Seizures and Status Epilepticus in the Intensive Care Unit

Wendy C. Ziai, M.D., M.P.H.,1,2,3 and Peter W. Kaplan, M.B., F.R.C.P.1

ABSTRACT

Persistent seizures and failure to regain consciousness following witnessed seizure activity require emergency neurological consultation. Although outcome is largely dependent on underlying cause, early maximal anticonvulsant therapy is critical to reducing morbidity. This review covers important concepts in the clinical and EEG diagnosis of status epilepticus, and discusses treatment algorithms for single and recurrent seizures, emphasizing the need to rationalize therapy depending on the presumed duration of seizure activity. The review takes the perspective of the neurological consultant in the intensive care unit, and considers all pharmacological approaches available to the intensivist as described in the current literature and from clinical experience.

KEYWORDS: Neurological emergencies, status epilepticus, nonconvulsive status epilepticus, refractory status epilepticus, intensive care

The neurologist or neurointensivist may be called on for consultation on an intensive care unit (ICU) patient with overt clinical convulsions, more subtle manifestations of subclinical or of nonconvulsive status, or occasionally on a patient misdiagnosed as being in status epilepticus. This article addresses the diagnosis and management of such patients.

EPIDEMIOLOGY

In the ICU, the reported risk of seizures as a complication or as the principal reason for ICU admission is 3.3%, although the actual incidence is likely to be significantly higher.1 In a prospective clinical evaluation of all medical ICU admissions for over 2 years, seizures were second only to metabolic encephalopathy as the cause of neurological complications, occurring in 61 of 217 patients (28.1%).1 Status epilepticus (the state of ongoing seizure activity typically >30 minutes, or of multiple seizures without return to baseline) is the diagnosis most often associated with seizures in the ICU, but is rare as an admission diagnosis (0.2%).2 In a nonneurological ICU, the reported incidence of status epilepticus is 3% with a mortality of 30%. The primary cause of seizures in the ICU is antiepileptic drug (AED) withdrawal or non-compliance, followed by alcohol withdrawal.3,4 Other common causes are stroke, anoxic brain injury, central nervous system infection, head trauma, sepsis, metabolic disorders, and other acute drug toxicity states or withdrawal (Table 1). Status epilepticus in the critically ill patient is most often caused by the acute illness in patients who did not previously have seizures.5-7 Nonconvulsive status epilepticus has been described in 8 to 34% of neurological ICU patients in comatose states.8,9 The most common etiologies in one study were hypoxia in 42%, followed by stroke in 22%.8 In elderly populations, the mortality from nonconvulsive status epilepticus is as high as 57%. The diagnosis and management of a single seizure, convulsive, and nonconvulsive status epilepticus are reviewed as they pertain to patients in the ICU.
10 minutes, or even 5 minutes are likely to persist, and only a few minutes; therefore, those lasting 20 minutes, for at least 30 minutes. However, seizures usually last perceived sensory, motor, and/or cognitive dysfunction to baseline, resulting in observable or even subjectively ouss state of seizures, or multiple seizures, without return Chronic recurrent seizures define an epileptic syndrome. Structural normal or has suffered a cerebral insult. Vulsions), sensory or cognitive dysfunction. They may be defined status epilepticus and partial status epilepticus.12 Status epilepticus has been defined as a continu- a condition of ongoing or intermittent clinical epileptic activity without convulsions, for at least 30 minutes, with electroencephalographic evidence of seizures. Noncon- vulsive status epilepticus has traditionally been divided into two groups, based on electroencephalogram (EEG) criteria: (1) generalized nonconvulsive status epilepticus, often called absence status, and (2) focal nonconvulsive status epilepticus, usually referred to as complex partial status epilepticus.13 To make a definite diagnosis of nonconvulsive status epilepticus, the EEG correlate is required. In some cases of obtundation associated with epileptiform EEG changes, a rapid clinical response to medication differentiates nonconvulsive status epilepti- us from other forms of encephalopathy. The return to consciousness, however, should not be confused with the return to the baseline state, which may take several days.13–15 Two distinct clinical patterns of nonconvulsive status epilepticus have been described; one in ambulatory patients with confusion who usually respond quickly to medication, and one in patients with coma or stupor who have a poor prognosis and rarely have significant im- provement in mental status with treatment.16

### DEFINITIONS
Seizures are defined as hypersynchronous paroxysmal cortical discharges of neurons that interfere with normal function.10 They may manifest as motor findings (con- vulsions), sensory or cognitive dysfunction. They may be single or recurrent depending on whether the brain is structurally normal or has suffered a cerebral insult. Chronic recurrent seizures define an epileptic syndrome.

Status epilepticus has been defined as a continuous state of seizures, or multiple seizures, without return to baseline, resulting in observable or even subjectively perceived sensory, motor, and/or cognitive dysfunction for at least 30 minutes. However, seizures usually last only a few minutes; therefore, those lasting 20 minutes, 10 minutes, or even 5 minutes are likely to persist, and functionally represent status epilepticus.11

Two major types of status epilepticus based on seizure semiology were distinguished by Gastaut: general- ized status epilepticus and partial status epilepticus.12 Generalized status epilepticus includes generalized convulsive status epilepticus, described as tonic clonic status epilepticus, tonic status epilepticus, clonic status epilepticus or myoclonic status epilepticus, and nonconvulsive status epilepticus (see below). Partial status epilepticus includes simple partial status epilepticus, either motor (epilepsia partialis con- tinua), sensory, or aphasic and complex partial status epilepticus.

Nonconvulsive status epilepticus can be defined as a condition of ongoing or intermittent clinical epileptic activity without convulsions, for at least 30 minutes, with electroencephalographic evidence of seizures. Noncon- vulsive status epilepticus has traditionally been divided into two groups, based on electroencephalogram (EEG) criteria: (1) generalized nonconvulsive status epilepticus, often called absence status, and (2) focal nonconvulsive status epilepticus, usually referred to as complex partial status epilepticus.13 To make a definite diagnosis of nonconvulsive status epilepticus, the EEG correlate is required. In some cases of obtundation associated with epileptiform EEG changes, a rapid clinical response to medication differentiates nonconvulsive status epilepti- us from other forms of encephalopathy. The return to consciousness, however, should not be confused with the return to the baseline state, which may take several days.13–15 Two distinct clinical patterns of nonconvulsive status epilepticus have been described; one in ambulatory patients with confusion who usually respond quickly to medication, and one in patients with coma or stupor who have a poor prognosis and rarely have significant im- provement in mental status with treatment.16

### PRESENTATION AND DIFFERENTIAL DIAGNOSIS
Most seizures in the ICU are generalized tonic–clonic seizures with or without secondary generalization. Although generalized tonic clonic seizure activity is rarely a diagnostic dilemma, many clinical seizures in the ICU may be difficult to differentiate from posturing, myoclonic jerks, or syncopal episodes. Even more difficult to diag- nose, nonclinical seizures may be misinterpreted as ence- phalopathies or other neurological or psychiatric disorders. Several toxic, metabolic, and infectious ence- phalopathies may present with an altered level of con- sciouness, body tone, and diminished speech.13,15,17–19 Staring and mutism can be seen with benzodiazepine withdrawal, encephalopathy, lithium toxicity, and psy- chogenic states. Increased tone with diminished con- sciouness can occur with serotonin syndrome, neuroleptic malignant syndrome, and tiagabine encephalopathies. All of these, as well as amnestic states such as transient global amnesia, can be differentiated from non- convulsive status epilepticus with the help of EEG. Comparisons of clinical features in syndromes resembling nonconvulsive status epilepticus are given in Table 2.

Nonconvulsive status epilepticus should be con- sidered in elderly patients with major irreversible brain injury, after sudden withdrawal of AEDs, after sudden withdrawal of benzodiazepines or propofol, and in any
<table>
<thead>
<tr>
<th>Distinguishing Features</th>
<th>Clinical Features</th>
<th>Lithium Toxicity</th>
<th>Neuroleptic Malignant Syndrome</th>
<th>Serotonin Syndrome</th>
<th>Creutzfeld-Jacob Disease</th>
<th>Malignant Hyperthermia</th>
<th>Baclofen Toxicity</th>
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<tr>
<td><strong>Clinical Features</strong></td>
<td>Confusion*</td>
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<td>Rigidity</td>
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<td>Myoclonias*</td>
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<td>Nausea</td>
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<td>Anorexia</td>
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<td>Visual changes</td>
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<td>Papiledema</td>
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<td>↑ Reflexes</td>
<td>Nystangmus</td>
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<td>Visual blurring</td>
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<td>Diarrhea*</td>
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<td>Other tests</td>
<td>WBC ↑</td>
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<td>CPK ↓; K ↑</td>
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<td>Myoglobinuria</td>
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<td>EEG</td>
<td>Seizure activity</td>
<td>Slow; TWs, focal, multifocal, or diffuse epileptic activity; seizures</td>
<td>Slow; TWs</td>
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<td>TWs/θ→Δ</td>
<td>Periodic waves</td>
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patient who does not awaken within 20 minutes of seizure onset.\textsuperscript{20} Nonconvulsive status epilepticus typically presents as an ictal impairment of cognition, subtle facial or limb twitches, eyes-open mutism, head or eye deviation, automatisms, and behavioral change. In the elderly, diagnosis is often delayed and mistaken for delirium, stupor, or other causes of confusion.\textsuperscript{21} This age group is particularly prone to de novo absence status, in which typical triggers are benzodiazepine dependence or withdrawal, a heavy burden of neuroleptic medications, female gender, intercurrent infections, or metabolic disturbance and epilepsy.\textsuperscript{21} Almost 75% of patients older than the age of 40 are women.\textsuperscript{22,23} Typical clinical features include mutism and perseveration, agitation, emotional lability, aggressiveness, and hallucinosis with face, eye, and limb myoclonus.

Once it is established that epileptic seizures are the diagnosis, it is prognostically useful to categorize patients according to distribution of EEG seizure activity and level of consciousness (e.g., acute status epilepticus for generalized seizure activity in the mildly confused patient, and electrographic status or subtle status (“burnt-out” status) when the patient is obtunded or in coma with generalized epileptiform activity after convulsive status. Such a categorization according to level of consciousness has been helpful in determining outcomes after nonconvulsive status epilepticus.\textsuperscript{24} Shneker and Fountain\textsuperscript{25} clearly demonstrated the importance of obtundation in prognosis, finding that 39% of patients died if they had severe mental status impairment, but only 7% if only mildly impaired.

**Electroencephalogram Diagnosis**

**CONVULSIVE SEIZURES**

Most clinical seizures do not need EEG confirmation. When motor activity is atypical or subtle, however, the EEG can be extremely useful to confirm or exclude the diagnosis and the response to anticonvulsant therapy.

**NONCONVULSIVE SEIZURES**

A typical EEG feature of nonconvulsive status epilepticus is a spike-and-wave at 3 to 3.5 Hz. They can be (1) rhythmic, generalized, synchronous, and symmetric; (2) an atypical spike and wave that lack one or more of these features; (3) multiple spike-and-wave-repetitive complexes of two or more spikes followed by a slow wave; and (4) rhythmic delta with intermittent spikes—characterized by high amplitude, repetitive, rhythmic, focal, or generalized delta activity with intermixed spikes or sharp waves.\textsuperscript{26} Generalized nonconvulsive status epilepticus patterns are varied.\textsuperscript{21} Discharges may be continuous, persistent with brief pauses of a few seconds, or intermittent (with pauses lasting several seconds or more). Ambiguous discharges, with more blunted morphologies at < 1.5 Hz, may resemble triphasic waves.\textsuperscript{15,18} Generalized nonconvulsive status epilepticus should have no significant EEG lateralization and no history of focal epilepsy. Patterns may evolve in morphology, amplitude, and frequency over time and may wax and wane, often with periods of normal or more normal background. For example, in one study, most generalized nonconvulsive status epilepticus were atypical spike and wave, with frequencies of $2.2 \pm 0.6$ Hz, in a persistent or continuous pattern.\textsuperscript{26} Young et al\textsuperscript{27,28} have added context and evolution features to the primary EEG criteria of frequency and morphological features in nonconvulsive status epilepticus. In borderline situations that lack pathognomonic features, the ictal nature of the disorder may be confirmed by the rapid clinical and EEG regression shortly after parenteral benzodiazepine administration.

Borderline EEG abnormalities include periodic epileptiform discharges and triphasic waves. Periodic epileptiform discharges refer to an *irritative* pattern temporally related to seizures proper. Such distinctions may assist with diagnosis, prognosis, and the intensity of patient clinical management. The clinical and EEG categorization of periodic epileptiform discharges, and its nomenclature, are largely derived from case series reports. Periodic epileptiform discharges that may occur without frequent clinical motor correlates include periodic lateralized epileptiform discharges (PLEDs), BIPLEDs (bilateral independent synchronous PLEDs), PLEDS-plus (PLEDs with transitional rhythmic discharges), GPEDs (generalized periodic discharges), and more recently SIRPIDs (stimulus-induced rhythmic periodic or ictal discharges).\textsuperscript{29} Periodic lateralized epileptiform discharges are surface-negative bi-, tri-, or polyphasic discharges consisting of spike, sharp, polyspike components, variably with slow-wave complexes lasting 60 to 600 milliseconds (mean 200 milliseconds), of 50 to 150 uV (sometimes 300 uV) in amplitude, usually occurring at 0.5 to 2.0 Hz (ranging from 0.2 to 3 Hz). PLEDS are commonly associated with seizures, which occur in 83 to 87% of patients during their illness.\textsuperscript{30,31} They usually occur 1 to 4 days after clinical seizure activity. They must last at least 10 minutes, and typically, the entire 20 minute recording. Clinical correlates include minor facial twitching, subtle limb jerks, and usually diminished level of consciousness. Pseudo-periodic lateralized epileptiform discharges reflect cortical irritability, often in the context of seizures in patients with structural brain abnormalities (abscess, stroke, or tumor). The PLED discharge frequency is usually slower than 1 Hz and usually occurs without a motor correlate. BIPLEDs are associated with seizures in 78% of patients with this finding.\textsuperscript{32} PLEDs-plus are associated with seizures in 74%.\textsuperscript{33} GPEDs are associated with seizures in 32 to 90%.\textsuperscript{34,35} GPEDs have been viewed
as “end-stage status epilepticus,” and those consistent with nonconvulsive status epilepticus had higher amplitude (110 v 80 uV); duration (0.5 v 0.3 seconds); and inter-GPED amplitude (34 uV v 17 uV). The concordance between PLEDs and seizures is 74 to 90% and between PLEDs and status epilepticus is 0 to 66%. 41 94% occur in hospitalized patients, leading to the conclusion that PLEDs were “equivalent to the terminal phase of status epilepticus.”

SIRPIDs also lie along an ictal–interictal continuum when cases lack a motor clinical correlate, but are more clinically consistent with an ictal phenomenon when elicited together with facial or limb jerking (a minority of patients). 36 This determination is somewhat arbitrary because seizures in motor (frontal) areas may induce more apparent clinical features. Many authors define PLEDs as nonictal, their distinguishing characteristics being their bi-, tri-, or polyphasic morphology; and their relatively static, nonevolving rhythmicity. 27,37,38 PLEDs in the context of status epilepticus, however, may be ictal as determined by their temporal relationship with clinical seizures, their timing, the clinical course, the PLED response to benzodiazepines, and an EEG evolution of frequency and amplitude change, terminating in a more typical seizure pattern. 39 Some studies have shown that PLEDs are associated with increased focal metabolism, again favoring an ictal rather than a nonictal nature. 40,41 The place of periodic epileptiform discharges along an ictal–interictal continuum, therefore, may occupy different points depending on their context. 38,42

Triphasic waves are defined by a low-amplitude initial negative–phase, a dominant positive slow rising second phase, and a slow-wave–appearing third phase. They appear as bursts of moderate- to high-amplitude (100 to 300 uV) rhythmic complexes, usually at 1 to 2 Hz, and occur in clusters. Triphasic waves frequently appear in toxic and metabolic encephalopathies; and in the context of behavior, cognition, tone, and motor disturbances are clinically indistinguishable from nonconvulsive status epilepticus. Common toxic and metabolic encephalopathies include hepatic and renal insufficiency; intoxication with lithium, baclofen, tia- gabine, ifosfamide, cefepime, and neuroleptic and serotonin syndromes. The distinction between triphasic waves and nonconvulsive status epilepticus may depend on the resolution of EEG rhythmic activity after benzodiazepine therapy, but without concomitant clinical improvement. This lack of clinical improvement in triphasic wave encephalopathy may be due to the underlying encephalopathic state causing the triphasic waves, rather than to conclusive evidence of a nonictal state. Arousal often causes triphasic waves to reappear. Working EEG distinctions between triphasic waves and nonconvulsive status epilepticus can be found in the literature. 43

**NONEPILEPTIC “SEIZURES”**

Pseudostatus epilepticus resembles recurrent epileptic attacks but without abnormal electrical discharges on EEG. Psychogenic seizures and pseudostatus epilepticus are estimated to occur in up to 28% of patients referred to epilepsy centers with intractable seizures, 44 although only 10% of patients with documented psychoseizures have been found to have EEG evidence of epilepsy. 45 The major concern is that treatment of pseudoseizures with anticonvulsants is associated with considerable morbidity including respiratory arrest. 46 Postoperative pseudostatus may not be uncommon. In a series of five patients with postoperative “status,” typical findings differentiating psychogenic attacks from an epileptic seizure syndrome were convulsive episodes lasting longer than 90 seconds, out-of-phase limb jerking, resistance to eye opening and closed eyes during a tonic-clonic attack, retained pupillary responses, and a history of multiple admissions for status epilepticus or previous postoperative “status.” 47 Pseudostatus epilepticus is not difficult to diagnose, but requires close observation of clinical findings.

**MANAGEMENT**

Treatment of seizures in the critically ill patient is complicated by multiple factors reducing the seizure threshold, which include multisystem organ dysfunction, metabolic abnormalities, use of sedatives and paralytics, therapeutic drugs that lower the seizure threshold, and a suboptimal environment for EEG recording. The importance of adequate EEG monitoring for prolonged periods cannot be overemphasized in this population. Up to 83% of patients successfully treated for convulsive status epilepticus and 100% treated for nonconvulsive status epilepticus remain comatose 12 hours after initiation of therapy. 48 Between 25 and 42% of patients presenting with status epilepticus have nonconvulsive status epilepticus, which would otherwise have been missed without EEG. 49-51 In a series of 101 patients with nonconvulsive seizures detected only by EEG, only half had the first seizure within the first hour of recording and only 80% had their first seizure by 24 hours. 52 It is recommended to provide at least 48 hours of EEG in comatose patients in whom seizures may be contributing to altered mental status (Table 3).

Several other important principles arise in the acute management of seizures:

- First, timely administration of effective AEDs within 5 to 10 minutes has been shown to be essential to prevent the emergence of status epilepticus and its associated neuronal damage and permanent cerebral injury. 53-56
GABA (gamma-aminobutyric acid) agonists penetrate with a benzodiazepine, usually lorazepam (Table 4). The witnessed clinical seizure in the ICU is initially treated

### Table 3 Status Epilepticus Treatment Algorithm in the Critically Ill Patient

<table>
<thead>
<tr>
<th>Clinical Seizure Activity in the Intensive Care Unit</th>
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<tbody>
<tr>
<td>Immediate Actions:</td>
</tr>
<tr>
<td>1. ABCs: give oxygen, start IV, and send appropriate blood work including glucose, AED levels, and toxicology screen if patient presents from outside of hospital; monitor EKG</td>
</tr>
<tr>
<td>2. Administer Thiamine 100 mg IV if alcohol abuse or poor nutrition suspected and then D50W 50 mL IV (unless glucose level known and adequate)</td>
</tr>
<tr>
<td>3. Lorazepam 2–4 mg IV OR diazepam 20 mg PR; repeat lorazepam in 5 minute if seizures persist</td>
</tr>
<tr>
<td>Second Line Therapy to maintain adequate AED levels:</td>
</tr>
<tr>
<td>1. Fosphenytoin (150 mg/min) or phenytoin (50 mg/min): 20 mg/kg IV with blood pressure and EKG monitoring OR</td>
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<tr>
<td>2. Valproate: 15–20 mg/kg IV OR</td>
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<tr>
<td>3. Levetiracetam: 500–2000 mg depending on renal function OR</td>
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<td>4. Phenobarbital</td>
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<tr>
<td>Third-Line Therapy if seizures persist:</td>
</tr>
<tr>
<td>1. Intubate patient</td>
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<tr>
<td>2. Midazolam IV: loading dose: 0.2 mg/kg; infusion rate: 0.1 mg/kg/h OR</td>
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<tr>
<td>3. Propofol IV: loading dose: 3–5 mg/kg; infusion rate: 1–15 mg/kg/h OR</td>
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<tr>
<td>4. Phenobarbital</td>
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<tr>
<td>5. Thiopental IV: loading dose: 75–125 mg boluses; infusion rate: 1–5 mg/kg/h</td>
</tr>
</tbody>
</table>

**ABCs**, airway, breathing, circulation; IV, intravenous; AED, antiepileptic drug; EKG, electrocardiogram; PR, anal. 

- Second, the efficacy of AEDs is highest (80% response rate) when treatment is initiated within 30 minutes, and their effectiveness declines progressively as treatment is increasingly delayed. 57
- Third, early treatment of seizures is associated with better outcomes. 58

### Single Seizure Progressing to Status Epilepticus

A witnessed clinical seizure in the ICU is initially treated with a benzodiazepine, usually lorazepam (Table 4). The GABA (gamma-aminobutyric acid) agonists penetrate the brain rapidly and improve local inhibition of signal transmission. Although diazepam, midazolam, or lorazepam can all be used successfully, lorazepam (Ativan®), Biovail Pharmaceuticals, Inc., Bridgewater, NJ has a longer therapeutic effect than diazepam with lower risk of venous thrombophlebitis and respiratory suppression, particularly in children. 58–60 Lorazepam is superior to phenytoin alone in terminating clinical and EEG seizures. 48 The usual dose is 0.1 mg/kg based on the results of the VA cooperative trial. A concurrent loading dose of intravenous phenytoin/fosphenytoin or other appropriate “second line” AED should be administered with continuous ECG and hemodynamic monitoring due to the potential for hemodynamic complication, especially hypotension (27%), respiratory depression (9.9%), and cardiac arrhythmia (6.9%) with phenytoin. 48 Phenytoin, which prolongs recovery of activated voltage-gated sodium channels, will successfully terminate seizures in 40 to 50% of patients who do not respond to initial benzodiazepine therapy. 53 Fosphenytoin, a water-soluble prodrug of phenytoin, is increasingly used over phenytoin due to the lower incidence of venous irritation. Fosphenytoin can be administered intravenously (IV) or intramuscularly (IM) at a rate up to 150 mg/min, although time to peak serum phenytoin levels is only slightly faster due to the need for enzymatic dephosphorylation. Phenytoin should almost always be administered by the IV route in critically ill patients due to impaired enteral absorption in patients receiving continuous nasogastric feeding. 62 The recommended goal free phenytoin level after a seizure is 1.5 to 2.5 μg/mL, corresponding to a total phenytoin level of 15 to 25 μg/mL in patients with normal protein binding. 63 Free phenytoin levels may become excessive in patients with low albumin, or on treatment with other highly protein bound drugs, such as valproate. Monitoring is important in the initial therapeutic phase to avoid phenytoin toxicity associated with a decrease in mental status and potential seizure worsening.

Although valproate sodium has not been approved in the United States for use in treating status epilepticus, Valproic acid (VPA) should be considered an alternative to phenytoin or as a third line agent if seizures persist after phenytoin loading, especially in patients in whom intubation is not an option. Valproate has been compared with phenytoin for status epilepticus in two prospective randomized trials. 64,65 In a randomized trial of 100 patients with benzodiazepine refractory status epilepticus, clinical seizure control within 20 minutes of start of infusion was similar in 50 patients treated with IV valproate 20 mg/kg (88% successful), and 50 patients treated with IV phenytoin 20 mg/kg (84% successful). There was no difference in seizure recurrence or tolerability between the two agents. Misra et al performed a randomized controlled trial of IV VPA (30 mg/kg) versus IV phenytoin (18 mg/kg) in 68 patients with convulsive status epilepticus. VPA was more effective than phenytoin in controlling convulsive status epilepticus, both as the first drug (66% vs 42%) and as the second drug (79% vs 25%). 55 In this study serum albumin levels were similar between groups and VPA was the first agent administered so that increased free levels of other AEDs (via displacement from albumin) and synergism do not explain the better efficacy of VPA over phenytoin as a first-line agent.
Valproate has a similar mechanism of action to phenytoin on sodium channels, but has other effects on neuronal calcium channels and on GABA metabolism. Valproate administered as a bolus followed by an infusion was successfully used to treat partial and generalized status epilepticus (absence, myoclonic, and tonic-clonic seizures) in 23 patients. In 19 of the 23 patients, status epilepticus regressed within 20 minutes of the intravenous bolus of 15 mg/kg followed by a 5- to 6-hour infusion of 1 mg/kg/h, starting 30 minutes after the bolus (the infusion rate of the bolus was not specified).

The adverse effects from VPA include hyperammonemic encephalopathy, hemorrhagic pancreatitis, bone marrow suppression, parkinsonism, rarely liver failure (VPA-induced hepatotoxicity – VHT), and thrombocytopenia which is usually dose related and benign. Hyperammonemia, defined as a serum ammonia level > 80 mg/dL occurs in 35 to 45% of patients on long-term VPA therapy. The hyperammonemia is predominantly of hepatic origin due to impaired urea cycle function (inhibition of carbamoylphosphate synthetase-I, the enzyme that begins the urea cycle) and inability to metabolize nitrogen loads. Hyperammonemia leads to an increase in brain glutamine levels which can produce astrocyte swelling and cerebral edema. VPA-induced hepatotoxicity and hyperammonemic encephalopathy may be the result of VPA-induced carnitine deficiency. Carnitine supplementation can decrease these adverse effects, although its clinical value has not been thoroughly investigated in large studies. We do not currently recommend routine carnitine supplementation during VPA therapy in the management of status epilepticus.

An intravenous phenobarbital bolus remains an effective second-line drug option, although this drug is used less frequently due to adverse effects, including respiratory depression, which in many cases requires intubation, decreased consciousness, and hypotension. The prolonged effect is advantageous and many patients can come off the ventilator quickly due to acute tolerance. The loading dose is 15 to 20 mg/kg IV and the recommended serum level is > 30 mg/mL. High-dose phenobarbital has been reported to stop refractory status epilepticus in 70% (7/10) of adult patients in one study from Thailand. Phenobarbital dosage ranged from 40 to 140 mg/kg/day.

Levetiracetam (Keppra, UCB Pharma, Inc., Brussels, Belgium) is increasingly being used in the early management of seizures and status epilepticus. The mechanism of action, which is not well understood, involves inhibition of high-voltage-activated Ca\(^{2+}\) channels and enhanced activity of potassium channels that maintain resting membrane potential. Advantages include lack of hepatic metabolism or interactions with other medications and few cardiac or peripheral venous effects compared with phenytoin. The half-life is 6 to 8 hours. Approximately half of levetiracetam is removed during hemodialysis such that supplemental doses are required after dialysis. Several small studies suggest intravenous levetiracetam can be used successfully in patients with status epilepticus unresponsive to benzodiazepines or other initial therapy.
doses have ranged from 500 to 3000 mg/day and rapid administration of high doses up to 4000 mg over 15 minutes was tolerated in healthy subjects based on tolerability and safety studies of intravenous leviteracetam.\textsuperscript{78} Large prospective randomized controlled studies are planned to investigate the efficacy and safety of leviteracetam for treatment of status epilepticus.

**Refractory Convulsive Status Epilepticus**

Many patients with clinical seizures improve quickly on standard AED regimens. However, failure of first and second-line anticonvulsant agents to terminate status (defined as refractory status epilepticus) should lead to the use of definitive infusion therapy in general anesthetic doses in association with endotracheal intubation. Only 7% of patients will respond to a loading dose of a third agent (such as phenobarbitol) if they did not respond to appropriate doses of first and second-line agents.\textsuperscript{48} Refractory status epilepticus develops in 31 to 44% of all patients with status epilepticus.\textsuperscript{48,79,80} Midazolam, propofol, and pentobarbital are most frequently used; alternatives include ketamine, thiopental, and isoflurane, or other halogenated hydrocarbon anesthetic gases. The role of newer agents (e.g., valproate, levetiracetam, or topiramate) remains to be determined. Intubation for patients with generalized convulsive status epilepticus usually requires neuromuscular blockade. A short-acting nondepolarizing agent such as rocuronium bromide or vecuronium is preferred over succinylcholine (defined as refractory status epilepticus) should lead to the use of definitive infusion therapy in general anesthetic doses in association with endotracheal intubation. Only 7% of patients will respond to a loading dose of a third agent (such as phenobarbitol) if they did not respond to appropriate doses of first and second-line agents.\textsuperscript{48} Refractory status epilepticus develops in 31 to 44% of all patients with status epilepticus.\textsuperscript{48,79,80} Midazolam, propofol, and pentobarbital are most frequently used; alternatives include ketamine, thiopental, and isoflurane, or other halogenated hydrocarbon anesthetic gases. The role of newer agents (e.g., valproate, levetiracetam, or topiramate) remains to be determined. Intubation for patients with generalized convulsive status epilepticus usually requires neuromuscular blockade. A short-acting nondepolarizing agent such as rocuronium bromide or vecuronium is preferred over succinylcholine chloride due to the potential for hyperkalemia and cardiac arrhythmia in the setting of possible rhabdomyolysis. Continuous EKG monitoring and pulse oximetry is essential for patients with status epilepticus. Sudden unexpected death in epilepsy rarely occurs and is thought to be due to sympathetically mediated cardiac arrhythmias.\textsuperscript{81} Hypoxemia secondary to apnea, airway obstruction, aspiration or neurogenic pulmonary edema is common, and most patients will require intubation after large doses of benzodiazepines.

Although the dose of the AED is the most important factor determining success of first and second line drugs, the mechanism of the AED may be important as seizures evolve. Clark and Prout\textsuperscript{82} described three sequential phases of status epilepticus: impending status epilepticus—continuous or intermittent seizures without full recovery of consciousness between seizure of more than 5 minutes; established status epilepticus—clinical or EEG seizures lasting more than 30 minutes without regaining consciousness between seizures; and subtle status epilepticus—a late, burned out stage of status epilepticus when motor and EEG manifestations are attenuated.\textsuperscript{78,79,82,83} Resistance to anticonvulsants follows a similar time-dependent course. Experimentally, the initiation of self-sustaining status epilepticus is easily stopped by agents that either enhance inhibition or reduce excitation.\textsuperscript{84,85} After the first 30 minutes of status epilepticus, the potency of benzodiazepines decreases 20 times, whereas phenytoin potency decreases more slowly.\textsuperscript{86} In established self-sustaining status epilepticus, seizures can only be terminated by a few agents that mostly inhibit glutamatergic transmission such as ketamine.\textsuperscript{84} N-methyl-D-aspartic acid blockers are not effective in the initial 10 to 15 minutes of seizures, but become more effective later in the course of status epilepticus.\textsuperscript{84} Pathophysiologically, the transition from seizures to status epilepticus is associated with endocytosis and a decrease in functional hippocampal GABA\textsubscript{A} receptors, which has been postulated as a mechanism of failure of GABA agonists such as benzodiazepines during the course of status epilepticus.\textsuperscript{86,87} Simultaneously, recruitment of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-D-aspartic acid receptor subunits occurs from subsynaptic sites to the synaptic membrane enhancing the proconvulsant state and possibly explaining the improved potency of N-methyl-D-aspartate (NMDA) blockers late in the course of status epilepticus.\textsuperscript{83,88}

It would seem optimal to choose AEDs initially with potent GABA\textsubscript{A} receptor activity and then add an agent with NMDA antagonism if seizures become refractory. Midazolam, a GABA\textsubscript{A} agonist, is shorter acting than barbiturates with less hypotension than either barbiturates or propofol and is a reasonable first choice, usually terminating status epilepticus in less than 1 hour.\textsuperscript{16} Doses typically range from 0.1 to 0.4 mg/kg/h after a loading dose of 0.2 mg/kg IV. The initial half-life is 1.5 to 3.5 hours, although with prolonged use, persistent escalation of dose is needed due to tolerance and tachyphylaxis, and the half-life increases up to several days.\textsuperscript{89} The EEG cannot be fully suppressed with midazolam. A meta-analysis of midazolam, propofol, or pentobarbital for the treatment of refractory status epilepticus found that titration of treatment to EEG background suppression was associated with a lower frequency of breakthrough seizures (4 vs 53%; \( p < 0.001 \)).\textsuperscript{90} In the same study, midazolam was associated with slightly (nonsignificant) lower mortality (midazolam 46% vs propofol 52% vs pentobarbital 48%), but more breakthrough seizures (midazolam 51% vs propofol 15% vs pentobarbital 12%) and more withdrawal seizures within 48 hours of discontinuation (midazolam 63% vs propofol 46% vs pentobarbital 43%).

If benzodiazepines are insufficient to control seizure activity, many practitioners will either switch to or use propofol (2,6-diisopropylphenol) as the first choice infusion agent. The major benefits of propofol are a rapid onset of action of < 3 minutes, and a short wash-out time due to its short half-life (1 to 2 hours after prolonged administration).\textsuperscript{91} Propofol is a sedative-hypnotic agent with a diverse mechanism of action. It activates GABA\textsubscript{A} receptors directly, inhibits the
NMDA receptor, and modulates calcium influx through slow calcium-ion channels. It reduces cerebral blood flow and intracranial pressure (ICP), is a potent antioxidant, and has antiinflammatory and immunomodulatory activity. The loading dose of propofol for status epilepticus is 2 mg/kg, followed by an infusion rate of 2 to 10 mg/kg/h. Vasopressors are usually required to maintain adequate blood pressure. It is reasonable to wean off propofol after 24 hours of successful seizure control, although the data for this is lacking. Practice guidelines support either elimination of EEG epileptic activity or titration to burst suppression for 12 to 24 hours with propofol, barbiturates, or midazolam.93–95 Propofol should be weaned slowly with continuous EEG monitoring as both induction and withdrawal of propofol has been associated with seizures.96 Propofol infusion syndrome has been described in case reports of adults being treated with propofol for status epilepticus.97,98 The clinical features of propofol infusion syndrome are acute refractory bradycardia leading to asystole, in the presence of one or more of the following: metabolic acidosis, rhabdomyolysis, hyperlipidemia, and enlarged or fatty liver.99 The identified risk factors are lean body mass index, high dose (>4 mg/kg/h), and administration of more than 48 hours duration. Creatine phosphokinase, lactic acid levels, lipids, electrolytes, and arterial blood gases should be monitored frequently. Hemodialysis is recommended if this syndrome is suspected. Combining propofol at the lowest effective dose with a benzodiazepine (clonazepam) in 31 patients with refractory status epilepticus was associated with a low mortality rate (22%) and no occurrence of propofol infusion syndrome.100

The barbiturates act on GABA_A receptors, but are also NMDA antagonists and have an effect on calcium channels.101 Thiopental, used in Europe for treating status epilepticus, is loaded at 2 to 4 mg/kg and then infused at 3 to 5 mg/kg/h. The half-life is 3 to 11 hours at serum levels <30 mg/L, but is significantly prolonged up to 60 hours at higher serum concentrations.16 Pentobarbital, used more often in North America, is loaded repeatedly at 5 mg/kg until seizures stop and then infused at a rate of 0.5 to 10 mg/kg/h. With prolonged administration, the half-life of pentobarbital is similar to that of thiopental (15 to 22 hours vs 14 to 36 hours). Hypotension appears to be most profound with barbiturate therapy. These agents have several inhibitory effects on lymphocyte and leukocyte functions causing increased infection rates in patients treated with barbiturate coma.102 Routine surveillance cultures of blood, urine, and sputum are recommended for patients on long-term therapy.

Ketamine, an NMDA receptor antagonist with agonist effects at the GABA_A receptor and neuroprotective properties, has been reported to successfully terminate status epilepticus in case reports, although most literature is experimental.103,104 In animal models, it appears to be more useful in controlling prolonged status epilepticus (after 1 hour) as opposed to early status epilepticus.105 The loading dose of ketamine is 2 mg/kg followed by an infusion of 10 to 50 μg/kg/min. The main hemodynamic effects are hypertension and tachycardia. Prolonged infusion may be associated with neurotoxicity (cerebellar and cortical atrophy).104

Other agents with reports of successful termination of status epilepticus include lidocaine, inhalation anesthetics, and topiramate. The usefulness of lidocaine for status epilepticus is supported by many case reports.106 The benefits include a short half-life and low risk of central nervous system and respiratory depression. The initial intravenous lidocaine dose ranges from 1 to 3 mg/kg followed by a maintenance infusion after termination of status epilepticus. Contraindications to lidocaine use are sinoatrial node disorders, atrioventricular block, and severe myocardial depression. The inhalational anesthetics, isoflurane with or without desflurane, have been described for use when other agents have failed.107,108 Epileptic discharges are effectively stopped and burst suppression rapidly achieved. Other advantages include rapid elimination and the reduced potential for toxic effects on organs owing to their relative resistance to biotransformation.109 Nasogastric topiramate was described as effective in terminating both generalized convulsive and nonconvulsive refractory status epilepticus in six patients, including one in prolonged pentobarbital coma.110 Effective doses ranged from 300 to 1,600 mg/d. The authors postulated decreased potential for pharmacoresistance due to topiramate’s multiple mechanisms of action. The only reported side effect was lethargy.

For any of the above infusions, patients should have continuous EEG and close hemodynamic monitoring, and be mechanically ventilated. Concurrently, other nonsedating anticonvulsants should be optimized. Seizure control may not require reaching burst suppression, and burst suppression does not always imply seizures have been terminated. A more appropriate goal, therefore, is suppression of all seizures, as burst suppression has not been associated with improved clinical outcome nor has an optimal burst-suppression interval been defined.80,111

Malignant status epilepticus has been defined as persistent clinical and/or electrophysiologic epileptic activity immediately recurring within 5 days after tapering of the maximal dose of IV anesthetic anticonvulsants required to achieve burst suppression on EEG.112 In a retrospective cohort study, 20% of 35 episodes of refractory status epilepticus evolved to malignant status epilepticus. Compared with refractory status epilepticus (failure to respond to first-line anticonvulsants), patients with malignant status epilepticus were younger and more
likely to have encephalitis. Outcomes were poor with a high level of functional dependency (five of six surviving patients). The management of malignant status epilepticus is not well defined, although administration of non-GABAergic drug, such as ketamine hydrochloride, is encouraged with anecdotal evidence of clinical success after failure of GABAergic anesthetics.\textsuperscript{113,114} The mechanism supports increased NMDA receptor expression with ongoing seizure activity.

Nonconvulsive Status Epilepticus

Currently, the literature does not support aggressive treatment requiring intubation outside of the setting of generalized convulsive status epilepticus, although this has not been adequately studied. In the case of nonconvulsive status epilepticus, treatment needs to be tailored to the perceived urgency and morbidity of the condition.\textsuperscript{115} Because prognosis varies by cause and may be a byproduct of the morbidity conferred by the inciting brain insult, some experts advocate oral or intramuscular treatment, or supplementation with antiepileptic drugs; others recommend careful monitored use of IV benzodiazepines. In absence status, IV valproate has also been successful.\textsuperscript{67,116} We have used IV valproate sodium to treat a patient with generalized nonconvulsive status epilepticus, thus avoiding sedation and hospital admission.\textsuperscript{116} Most experts, except for unusual cases, are reluctant to advocate the use of anesthetic agents or iatrogenic coma for nonconvulsive status epilepticus.\textsuperscript{115} Some suggestions on treatment in nonconvulsive status epilepticus are given in Table 5.

Nonpharmacological and Experimental Therapies for Status Epilepticus

Nonpharmacological approaches to refractory status epilepticus include cortical and deep brain stimulation, vagal nerve stimulation,\textsuperscript{117} transcranial magnetic stimulation,\textsuperscript{118} electroconvulsive therapy,\textsuperscript{119} plasmapheresis,\textsuperscript{120} and surgical resection of cortical tissue for focal electrographic status epilepticus.\textsuperscript{121} Recently, Corry et al reported four patients with refractory status epilepticus treated with hypothermia to a target temperature of 31°C to 35°C using an endovascular cooling system.\textsuperscript{122} Patients required transient neuromuscular blockade during induction to facilitate rapid cooling and prevent excessive EEG artifact. Seizure activity was aborted in all patients allowing discontinuation of midazolam infusions. Two patients remained seizure free with rewarming and all had a significant reduction in seizure activity. It is well established that hypothermia can produce electrocortical silence in humans possessing both neuroprotective and antiepileptic properties.\textsuperscript{123} Further research into hypothermia for refractory status epilepticus is needed.
epileptics is needed to determine the best target temperature, optimal duration of therapy, and extent of EEG suppression.

Outcome after status epilepticus is primarily determined by underlying etiology of the seizures, patient age, duration of status epilepticus, and the occurrence of ICU-related medical complications, such as sepsis. Two large American studies and one large French study all had similar overall mortality after status epilepticus of 21 to 22%. Prolonged status epilepticus (> 60 minutes) was associated with a 30-day mortality rate of 32%, compared with 2.7% in shorter duration status epilepticus (30 to 59 minutes). Nonconvulsive status epilepticus has a reported mortality rate of 18% when associated with significant medical comorbidity. In a recent study of 140 adults with status epilepticus, independent predictors of 30-day mortality were patient age, initial Glasgow Coma Score (GCS), and seizure severity with continuous, symptomatic and refractory seizures having the worst prognosis. Refractory status epilepticus is associated with encephalitis and not with insufficient levels of AEDs. Alcohol and drug withdrawal-related status epilepticus has a better prognosis than etiologies associated with structural brain injury, such as anoxic brain injury, vascular lesions, and brain tumors, which are all associated with poorer outcomes. Progression to chronic epilepsy occurs in up to 90% of patients with status epilepticus and develops significantly more often following refractory status epilepticus.

SUMMARY

Management of status epilepticus is particularly challenging due to its heterogeneous etiologies, manifestations, and response to therapy. The importance of continuous digital format EEG recording cannot be overestimated in the diagnosis and management of the seizure patient. Although rapid initiation of empiric therapy remains the cornerstone of successful management, future research is required to individualize therapy based on seizure mechanism, etiology, duration, and an improved understanding of dynamic and cellular changes that potentiate status epilepticus and neuronal injury.

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