achieved rapidly. Treatment should be aggressive with intravenous (IV) therapy used when possible.

The first step in management of GCSE is ensuring a secure airway. If required, endotracheal intubation of the patient should be undertaken promptly, especially when there is loss of pharyngeal tone due to prolonged seizures. In difficult situations, as for patients with GCSE, short-acting paralytics (succinylcholine chloride) and hypnotics (etomidate) may be used to facilitate intubation (ie, rapid sequence protocol). Once a patient is paralyzed, it is essential to provide continuous EEG monitoring because brain seizures may continue despite the absence of physical manifestations.

Once the airway is secure, the next step is to break the seizure by IV administration of benzodiazepines, such as lorazepam, 4 mg, or diazepam, 10 mg, for adults (Figure 4). The preferred route of administration is IV, and access should be obtained as soon as possible. Should IV access be unavailable, however, these benzodiazepines can be administered intramuscularly. Diazepam also comes in a rectal formulation.

Intravenous lorazepam is the most widely used benzodiazepine in the initial treatment of SE. Furthermore, it is the medication of choice because it is associated with a longer effective CNS half-life than diazepam with a lower risk of early relapse.34,35 The Veterans Affairs Status Epilepticus Cooperative Study Group36 compared IV lorazepam to diazepam (plus phenytoin sodium), phenobarbital, and phenytoin with a success rate of 64.9%.

Benzodiazepine therapy is followed by IV administration of a prodrug or anticonvulsant, respectively: fosphenytoin sodium, 10 mg PE/kg, or phenytoin, 10 mg/kg. Use of fosphenytoin has several advantages, namely more convenient and rapid IV administration (ie, 150 mg/min vs phenytoin’s 50 mg/min), intramuscular administration when necessary, and low incidence of adverse reaction at the site of injection.37 Also, the hemodynamic instability generally associated with phenytoin is rarely a problem with fosphenytoin.38

For patients with benzodiazepine refractory SE, IV valproic acid may be as effective as—and better tolerated than—phenytoin.39 Valproic acid can be used as an alternative to phenytoin, especially in cases where comorbid cardiac disease or severe hemodynamic instability are present.39-41

If seizures continue for more than 10 minutes after the first injection of an IV benzodiazepine, a second dose is recommended.42 After initial administration of lorazepam, response to treatment undergoes rapid decline. The Veterans Affairs cooperative study36 demonstrated that the aggregate response to a repeat dose of AEDs was 7.0%; to the third, 2.3%.

After the initial dose of fosphenytoin, additional anticonvulsants may be used intravenously: phenobarbital, 10-20 mg/kg (25-50 mg/min); valproic acid, 20 mg/kg; or levetiracetam, 20 mg/kg. Specific conditions may prove more responsive to one or the other AED, however. For example, in status myoclonus associated with hypoxia, both valproic acid and levetiracetam43 have been used successfully, and a response to propofol has also been shown.44 In a patient with a history of idiopathic generalized epilepsy who is in SE, the use of phenytoin or fosphenytoin may exacerbate GCSE.45 Early institution of valproic acid in such cases has been a successful alternative.45

Treatment with IV lorazepam or with diazepam and phenytoin will control seizures in as many as 70% of patients.46 Refractory SE occurs when seizures become resistant to the initial therapeutic dose of benzodiazepine. Continuous IV infusion with midazolam, propofol, or pentobarbital sodium has been used for patients with refractory SE.47

To prevent the occurrence of propofol-infusion syndrome, prolonged (>48 hours) and high (>5 mg/kg/hr) doses of propofol should be avoided. Propofol-infusion syndrome is a rare but potentially fatal disorder characterized by refractory cardiac arrhythmia and at least one of the following conditions: hepatomegaly, hyperlipidemia, metabolic acidosis, or rhabdomyolysis.48 This syndrome is most likely to occur in children, patients with severe brain or lung injury, exogenous catecholamine or glucocorticoid administration, inadequate carbohydrate intake, or subclinical mitochondrial disease.49

Continuous EEG monitoring is necessary during clinical management of refractory SE to ensure treatment success by demonstrating the absence of ongoing electrographic seizures.
Figure 3. To minimize neural damage, resuscitation, correction of metabolic defects, and seizure termination should be achieved rapidly. Clinical management of status epilepticus should be aggressive, with intravenous therapy used when possible. An algorithmic approach to clinical management for adults is presented here. Dosage guidelines for pediatric patients are provided in Figure 4 on page 242. **Abbreviation:** PE, administered and dispensed in phenytoin sodium equivalent units.
A “burst-suppression” pattern on the EEG (Figure 5) is the goal of pharmacologic treatment, though the precise clinical necessity and parameters currently remain unvalidated in the medical literature.\textsuperscript{50} During the next 24 to 48 hours, patients diagnosed with SE are slowly weaned from IV infusion if EEG results indicate resolution of electrographic seizure.

There is no consensus as to the length of time patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Intravenous Dosing (Maximum Dose)</th>
<th>Maximum Rate of Administration</th>
<th>Potential Adverse Effects</th>
<th>Advantage(s) of Treatment Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>Adult: 4 mg (Max, 8 mg/12 h)</td>
<td>2 mg/min Bolus, 2-5 min</td>
<td>□ Respiratory depression □ Sedation</td>
<td>□ Rapid onset of action □ Longer duration of action than diazepam □ Can also administer intramuscularly</td>
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<tr>
<td></td>
<td>Pediatric: 0.1 mg/kg (Max, 4 mg)</td>
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<td></td>
<td>Bolus 2-3 min</td>
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<tr>
<td>Diazepam</td>
<td>Adult: 10 mg every 10-20 min</td>
<td>Bolus</td>
<td>□ Respiratory depression □ Sedation</td>
<td>□ Rapid onset of action □ Can also administer intramuscularly or rectally</td>
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<td></td>
<td>(Max, 30 mg/8 h)</td>
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<td></td>
<td>Pediatric: 0.05-0.3 mg/kg</td>
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<td></td>
<td>every 15-30 min (Max, 10 mg)</td>
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<td>Fosphenytoin</td>
<td>Adult: Load 20 mg PE/kg</td>
<td>150 mg PE/min</td>
<td>□ Arrhythmia □ Hypotension □ Pruritis</td>
<td>□ Adverse effects rare □ Rapid rate of administration</td>
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<tr>
<td>sodium</td>
<td>(Max, 30 mg PE/kg)</td>
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<tr>
<td></td>
<td>Pediatric: same</td>
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<tr>
<td>Phenytoin sodium</td>
<td>Adult: Load 20 mg/kg</td>
<td>50 mg/min</td>
<td>□ Arrhythmia □ Hypotension □ Prolonged QT interval □ Purple glove syndrome</td>
<td>Relatively inexpensive</td>
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<td></td>
<td>(Max, 30 mg/kg)</td>
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<tr>
<td></td>
<td>Pediatric: same</td>
<td></td>
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<tr>
<td>Phenobarbital</td>
<td>Adult: Load 20 mg/kg</td>
<td>100 mg/min</td>
<td>□ Hypotension □ Respiratory depression □ Sedation</td>
<td>Long half-life</td>
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<td></td>
<td>(Max, 40 mg/kg)</td>
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<td></td>
<td>Pediatric: same</td>
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<tr>
<td>Valproic acid</td>
<td>Adult: Load 20 mg/kg</td>
<td>20 mg/min</td>
<td>□ Hepatic failure □ Pancreatitis</td>
<td>□ Adverse effects rare □ Effective for myoclonic seizures</td>
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<td></td>
<td>(Max, 60 mg/kg/d)</td>
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<td>Pediatric: same</td>
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<tr>
<td>Levetiracetam</td>
<td>Adult: Load 20 mg/kg</td>
<td>15-min infusion</td>
<td>Sedation</td>
<td>□ Well tolerated □ Effective for myoclonic seizures</td>
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<td></td>
<td>(Max, 3000 mg/d)</td>
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<td></td>
<td>Pediatric (age ≥ 16 y): same</td>
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<tr>
<td>Midazolam</td>
<td>Adult: Load 0.2 mg/kg, then 0.75 (\mu)g/kg/min</td>
<td>10 (\mu)g/kg/min</td>
<td>□ Respiratory depression □ Sedation</td>
<td>Rapid onset of action</td>
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<tr>
<td></td>
<td>Pediatric: Load 0.15 mg/kg, then 1 (\mu)g/kg/min</td>
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<tr>
<td>Propofol</td>
<td>Adult: Load 2 mg/kg, then 100 (\mu)g/kg/min</td>
<td>200 (\mu)g/kg/min</td>
<td>□ Hypotension □ Lipidemia □ Metabolic acidosis □ Propofol-infusion syndrome □ Sedation</td>
<td>□ Rapid onset of action □ Rapid elimination</td>
</tr>
<tr>
<td></td>
<td>Pediatric (age ≥ 3 y): Load 2.5-3.5 mg/kg, then 125 (\mu)g/kg/min</td>
<td>300 (\mu)g/kg/min</td>
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<tr>
<td>Pentobarbital</td>
<td>Adult: Load 5-15 mg/kg, then 5 mg/kg/h</td>
<td>50 mg/min</td>
<td>□ Bradycardia □ Hypotension □ Respiratory depression □ Sedation</td>
<td>Rapid onset of action</td>
</tr>
<tr>
<td>sodium</td>
<td>Pediatric: same</td>
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Figure 4. Intravenous therapy should be used when possible in the aggressive clinical management of status epilepticus. Abbreviation: PE, administered and dispensed in phenytoin sodium equivalent units.
should be kept in a “therapeutic coma.” Unfortunately, there are scenarios where cessation of SE becomes an impossible task in spite of aggressive therapy.

It is important to note that, despite termination of clinically obvious seizure activity, some patients may continue to have subclinical seizures that are detectable electrographically by EEG. In more than 14% of cases where patients are successfully treated for convulsive SE, they may continue to have NCSE. It is therefore imperative to obtain EEG monitoring if a patient remains with altered sensorium after successful treatment of convulsive SE, especially if no other reasonable explanation for the condition exists.

**Conclusion**

Status epilepticus is a common and serious condition encountered in the neuro-ICU. It is associated with an estimated mortality rate of 20%. Although clinical studies show little evidence to document the effects of permanent neurologic injury in NCSE, prolonged memory dysfunction and the similarities to convulsive status suggest that this condition should be managed expeditiously.

Rapid treatment requires prompt recognition of SE’s signs and symptoms and a high index of suspicion for this condition. Ideally, medical care should be guided closely by a neurologic specialist in the ICU. No matter what medications are selected, a goal-directed protocol is essential in facilitating delivery of appropriate treatment as efficiently as possible.

As more treatment modalities become available, a focus of newer therapies will be on minimizing the consequences of electrophysiologic insults—in addition to seizure suppression. Neuroprotective agents may become useful to prevent the cascade of delayed neuronal injury.

(continued)
In the future, a combination of treatments including seizure suppressants that are capable of becoming maintenance AEDs, neuroprotectants such as N-methyl-D-aspartate antagonists, free radical scavengers, second messenger modulators (ie, nitric oxide or adenosine), and earlier therapies may become available for the many as yet unrecognized incidents of SE in the neuro-ICU.

References

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JAOA call for case reports

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