INTRODUCTION

Definitions and Classifications

The classification system used by the International League Against Epilepsy (ILAE) is probably the most commonly used system for epilepsy. Herein, I talk about status epilepticus (SE) using parts of their more recent classification documents (1,2), except for that which does not address SE (3).

The definition of SE is, itself, embroiled in controversy. The 1993 ILAE guidelines for epidemiologic studies give a definition of SE as a seizure lasting more than 30 minutes, or more than one epileptic seizures where function has not been regained for more than 30 minutes (4). In certain animal models, 30 minutes is the time in which neuronal injury occurs, so there is logic to the 30-minute window; unfortunately, none of the American Academy of Neurology (AAN) class I trials on SE use the 30-minute definition. The Veterans Administration SE cooperative trial, for example, used 10 minutes as its inclusion criteria; others have suggested time periods ranging from 5 to 15 minutes (5). In keeping with this definitional controversy, a Yale University study of patients with complex partial seizure control criteria; others have suggested time periods ranging from 5 to 15 minutes (5). In keeping with this definitional controversy, a Yale University study of patients with complex partial status epilepticus found no significant difference between episodes of SE lasting more or less than 30 minutes (6). This has led some to create an operational, or impending, definition of SE, in which a seizure is treated as if it were SE after 5 minutes, even if it cannot be formally diagnosed until 30 minutes.

The classification of SE contains 11 different types and subtypes:

1. Epilepsia partialis continua (EPC) of Jevnikov: This is a combination of focal seizures with ongoing twitching of the same area. There are three subtypes of EPC:
   a. Rasmussen syndrome—EPC with Rasmussen syndrome has focal myoclonus and focal seizures emanating from the same hemisphere. There is variability to the EEG correlate of the myoclonic jerks, and there is persistence of the jerks in sleep. The EEG shows progressive background slowing in the affected hemisphere. Antiepileptic drugs (AEDs) are largely ineffective for the treatment of Rasmussen-related EPC (7).
   b. Focal lesions—EPC with focal lesions have jerks affecting the same area as the focal seizures, but do not persist in sleep. These can persist for days to months and may also be seen with nonketotic hyperglycemia. Treatment is generally with AEDs and discovering the underlying cause. Focal lesions do not represent the same kind of emergency as generalized convulsive SE. One group noted that the range of EPC lasted from 1 hour to 48 months (8). In their series, there were 26 patients in whom seizures remained uncontrolled; only three died. In another series of 46 patients with EPC, four died due to underlying infarction, nine had morbidity: six due to underlying cause, one due to the status, and two of unclear etiology (9).
   c. Inborn errors of energy metabolism—EPC with inborn errors of metabolism have unilateral then bilateral rhythmic jerks, which persist in sleep, with an EEG correlate. These inborn errors of metabolism for which EPC occurs are the ones affecting energy metabolism, like MERRF (myoclonic epilepsy with ragged red fibers) or Alpers syndrome. These cases are quite rare, and there are only case reports and small case series of published experience. In general, expert consultation is advised, and treatment is not particularly likely to be successful. It is probably best to avoid the use of valproic acid in these patients (10).

2. Supplementary motor area (SMA): There are two subtypes of SMA.
   a. Subgroup 1 is composed of individual tonic motor seizures that occur every few minutes through the night.
   b. Subgroup B is composed of repetitive seizures, which evolve to a bilateral, convulsive seizure, which then become repetitive asymmetrical tonic motor seizures with impairment of consciousness.

3. Aura continua: These involve seizure episodes without impairment of consciousness, with symptoms—depending upon localization—which wax and wane, often for hours. Symptoms may include a motor component, dysesthesia, painful sensations, or visual changes. Perhaps the most common form is limbic aura continua, which may include fear, epigastic rising, or other limbic features, which recur every few minutes for hours or longer; EEG correlation is variable and these can evolve into, or alternate with, dyscognitive focal status (see below section 4). In such cases, the seizures are categorized as dyscognitive focal seizures. Treatment depends upon etiology; if the seizure develops after a neurosurgical procedure, it may explain hemiparesis or aphasia of unknown etiology, even days after surgery, and can be treated with an AED (11). If the etiology is related to a nonsurgical cause of epilepsy, the condition is typically chronic, and treatment is meant to provide symptomatic relief (12); in these cases, there is no emergency.

4. Dyscognitive focal (focal seizures with impairment of consciousness or awareness leading to status epilepticus). These are most commonly called complex partial seizures and are divided into two types.
   a. Mesial temporal dyscognitive focal SE are a series of dyscognitive focal seizures without clear return of consciousness between events. Electrographic onset can be unilateral, or can alternate sides.
   b. Neocortical dyscognitive focal status epilepticus is unpredictable. It may mimic absence status, generalized tonic–clonic status, or repetitive discrete seizures; the
Genetic epilepsy is one in which a known or presumed genetic and structural/metabolic causes, commonly (but not always) evolving into bilateral, convulsive seizures from a focal start; sometimes the process is unilateral. There are several important features that are not mentioned in the ILAE classification. For example, with GCSE there is always profound impairment of consciousness. There can be variable combinations of tonic, clonic, or tonic–clonic seizures in an episode of SE. It is important to note that, at least for focal-onset tonic–clonic seizures, they are in a dynamic state. If SE continues, the motor manifestations may wane, until there are only subtle movements, often termed subtle status (see below section 9) Before the motor manifestations wane, there will be a clear ictal EEG component which ends abruptly when the seizure ends. If the patient does not fully return to baseline before the next tonic–clonic seizure starts, it is termed tonic–clonic SE. Treatment of GCSE will be dealt with in a later section.

Genetic epilepsy is one in which a known or presumed genetic defect(s) results in seizures which are the core symptom of the disorder. A structural/metabolic epilepsy is one in which there is a demonstrated increased risk of epilepsy with the structural or metabolic condition.

5. Tonic–clonic seizures are what people generally think about when they consider status epilepticus, but the more proper term is generalized convulsive status epilepticus (GCSE); some use the term status epilepticus to mean GCSE, but this is confusing, and should be avoided. GCSE may appear as a primary generalized event from genetic and structural/metabolic causes, commonly (but not always) evolving into bilateral, convulsive seizures from a focal start; sometimes the process is unilateral. There are several important features that are not mentioned in the ILAE classification. For example, with GCSE there is always profound impairment of consciousness. There can be variable combinations of tonic, clonic, or tonic–clonic seizures in an episode of SE. It is important to note that, at least for focal-onset tonic–clonic seizures, they are in a dynamic state. If SE continues, the motor manifestations may wane, until there are only subtle movements, often termed subtle status (see below section 9) Before the motor manifestations wane, there will be a clear ictal EEG component which ends abruptly when the seizure ends. If the patient does not fully return to baseline before the next tonic–clonic seizure starts, it is termed tonic–clonic SE. Treatment of GCSE will be dealt with in a later section.

Genetic epilepsy is one in which a known or presumed genetic defect(s) results in seizures which are the core symptom of the disorder. A structural/metabolic epilepsy is one in which there is a demonstrated increased risk of epilepsy with the structural or metabolic condition.

6. Typical and atypical absence seizures: Absence and atypical absence may actually be several different types of SE, which have a similar presentation. Both absence and atypical absence may be seen in genetic epilepsies, and are terminated by AEDs. In generalized structural/metabolic epilepsies, there may be overlap with focal SE, due to frontal focal lesions. In the elderly, new-onset absence SE may be seen; there are also drug-induced, and drug-withdrawal versions of absence SE. The ILAE terminology does not capture some significant details of these events, which make them appear to be different phenomena. However, there are five well-described versions of absence seizures, given below.

a. Absence status epilepticus is typically considered to be a component of genetic epilepsy, with impairment of consciousness. The level of impairment is often “individual-variable,” with about 20% having slight clouding of consciousness, about 60% a confusional state in which the patient is typically calm but does not interact with the environment, and about 20% with more severe impairment; there are sometimes accompanying subtle jerks of the eyelids during the event. The EEG correlate is bilateral and symmetric, typically bifrontally predominant, spike or polyspike and wave complexes at least 2.5 Hz, at least initially during the event; other patterns are also possible. This type of status recurs in most patients, and rarely can occur frequently (16). Neuronal damage is unlikely to occur with this type of status, and as such, aggressive treatment is not recommended (17). Most commonly, intravenous benzodiazepines will terminate the event. If ineffective, one may consider using intravenous valproic acid (18). Additionally, valproic acid may be effective in reducing recurrent events in patients with multiple episodes of absence status.

b. Atypical absence status is more commonly encountered in patients with structural/metabolic epilepsy, presenting with a fluctuating level of consciousness; it is also seen in patients with genetic epilepsy. This fluctuating confusional state is different than absence SE, which usually has a certain level of impairment. The ictal semiology is quite different than absence status, because it can include tonic, atonic, myoclonic, or otherwise lateralized phenomena. The EEG is spike, and polyspike and wave complexes, which are irregular, but even when quasirhythmic, occur at less than 2.5 Hz; these episodes may recur. The atypical episodes are generally not amenable to benzodiazepine treatment. In patients with recurrent atypical absence SE with an underlying genetic epilepsy, valproic acid may be particularly helpful in reducing recurrences. Atypical absence SE is likely a form of status not causing neuronal damage (19).

c. Absence SE with focal features is most typically encountered in frontal lobe localization-related epilepsy. There is impairment of consciousness, but the level of impairment may be individual dependent. The EEG is typically bilateral, but asymmetric and may develop into one looking like absence SE later in the episode. Treatment response varies with individual.

d. Late-onset, de novo absence SE occurs in older adults, with an underlying toxic or metabolic issue leading to seizures. Such patients can have repeated episodes with recurrent toxic/metabolic issues causing further episodes of SE. The preferred treatment is to deal with— including prevention—the underlying toxic/metabolic cause, but the individual episode can be typically easily terminated with benzodiazepines (18). Of note, there may not be a need to treat these patients with long-term AED therapy (20).

e. Myoclonic absence seizures are proximal, predominantly upper extremity myoclonic jerks synchronized to the 3 Hz spike and wave seen on the EEG during the SE. These can last for hours or days, and are most commonly refractory to therapy. Treatment is possible for some patients, and, in particular, withdrawal of agents known to aggravate idiopathic generalized epilepsies (like carbamazepine) may be beneficial (21).

7. Myoclonic seizures do not cause a change in consciousness. There is irregular, typically bilateral, myoclonic jerking which may persist for hours. Seen in conjunction with Dravet syndrome, myoclonic atactic epilepsy, nonprogressive myoclonic epilepsy in infancy (especially Angelman syndrome), and incompletely controlled juvenile myoclonic epilepsy. It can be benign, without untoward sequelae (22).

The ILAE report makes no mention as to whether negative myoclonic status, like that which may be seen in continuous spike-wave in slow wave sleep qualifies as myoclonic
seizures; there is a logic to including it in this part of the classification schema. In myoclonic SE, there is a limb, often in the upper extremity, which becomes paralyzed, but has continued, brief atonic episodes. There can be alteration of consciousness with these events, which can appear during the episode, with risk that the abnormalities may persist after the episode ends. Myoclonic seizures are associated with anoxic encephalopathy. In the era before induced hypothermia was used, the appearance of these seizures heralded a dire prognosis; this may no longer be the case.

8. In tonic SE, the patient will have brief tonic spasms, which can continue for hours, interspersed with periods of apparent calm. Most typically, if the patient is lying down, the neck and arms are flexed. Tonic SE may occur with both structural/metabolic and genetic epilepsies; with structural/metabolic seizures, the duration can be longer than hours.

9. Subtle SE is the end result of uncontrolled tonic–clonic SE, with focal or multifocal myoclonias, coma, periodic lateralized epileptiform discharges (PLEDs), and a slow suppressed background EEG (23,24); the myoclonias may not be epileptic in nature. The ILAE guidelines do not provide details of the myoclonias, but they are typically in the form of subtle twitches of the trunk or extremities, and can also present as nystagmus. The EEG typically is composed of ictal, but asymmetrically bilateral, rhythmic discharges. While the ILAE guidelines are silent about progression, eventually, there is complete loss of motor component, with only ongoing ictal EEG activity; electrocerebral silence ensues if the seizure is not controlled.

10. Nonconvulsive status epilepticus (NCSE) is not part of the ILAE definition, yet is likely more frequently encountered in properly monitored ICU patients than all other forms of SE. While NCSE rarely appears as the end stage of tonic–clonic SE, it is far more frequently found in ICU patients with unexplained mental status. While NCSE represents about 30% to 40% of all cases of SE, with an estimated incidence of 5 to 9 per 100,000 individuals per year. However, the true incidence of NCSE may be underestimated. In fact, in various studies the reported incidence of NCSE in ICU patients with altered mental status ranged from 8% to 37% (31–35). Diagnosis requires clinical suspicion and long-term EEG monitoring, which is not routinely performed on critically ill patients in many institutions.

Mortality from SE, estimated in most studies at 10% to 20%, rises significantly with age (36), reaching 38% in the elderly (60 years of age or greater) (27). One of the primary predictors of poor outcome is prolonged seizure; a seizure lasting more than 1 hour has mortality reaching 32%, compared to 2.7% with shorter seizures (36,37). Mortality from NCSE seems to be higher, averaging 50% (38).

**Etiology**

In about 30% of cases, SE occurs in patients with chronic epilepsy and is due to withdrawal, or low blood concentrations, of AEDs (37,39,40). In the majority of cases, SE occurs in patients with no history of epilepsy and may be due to a variety of causes, most commonly intracranial pathology, such as ischemic stroke, intracerebral ICH and subarachnoid hemorrhage (SAH), CNS infections, head trauma, and brain tumors. Other etiologies include cardiac arrest and hypoxic/anoxic brain injury, alcohol-withdrawal, metabolic disturbances, and toxic causes. In some patients, no cause is identified (39,40).

Both acute and chronic intracranial pathology can cause seizures. Seizures and SE may actually be the presenting signs of several neurologic conditions. This is true for intracranial hemorrhage, including SAH and ICH, acute embolic stroke, and brain tumors. Approximately 50% of patients with brain tumors experience seizures (41,42), and a seizure is the presenting sign of a tumor in 23% of cases (43). Seizures can also be the presenting sign of an acute stroke (44) and frequently occur in the first 2 weeks after a stroke. It is estimated that seizures occur in up to 6% of patients with ischemic stroke, up
to 18% of patients with ICH, and up to 26% of patients with SAH (44,45). Up to 2.8% of patients with stroke go into SE either at presentation, or within 2 weeks, of their stroke (46). The risk of chronic epilepsy is 17 times higher after an ischemic stroke than the general population (47), and the risk of having a seizure or developing chronic epilepsy after any type of stroke is 11.5% (48). In SAH, generalized tonic–clonic seizures have been reported in up to 26% of patients at the time of onset or shortly after onset (45,49), and NCSE occurred in 8% of patients who survived the first 48 hours and had an unexplained decline in their level of consciousness (50).

Metabolic disturbances that may cause seizures include hyponatremia, hypoglycemia, hypocalcemia, hypomagnesemia, uremia, hepatic encephalopathy, and hyperosmolar states (50). However, it is important to note that metabolic encephalopathies can frequently cause EEG abnormalities that can be difficult to distinguish from subtle seizure activity, such as high-amplitude slowing and triphasic waves. Therefore, extra care should be taken to avoid both over- and underdiagnosing patients as having SE when they have a clear metabolic dysfunction; response to treatment may be critical in these situations.

Several drugs can cause seizures at toxic levels, including some analgesics such as meperidine, propoxyphene, and tramadol; some psychiatric medications such as bupropion, tricyclic antidepressants, lithium, olanzapine, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and clozapine. Theophylline, isoniazid, lidocaine, phenothiazines, and some antibiotics such as imipenem/cilastatin, penicillins, and ciprofloxacin may also induce seizures. Furthermore, several commonly abused drugs can cause seizures, most notably cocaine, amphetamines, phencyclidine, and γ-hydroxybutyric acid (51,52).

**PATHOPHYSIOLOGY AND MECHANISMS**

The great majority of seizures stop spontaneously in less than 2 minutes (53). This is most likely due to inhibitory mechanisms that attempt to deter any excessive, abnormal neuronal activity. This inhibition is evident on the EEG as postictal slowing and attenuation. It is believed that SE occurs when inhibitory mechanisms fail, resulting in a self-sustaining and prolonged seizure activity; the exact cause of this failure is not well understood. A large number of elegant experiments done on animal models of SE have attempted to shed light on the underlying mechanisms causing SE. Review of these studies is beyond the scope of this chapter; however, two points are worth discussing, since they have important implications on treatment strategy.

Self-sustaining SE can be easily triggered in animal models using electrical stimulation (54). However, this can be blocked by many drugs that increase inhibition or reduce excitation only if administered early, prior to the development of a self-sustained seizure (55). In contrast, once a self-sustaining state is established, it becomes more difficult to stop the seizure (56), and much higher dosages of inhibitory drugs are required, leading to significant toxicity, including cardiovascular depression (57). Another important feature of self-sustaining SE is the progressive development of resistance to AEDs. The anticonvulsant potency of benzodiazepines can decrease by 20 times within 30 minutes of self-sustaining SE (58). The same phenomenon was observed with other anticonvulsants, such as phenytoin; however, the decline in potency was slower (59).

Pathophysiologically, SE produces a number of neurologic and systemic changes. Primary neurologic complications occur in both convulsive and some forms of nonconvulsive SE, and are time dependent and probably preventable with early termination of the seizure. In animal models of SE, neuronal injury occurs even in the absence of convulsive activity (60,61), and cell death is thought to result from excessive neuronal firing through excitotoxic mechanisms (62). It is impossible to replicate these experiments in human beings; however, there is widespread belief—supported by some anecdotal evidence—that neuronal injury and death occur after prolonged seizures. For example, brain damage and decreased hippocampal neuronal density are often seen in patients who die from SE (63,64). Furthermore, cerebral edema and chronic brain atrophy seen on neuroimaging studies have been reported after SE (65–68).

Systemic complications of prolonged seizures are seen primarily in GCSE, and are due to autonomic hyperactivity and excessive muscle activity. Therefore, systemic complications can potentially be prevented, or minimized, with early termination of seizure activity or induction of muscle paralysis and artificial ventilation (61). Pathophysiologic manifestations include increased systemic blood pressure, tachycardia, and cardiac arrhythmias; increased pulmonary blood pressure; increase in cerebral blood flow; elevation of body temperature; increased peripheral white cell count; transient pleocytosis in the spinal fluid; and a marked metabolic acidosis (60,69,70). Epinephrine levels are elevated and reach the dysrhythmogenic range; these may play a role in sudden death (70). With prolonged convulsive SE—defined as lasting 30 minutes or more—systemic blood pressure and cerebral blood flow can drop significantly (60). Additionally, blood glucose is initially elevated in response to excessive adrenergic stimulation; however, after 30 minutes of GCSE, hypoglycemia may occur (60). Both hypoglycemia and decreased cerebral blood flow contribute to further neuronal injury (71). Excessive muscle contraction often causes severe metabolic acidosis, breakdown of muscle tissue, and hyperkalemia (60,61,69). Arterial pH has been reported to fall below 7.0 (72) and contribute, along with hyperkalemia, to cardiac dysrhythmias. Rhabdomyolysis and myoglobinuria can also occur and may lead to acute renal failure (73).

**EVALUATION**

**Clinical Presentation**

Obtaining a focused history and examination may be very helpful for diagnosis and management (Table 121.1). Convulsive and nonconvulsive SE have very different clinical presentations, and their treatment is quite different. Convulsive SE frequently occurs outside the hospital, and management may start in the ambulance before patients arrive to the emergency room. The diagnosis is usually evident, unless there is a strong clinical suspicion of psychogenic nonepileptic seizure (PNES). Convulsive SE often starts as a focal seizure with secondary generalization. Rarely, primary generalized seizures evolve...
into SE. The generalized convulsion either becomes continuous, or stops and recurs before the patient regains full consciousness. In either case, the tonic-clonic activity changes in character with time and often patients go into a continuous clonic phase where clonic activity persists and gradually slows down and becomes more subtle. With time, the only persistent motor activity may consist of small-amplitude twitching of the face, hands, or feet or nystagmus jerking of the eyes (74,75). Sometimes the motor activity subsides completely, and patients remain stuporous or comatose; in this case, patients evolve from convulsive to NCSE (33).

By the time patients arrive to the emergency department (ED), they may already be in established SE. If there is strong clinical suspicion of PNES, an EEG is essential to confirm the diagnosis. The average duration of a PNES in one study was 5 minutes (76); however, they can be protracted and may mimic convulsive SE. Another study of patients in an epilepsy monitoring unit had nearly 20% of PNES patients, with PNES mimicking SE (77). Additionally, patients with PNES may also have epilepsy, making it all the more difficult to know how to treat.

NCSE has a different clinical presentation, with unexplained decline in mental status that cannot be completely explained by other causes. It may occur either outside the hospital or, frequently, in the hospital, in patients already admitted for other reasons such as stroke, intracranial hemorrhage, brain tumors, or metabolic disturbances. Frequently, the underlying etiology may account in part for the impair-ment in consciousness; however, patients frequently have an unexplained decline of mental status after a period of clinical improvement. Therefore, clinical suspicion should be strong, and evaluation for NCSE should be undertaken in any patient with unexplained impairment in mental status.

**Electroencephalogram**

The EEG is the only diagnostic tool that can confirm or refute the diagnosis of SE. In GCSE, an EEG may not be necessary initially, unless PNES must be excluded. However, if convulsive activity stops and patients do not recover their baseline level of consciousness, evaluation with an EEG is important to exclude the continuous presence of seizure activity. In NCSE, the EEG is essential. However, a single routine EEG of 20 minutes’ duration may not be adequate and may only capture seizure activity in 20% of cases. A longer EEG recording of at least 1 hour increases the sensitivity to 50%. More prolonged EEG monitoring is recommended if shorter-duration EEGs are nondiagnostic. Long-term EEG monitoring of 24 to 48 hours can increase the diagnostic accuracy to over 90% (35). Several EEG patterns have been described during SE, probably reflecting different stages of brain activity (75). In addition, several patterns have been described in NCSE. Discussion of these different EEG patterns is beyond the scope of this chapter; however, an important issue needs to be emphasized. Some EEG patterns can be difficult to distinguish from epileptiform activity, such as diffuse triphasic waves in metabolic encephalopathies (Fig. 121.1) and breaf rhythms after a craniotomy (Fig. 121.2). These patterns can be very deceiving and can often be misinterpreted as epileptiform. Therefore, it is very important for the EEG to be interpreted by an experienced electroencephalographer.

**Neuroimaging**

Neuroimaging studies are always recommended to assess for the presence of intracranial pathology. Even in patients with known pathologies, such as tumors or stroke, repeat imaging is recommended to exclude progression or complications of the underlying disease. For example, a stable tumor can become necrotic or hemorrhagic, or a stable acute or sub-acute infarct can turn hemorrhagic. Unenhanced computed tomography (CT) of the brain is adequate in the acute setting; however, magnetic resonance imaging (MRI) is much more sensitive and may detect lesions not seen on CT.

**Laboratory Evaluation**

Full laboratory evaluation is always recommended (Table 121.2), including blood cell count, renal function, liver function, electrolytes, calcium, magnesium, and AED levels. Toxicology should be performed when there is a clinical suspicion of intoxication or substance abuse. This is especially important in patients with a psychiatric illness at risk of suicide and in children who may have access to adult medications. Lumbar puncture is indicated if there is any consideration of an infectious etiology. Also, a lumbar puncture should be considered when SAH, not seen on CT scan, is suspected. However, in the presence of any sign of intracranial hypertension, lumbar puncture should be avoided, since it may increase the risk of transtentorial herniation. It is important to note that patients with convulsive SE often exhibit clinical features suggestive of meningitis, such as elevated temperatures, increased peripheral white blood cell counts, and pleocytosis in the cerebrospinal fluid (CSF) (70). These abnormalities have been reported in up to 18% of patients with convulsive SE, without any evidence of infection (70), and are thought to result from breakdown of the blood–brain barrier. Usually, the total white blood cell count in the CSF remains under 100 and glucose level remains normal. Treatment with antimicrobials should be initiated if there is clinical suspicion for a CNS infection.

<table>
<thead>
<tr>
<th>Table 121.1 History and Physical Examination</th>
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<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>History of epilepsy</td>
</tr>
<tr>
<td>List of current medications</td>
</tr>
<tr>
<td>History of psychiatric illness</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
</tr>
<tr>
<td>Signs of medical illness</td>
</tr>
<tr>
<td>Signs of substance abuse</td>
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</tbody>
</table>

TREATMENT

General Rubric

The most important thing to know is that this is a very complicated subject. Each of the 11 different kinds of status is considered differently. It can be confusing, when looking at papers on this subject, because there is often the assumption that when an author talks about SE, he or she means generalized convulsive SE.

Generalized Convulsive Status Epilepticus

Treatment Principles

GCSE is a medical emergency and should be dealt with as such. Therapies are aimed at early termination of seizure activity, identification and correction of the cause, prevention of seizure recurrence, and treatment of pathophysiologic complications. There is ample evidence that delayed treatment leads to poor outcome (36,78). In addition, there is a time-dependent loss of efficacy of anticonvulsant medications (58,59). Therefore, early initiation of aggressive treatment is essential in the management of GCSE. It is highly recommended that every ED and ICU have a well-defined and clear treatment protocol. This helps avoid many of the pitfalls leading to delayed and insufficient treatment of SE (79).

Prehospital Management

In many cases, patients with convulsive SE are brought into the ED by ambulance, making prehospital treatment possible. Initiation of treatment in the ambulance is highly recommended, when possible, given the importance of early intervention. Both rectal diazepam (80,81) and intravenous diazepam and lorazepam (82) can be safely and effectively used. In one randomized, double-blind, prospective study (82), seizures terminated before arrival to the ED in 59% of patients who received intravenous lorazepam, 43% of those who received intravenous diazepam, and 21% of those who received placebo. The safety profile was also good, with more patients having respiratory or circulatory complications in the placebo group than the treatment groups. Treatment in the ambulance with intravenous benzodiazepines should only be initiated if the paramedical team transporting the patient has the training and equipment to perform endotracheal intubation and artificial ventilation, in case of respiratory depression.

FIGURE 121.1 Generalized status versus generalized slowing with triphasic waves. A: Electroencephalogram (EEG) of a patient in hepatic encephalopathy showing diffuse background slowing and prominent triphasic waves.
Medical Management

Medical management should focus on the prevention and reversal of medical complications (Table 121.3) (83). As in any other medical emergency, basic life support should always be the initial step in management, including maintenance of airways and blood pressure. Vital signs should be continuously monitored, including pulse oximetry. Oxygen at an $\text{FiO}_2$ of 1.0 should be given by nonrebreather mask. Endotracheal intubation should be considered if there is evidence of respiratory failure, including hypoxemia and/or respiratory acidosis. Pharmacologic paralysis for intubation should be avoided if possible, since it can result in the false impression that the seizure has stopped. If the use of a paralytic agent is necessary, continuous EEG monitoring should be performed. Large-bore intravenous access should be established for the administration of intravenous medications. Hyperthermia is believed to contribute to neuronal damage and should be corrected (84,85). Systolic blood pressure should be maintained above 120 mmHg if possible, but definitely not lower than 90 mmHg, to ensure adequate cerebral blood flow (39). Correction of acidosis with intravenous bicarbonate remains controversial. Many experts recommend treatment if the patient becomes hypotensive and arterial pH falls below 7 (39). Results of laboratory abnormalities should guide further medical treatment, including electrolyte abnormalities, blood sugar levels, and AED levels. Mild hyperglycemia is frequently seen and usually does not require intervention (86). If hypoglycemia is present, or if the blood sugar level is not available, patients should receive 100 mg thiamine followed by 50 mL 50% glucose solution intravenously (87). If a metabolic abnormality is present, such as hyponatremia or hypoglycemia, the most effective treatment of status is correction of the underlying problem.

Pharmacologic Treatment

Treatment with AEDs should be started after 5 minutes of continuous generalized, convulsive seizure activity. Early initiation of treatment can potentially lead to a better response and prevent GCSE from becoming refractory. In fact, when treatment is started within 30 minutes of onset, up to 80% of patients achieve control, compared to only 40% achieving control when treatment is started after 2 hours of onset (40,88). The choice of initial treatment largely depends on the institution, with different protocols being used by various institutions and specialists (80,89). This is due primarily to the lack of sufficient class I evidence. Three controlled clinical trials on the treatment of SE have been published. One study compared diazepam to lorazepam and found no significant difference (90). The second compared four treatment protocols: phenytoin alone, phenytoin with diazepam, lorazepam alone, and phenobarbital alone. The highest percentage of responders was in the lorazepam arm; however, the only significant difference was between lorazepam alone and phenytoin.
SECTION 12  NEUROLOGIC DISEASE AND DYSFUNCTION

**FIGURE 12.1.2** Focal status versus focal slowing and breach rhythm. A: Electroencephalogram (EEG) of a patient with a history of left temporal benign tumor, surgically resected several years ago. The high-amplitude slowing seen focally from the left temporal and frontal regions represents a breach rhythm, believed to result from the loss of resistance to electrical flow after a craniotomy. B: EEG of a patient having a left temporal lobe seizure. Note the presence of well-organized rhythmic activity compared to A, where the rhythmic slowing is more random and intermittent.
The ideal initial drug would be easy to administer, have an immediate and long-lasting seizure-suppressing action, and be free of serious adverse effects on cardiorespiratory function and level of consciousness. Unfortunately, the ideal drug does not exist. Benzodiazepines and barbiturates depress consciousness and respiratory drive and may lower blood pressure; pentytoin can cause hypotension and cardiac arrhythmias, which limits the rate of intravenous infusion.

### Table 121.2 Laboratory Evaluation

- Fingerstick glucose
- Complete blood count
- Electrolytes, calcium, and magnesium
- Liver function studies
- Renal function studies
- Toxicology for drugs of abuse and alcohol
- Serum antiepileptic drug levels
- Continuous video-EEG monitoring
- CT brain imaging as soon as possible
- More comprehensive imaging by MRI including MRA or MRV, if there remains clinical concern
- Lumbar puncture if strong suspicion of meningitis/encephalitis
- If worrisome for toxidrome, consider testing for toxins that are associated with seizures: isoniazid, tricyclic antidepressants, organophosphates, and cyclosporine

Adapted from Brophy GM, Bell R, Claasen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3-23.

### Table 121.3 Initial Management of Status Epilepticus

**TABLE 121.3 Initial Management of Status Epilepticus**

<table>
<thead>
<tr>
<th>Step</th>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
<th>Maximum Rate</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lorazepam</td>
<td>0.1 mg/kg</td>
<td>IV bolus</td>
<td>2 mg/min</td>
<td>May repeat once if seizure activity continues after 5 min. If seizure activity stops, additional medications may not be required.</td>
</tr>
<tr>
<td>2</td>
<td>Phenytoin</td>
<td>20 mg/kg</td>
<td>IV bolus</td>
<td>50 mg/min</td>
<td>May give additional 5–10 mg/kg if seizure continues. Consider valproate in patients with epilepsy on valproate, especially with subtherapeutic level.</td>
</tr>
<tr>
<td>3</td>
<td>Phenytoin PE (fosphenytoin)</td>
<td>20 mg/kg</td>
<td>IV bolus</td>
<td>150 mg/min</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Phenobarbital</td>
<td>20 mg/kg</td>
<td>IV bolus</td>
<td>50 mg/min</td>
<td>Skip this stage and go straight to general anesthesia if status started more than 60 min ago.</td>
</tr>
<tr>
<td>5</td>
<td>Valproate</td>
<td>25 mg/kg</td>
<td>IV bolus</td>
<td>200 mg/min</td>
<td>May give additional 5–10 mg/kg if seizure continues.</td>
</tr>
<tr>
<td>6</td>
<td>Pentobarbital</td>
<td>5–10 mg/kg</td>
<td>IV bolus</td>
<td>50 mg/min</td>
<td>Repeat 5 mg/kg every 5–10 min until seizures stop. Titrated to 10 mg/kg/hr, until desired EEG pattern attained.</td>
</tr>
<tr>
<td>7</td>
<td>Midazolam</td>
<td>1 mg/kg/hr</td>
<td>IV infusion</td>
<td>—</td>
<td>Repeat 0.2–0.4 mg/kg every 5 min until seizures stop, maximum 2 mg/kg. Titrated to 2 mg/kg/hr until desired EEG pattern attained.</td>
</tr>
<tr>
<td>8</td>
<td>Propofol</td>
<td>0.2 mg/kg</td>
<td>IV bolus</td>
<td>—</td>
<td>Repeat 1–2 mg/kg every 5 min until seizures stop, maximum 10 mg/kg. Titrated to 1 mg/kg/hr = 16 µg/kg/min, until desired EEG pattern attained.</td>
</tr>
<tr>
<td>9</td>
<td>Ketamine</td>
<td>0.5 mg/kg/hr</td>
<td>IV infusion</td>
<td>2 mg/kg/hr</td>
<td>Titrated to burst suppression on continuous EEG, Maximum daily dose, 4,000 mg. Consider titration to burst suppression on continuous EEG.</td>
</tr>
</tbody>
</table>

### Table 121.4 Suggested Protocol for Antiepileptic Drug Treatment

<table>
<thead>
<tr>
<th>Step</th>
<th>Medication</th>
<th>Dosage</th>
<th>Route</th>
<th>Maximum Rate</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lorazepam</td>
<td>0.1 mg/kg</td>
<td>IV bolus</td>
<td>2 mg/min</td>
<td>May repeat once if seizure activity continues after 5 min. If seizure activity stops, additional medications may not be required.</td>
</tr>
<tr>
<td>2</td>
<td>Phenytoin</td>
<td>20 mg/kg</td>
<td>IV bolus</td>
<td>50 mg/min</td>
<td>May give additional 5–10 mg/kg if seizure continues. Consider valproate in patients with epilepsy on valproate, especially with subtherapeutic level.</td>
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<td>Titrated to burst suppression on continuous EEG, Maximum daily dose, 4,000 mg. Consider titration to burst suppression on continuous EEG.</td>
</tr>
</tbody>
</table>

- Usually burst-suppression pattern.
- PE, phenytoin equivalent; EEG, electroencephalogram; MAC, minimal alveolar concentration.

Adapted from Brophy GM, Bell R, Claasen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3-23.
Benztropines are the most commonly used first-line agents due to their potency and fast-acting effect. Pharmacologically, they enhance inhibitory γ-aminobutyric acid (GABA) transmission. The three most commonly used agents are lorazepam, diazepam, and midazolam. Direct comparison between lorazepam and diazepam revealed no significant difference (78). Diazepam is more lipid soluble, and may cross the blood-brain barrier and reach higher concentrations in the CSF more rapidly than lorazepam. However, this increased lipid solubility may be disadvantageous, and leads to a higher rate of redistribution in peripheral adipose tissue. Therefore, despite having a longer elimination half-life of 48 hours, the effective duration of action of diazepam is actually shorter—15 to 30 minutes—than that of lorazepam, which has a duration of action of 12 to 24 hours. This may lead to increased incidence of seizure recurrence after initial termination of SE when diazepam is used alone. The rapid onset of action and prolonged duration of seizure-suppressing effect has made lorazepam the preferred first-line agent by many neurologists. Midazolam has never been used in a double-blind study. Like diazepam and lorazepam, midazolam has a rapid onset of action, but its extremely short elimination half-life makes it more appropriately used as a continuous intravenous infusion in refractory SE.

The routine concomitant or sequential use of a second agent is advocated by many experts. It is recommended to use an agent with a different mechanism of action, such as phenytoin or fosphenytoin. However, as shown by the Veterans Affairs Cooperative Study (91), lorazepam alone may be sufficient in many cases, especially when SE is caused by a known and reversible process, such as low serum concentration of AEDs or acute metabolic disturbances. Some experts argue that the early use of phenytoin or fosphenytoin is important to prevent seizure recurrence. This is based on the experimental evidence that benzodiazepines are subject to rapid time-dependent loss of potency as opposed to phenytoin, which loses its potency at a much slower rate (58, 59); this claim, however, remains to be proven in controlled clinical trials.

The recommended dose of intravenous phenytoin is 20 mg/kg total body weight. The common practice of administering a standard loading dose of 1,000 mg of phenytoin is inadequate for most patients, and some patients require as much as 30 mg/kg to stop seizure activity (92). Phenytoin should be administered at a maximum infusion rate of 50 mg/min. A faster administration rate may result in cardiovascular complications, including hypotension, bradycardia, and ectopic beats. These effects are more common in elderly patients and patients with pre-existing cardiac disease. Cardiovascular complications are not due to phenytoin itself, but to the propylene glycol diluent (93). For this reason, fosphenytoin, a water-soluble prodrug of phenytoin, was introduced and has gained broad popularity. Fosphenytoin is rapidly converted to phenytoin, and is dosed in phenytoin equivalents. Because of its water solubility, fosphenytoin can be administered at a much faster infusion rate than phenytoin—up to 150 mg/min. Theoretically, the risk of cardiovascular adverse effects should be lower with fosphenytoin; however, this was never proven in clinical trials. In fact, in one study, the rate of complications was similar for intravenous phenytoin and fosphenytoin (94) as long as the recommended maximum rate of administration is followed, although infusion site reactions (phlebitis and soft tissue damage) were less common with fosphenytoin.

The main advantage of fosphenytoin in the treatment of SE seems to be related to the rapidity of infusion. The question of whether fosphenytoin reaches its peak concentration in the brain faster than phenytoin is not known. Fosphenytoin has to be hepatically converted to phenytoin, a process that may delay its true bioavailability. One study found that when phenytoin or fosphenytoin are administered at the maximum recommended infusion rate, the therapeutic serum concentration of phenytoin for either drug is attained within 10 minutes (95). Thus, fosphenytoin and phenytoin may very well have an equivalent onset of action; however, this will need to be studied in controlled clinical trials.

Phenobarbital is another effective treatment for SE; however, because of its powerful depressant effect on respiratory drive, level of consciousness, and blood pressure, it should be used only after benzodiazepines and phenytoin fail. The usual recommended loading dose is 20 mg/kg at an infusion rate of 50 mg/minute.

Intravenous valproic acid is another viable option for the acute treatment of SE, and may offer a significant advantage over phenobarbital, with a much safer side effect profile (96). Although the recommended infusion rate is 20 mg/minute, much faster infusion rates up to 555 mg/min have been safely used (97). Several anecdotal reports and uncontrolled trials were initially published, suggesting a potential usefulness for valproate in the treatment of SE (98–100). A single, double-blind controlled trial was published comparing phenytoin to valproic acid in acute convulsive SE (101), and found a higher rate of seizure termination with valproic acid as a first-line agent (66% vs. 43% for phenytoin). After failure of the first agent, valproic acid was also superior to phenytoin when used as a second agent. The current evidence and clinical experience are insufficient to recommend valproate as first-line treatment for SE; however, it may be safely and effectively used as a third- or fourth-line treatment when other agents are unsuccessful and before resorting to general anesthesia (102). The question of whether intravenous valproic acid should replace phenytoin as a second-line agent remains unanswered.

Topiramate has been reported to be useful in some patients with refractory SE (103, 104), including children (105). It is administered as suspension via a nasogastric tube, with a good rate of seizure termination and an excellent safety profile. Although intravenous formulations are most likely more effective, topiramate may be a safe alternative to more aggressive treatments. Controlled clinical trials are needed to establish its efficacy and safety in this setting.

Intravenous levetiracetam was recently introduced and seems to have a good safety profile (106). There are no published studies about its use in SE, and therefore, no recommendations can be made. Levetiracetam has, overall, very good pharmacokinetic properties and a good safety profile, and may offer another option for the treatment of SE in the future.

**Refractory Generalized Convulsive Status Epilepticus**

GCSE is considered refractory if it does not respond to two or three first-line treatments (107). In practice, if seizure activity continues after the administration of a benzodiazepine, phenytoin, or phenobarbital, status is considered refractory and more aggressive treatment should be pursued. In the Veterans
It is extremely important to make sure that patients are on a burst-suppression pattern on EEG—the infusion is main-
tained so that the desired level of anesthesia is attained—most often a 90% reduction in electrocerebral silence. Once seizure activity is completely suppressed and patients continue to have NCSE after the cessation of motor activity, which usually leads to increased duration of stay in the ICU, and subsequently, an increased rate of complications (95,115). Furthermore, patients with refractory GCSE are at significantly higher risk of developing chronic epilepsy than those with nonrefractory GCSE (115).

Patients with refractory GCSE tend to have a worse outcome (79). This is likely due to a combination of factors, including a more serious etiology and longer duration of seizure activity, which usually leads to increased duration of stay in the ICU, and subsequently, an increased rate of complications (95,115). Furthermore, patients with refractory GCSE are at significantly higher risk of developing chronic epilepsy than those with nonrefractory GCSE (115).

Patients with acute neurologic disease, such as infection, stroke, intracranial hemorrhage, or trauma, and patients with concomitant systemic illnesses tend to have worse outcomes (116); patients with anoxic brain injury have a very poor outcome (117). However, in these patients, the etiology and comorbid conditions are most likely the major determinants of outcome, with SE playing an additional complicating role. There is a scoring system that can be considered for help in determining likelihood of prognosis (118).

In a survey conducted among neurologists (89), there was strong agreement for the use of benzodiazepines and phe-
ytoin or fosphenytoin as first- and second-line therapies for SE. However, there was less consistency for the choice of third- and fourth-line therapy. Treatment options include intravenous phenobarbital or valproate, or continuous infusion of pentobarbital, propofol, or midazolam. It is important to note that once the choice of continuous infusion of antisei-
zure medication—often termed “general anesthesia,” although this is a serious misnomer—is made, patients are committed to undergo endotracheal intubation and artificial ventilation for a period of time. While it is extremely important to terminate seizure activity as rapidly as possible, intubation and ventilation are not, of course, complication free, which should be kept in mind when making such a decision. Although there is no consensus agreement on the treatment approach, one approach is to attempt a third-line agent before resorting to general anesthesia, especially given the safety profiles of intravenous valproate and levetiracetam.

Continuous intravenous infusion of pentobarbital, propofol, and midazolam at anesthetic doses is the treatment of choice for refractory SE. A published meta-analysis provides useful information on the relative advantages and disadvan-
tages of each drug (107). Overall, pentobarbital appears to be more effective in stopping seizures and preventing seizure recurrence. However, pentobarbital is associated with more severe hemodynamic instability and hypotension, often requiring the use of vasopressors and, even in young individuals, mandating the placement of invasive monitoring devices to manage the significant negative inotropic state-induced inade-
quate oxygen delivery. Of importance, there is no difference in mortality among the three treatments. Propofol and midazolam have become the preferred agents for refractory SE mainly because of their rapid onset of action and short half-life, with rapid clearance. However, a number of articles reporting data about the use of propofol in refractory SE raised several concerns about the safety of propofol in this set-
ting (109). In contrast, more recent emerging evidence suggests propofol to be superior and safer than pentobarbital (110), even in children (111).

Once continuous infusion of an anesthetic agent is initi-
ated, a multidisciplinary approach, including an experienced neurologist and a critical care team, is crucial to ensure ade-
quate treatment. Continuous EEG monitoring is strongly recommended, and can provide online information about the presence of seizure activity and the success of treatment. This is especially true if convulsive activity stops, since often patients continue to have NCSE after the cessation of motor activity. Once seizure activity is completely suppressed and the desired level of anesthesia is attained—most often a 90% reduction in electrocerebral silence—the infusion is main-
tained for 12 to 24 hours and is then gradually withdrawn. It is extremely important to make sure that patients are on adequate standing dosages and have adequate serum levels of other AEDs prior to withdrawal of the coma-inducing agent(s). If seizure activity recurs, therapy should be resumed for progressively longer periods, and the depth of anesthesia may be increased. In this situation, some experts advocate, but this is controversial, that attaining electrocerebral silence in severely refractory cases is helpful. If infusion of one agent is not successful in stopping seizure activity despite high dos-
ages, and significant side effects, then a second agent should be tried, either alone or in combination. Prolonged treatment with midazolam may lead to tachyphylaxis, leading to the need of very high dosages.

Other treatment options for refractory status epilepticus include inhalation anesthetic agents and ketamine. Both iso-
flurane and desflurane have been reported to rapidly suppress all electrographic seizure activity in patients who failed treatment with propofol, midazolam, and pentobarbital (112). However, the risk of complications is high and these agents should only be used as a last resort. Ketamine is another agent that has been advocated as a potential treatment option for patients with refractory SE (113). While ketamine can lower the seizure threshold, it has a novel mechanism of action: a noncompetitive glutamate antagonist acting at the NMDA receptor, which may be helpful in refractory status epilepticus. Ketamine offers the advantage of being neuroprotective and can increase blood pressure due to its sympathomimetic properties (79). The clinical experience with ketamine is very limited, and the potential for serious complications is unknown (114).

**PROGNOSIS**

Status epilepticus is associated with significant morbidity and mortality. Several factors influence outcome, including etiol-
ogy, age, and the duration of seizure activity (36,72). The overall mortality rate among adults is approximately 20% but rises significantly with age (36), reaching 38% in those older than 60 (27). Longer duration of SE usually leads to worse outcome, especially in the presence of severe physiologic disturbances. Mortality for seizures lasting more than 1 hour is 32%, compared to 2.7% when seizures are less than 1 hour long (36,37). Among survivors, the risk of develop-
ing chronic epilepsy and subsequent episodes of status is very high (88).
Key Points

- Status epilepticus is defined as continuous or rapidly repeating seizures.
- Any seizure type can turn into status epilepticus.
- Every institution should have a well-defined treatment protocol to avoid delays and inadequate treatment.
- In the majority of cases, status epilepticus develops in patients without any history of seizures or epilepsy.
- In patients with a history of epilepsy, the most common cause is low serum concentration of AEDs.
- Intracranial pathology and metabolic disturbances can cause status epilepticus.
- When possible, correction of the underlying etiology is the most effective treatment.
- GCSE is a medical emergency requiring aggressive and immediate therapeutic intervention; other kinds of status are not necessarily an emergency.
- Mortality and morbidity increase significantly if generalized convulsive seizure activity persists longer than 60 minutes.
- Delayed treatment may cause the generalized convulsive status to become refractory to therapy.
- Rapid sequential use of several anticonvulsive medications is strongly recommended.
- In refractory cases, general anesthesia is the recommended therapy.
- NCSE is frequently underdiagnosed in comatose patients, especially those with acute neurologic injury.
- Continuous EEG monitoring is strongly recommended in most cases.

Acknowledgment

I would like to thank G.A. Ghacibeh for doing the chapter for the 4th edition. While some of the chapter was updated, much remains his work.

References

5. Lowenstein DH, Bleck T, Macdonald RM. It's time to revise the definition of status epilepticus. Epilepsia. 1999;40(1):120.


