

Status epilepticus (SE) is defined as continuous or rapidly repeating seizures, and should be viewed as a life-threatening medical and neurologic emergency requiring prompt therapeutic intervention. The frequency of SE in the United States is estimated at 152,000 cases per year, with roughly 55,000 related deaths annually. SE can be the presenting sign of epilepsy in up to 30% of patients. Therefore, it is essential for all health care providers to be able to identify and treat patients with SE adequately.

DEFINITIONS AND CLASSIFICATIONS

Epileptic Seizure

According to the International League Against Epilepsy (ILAE), an epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormally excessive or synchronous neuronal activity in the brain (1). There are two components in this definition: The first component is the occurrence of clinical signs and symptoms, which are usually neurologic, and the second component is the presence of abnormal neuronal activity. Therefore, classification schemes of seizures can follow either of these two components. Seizures can be classified based on either their semiology or the pattern of neuronal activity. Neuronal activity is measured as neurophysiologic electrical signals seen as tracings on an electroencephalogram (EEG).

Seizures are divided into two types, depending on whether the abnormal neuronal activity starts in a specific region of the brain or diffusely in the entire brain. A seizure is called focal (previously called partial) when the electrical activity starts in a specific region of the brain. This can be a well-defined focus, a large brain region, or even an entire hemisphere. A seizure is called generalized when the electrical activity starts diffusely, involving the entire brain at onset. It is important to note that a seizure that starts focally can spread to involve the entire brain. In this case, the seizure is called secondarily generalized.

Classification based on semiology is more complicated due to the wide variety of clinical features. Although the division of seizures into focal and generalized does not take into account the clinical semiology, specific clinical features occur in each seizure type.

There are six distinct types of generalized seizures: Tonic-clonic (grand mal), tonic, clonic, atonic, myoclonic, and absence (petit mal). The clinical features of focal epilepsy are more varied, depending on the primary function of the brain region where the abnormal electrical activity occurs. For example, if the seizure focus is in the motor cortex, repeated contractions are expected to occur. The older classification divided focal seizures into three types, depending on the degree of impairment in consciousness. Seizures are considered simple partial if consciousness is not impaired, complex partial if consciousness is impaired; and secondarily generalized when a secondary generalized tonic-clonic seizure occurs after a focal onset. The distinction between simple partial and complex partial is sometimes difficult, especially when language remains intact. For this reason, the new classification proposed by the ILAE removed simple partial and complex partial from the focal seizure subtype. However, this classification remains widely used and can be clinically useful.

Epilepsy

According to the ILAE, epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure (1). Several epileptic syndromes have been proposed by the ILAE based on genetic, etiologic, and clinical features. However, for practical reasons, epileptic disorders can be best classified and understood depending on the type of seizures that occur. Focal epilepsy (previously called partial epilepsy) is a disorder characterized by the occurrence of focal seizures, and generalized epilepsy is a disorder characterized by the occurrence
of generalized seizures. The terms primary and secondary are frequently used to distinguish between idiopathic syndromes (primary), and syndromes with a known cause (secondary). Primary generalized epilepsy (PGE) refers to a set of epilepsy syndromes with different combinations of generalized seizures that have, in general, a good prognosis. Symptomatic (or secondary) generalized epilepsy refers to a set of heterogeneous disorders characterized by severe intractable epilepsy and several seizure types, and are associated with significant mental retardation and poor prognosis. Lennox-Gastaut syndrome is a common type of secondary, generalized epilepsy.

**Status Epilepticus**

Status epilepticus is defined as recurrent epileptic seizure activity lacking full recovery of neurologic function between seizures, or continuous clinical and/or electrical seizure activity that lasts 30 minutes or longer, whether or not consciousness is impaired (2). This original definition has been changed several times over the years, and the duration of continuous seizure activity that is accepted as SE has gradually decreased due to several factors. Research with animals shows that repetitive seizures become self-sustaining and resistant to medical treatment within 15 to 30 minutes (3,4). In addition, irreversible neuronal injury and death are likely to occur with prolonged seizure activity (5). Furthermore, it is extremely important to emphasize early aggressive treatment. Therefore, an operational definition was introduced by several experts, suggesting that 5 minutes of continuous seizure activity should be sufficient to define SE (6,7). This new definition has become widely accepted; however, the choice of 5 minutes is empirical and is dictated by the need to treat early and not wait until seizure activity becomes refractory to treatment and/or neuronal injury has occurred. The problem is that not all patients who have continuous seizures for 5 minutes are in established SE. In one study (8), more than 40% of the seizures lasting from 10 to 29 minutes stopped spontaneously without treatment, and overall mortality was 2.6% versus 19% for status epilepticus lasting over 30 minutes. For this reason, the term, impending status epilepticus (9), was recently introduced to describe those patients who have continuous seizure activity for at least 5 minutes but less than 30 minutes. The 5-minute cut-off is in agreement with the operational definition of status, and is based in part on the fact that the great majority of secondarily generalized tonic-clonic seizures terminate spontaneously after approximately 1 minute (10). However, this definition also takes into account the fact that there is a significant difference in terms of natural progression, response to treatment, and mortality between seizures lasting more than 30 minutes and those lasting less than 30 minutes (8,11,12). The term, established status epilepticus, was therefore used to describe seizures lasting more than 30 minutes (9). While this definition can be useful both in clinical practice and in clinical trials, it is important to remember that the transition from impending to established SE is a continuum.

Classification of status epilepticus follows the same scheme as the classification of seizures and, theoretically, any seizure can become SE if it does not terminate spontaneously. According to the ILAE, SE is divided into generalized and focal, depending on the mode of onset of the abnormal neuronal activity. However, it is important to note that a focal seizure can evolve either into focal or into generalized SE, depending on whether there is progression into secondary generalization. The most commonly used classification scheme divides SE into convulsive, nonconvulsive, and subtle, depending on the presence or absence of motor manifestations. Nonconvulsive status epilepticus (NCSE) manifests most commonly with impairment of consciousness of varying degrees, ranging from mild confusion to deep coma. The concept of subtle status epilepticus was introduced (13) to emphasize the point that prolonged convulsive SE changes in character with time, and the motor manifestations become less evident. Patients usually remain unconscious and have subtle motor manifestations, such as nystagmus, eyelid twitching, and finger twitching. However, the prognostic and therapeutic implications remain very similar to the convulsive state. Although this classification is somewhat simplistic and does not take into account the complexities of clinical and electrographic manifestations of various types of SE, it is very practical and useful in the clinical setting. In general, uncontrolled convulsive status is considered a life-threatening condition with a high morbidity rate, requiring prompt and aggressive treatment.

**EPIDEMIOLOGY**

The incidence of status epilepticus ranges from 10 to 41 per 100,000 individuals per year in various studies (14–17). All studies showed a significantly higher incidence in the elderly, especially after 60 years of age, raising a concern that the overall incidence may rise as the population ages. In addition, only 40% to 50% of patients with SE have a previous diagnosis of epilepsy (13,16). 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, various studies reported an incidence of NCSE in patients in the intensive care unit (ICU) with altered mental status ranging from 8% to 37% (18–22). Even when all patients with clinical evidence or history of seizures were excluded, the incidence of NCSE was 8% (18); in patients with intracerebral hemorrhage, the incidence rises to 28% (21). 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 (23), reaching 38% in elderly people (14). One of the primary predictors of poor outcome is prolonged seizure. When seizure activity lasts more than 1 hour, mortality reaches 32% compared to 2.7% with shorter seizures (23,24). Mortality from NCSE seems to be higher, averaging 50% (25).

**ETIOLOGY**

In about 30% of cases, status epilepticus occurs in patients with chronic epilepsy and is due to withdrawal, or low blood concentrations, of antiepileptic drugs (9,23,26). Hence, 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 and subarachnoid hemorrhage, central nervous system (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 can be identified (9,26).

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 subarachnoid and intracerebral hemorrhage, acute embolic stroke, and brain tumors. Approximately 50% of patients with brain tumors experience seizures (27,28), and a seizure is the presenting sign of a tumor in 23% of cases (29). Seizures can also be the presenting sign of an acute stroke (30) 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 intracerebral hemorrhage, and up to 26% of patients with subarachnoid hemorrhage (30,31). Up to 2.8% of patients with stroke go into SE either at presentation or within 2 weeks of their stroke (32). The risk of chronic epilepsy is 17 times higher after an ischemic stroke than the general population (33), and the risk of having a seizure or developing chronic epilepsy after any type of stroke is 11.5% (34). In subarachnoid hemorrhage, generalized tonic-clonic seizures have been reported in up to 26% of patients at the time of onset or shortly after onset (31,35), and nonconvulsive status epilepticus occurred in 8% of patients who survived the first 48 hours and had an unexplained decline in their level of consciousness (36).

Metabolic disturbances that may cause seizures include hypoglycemia, hyperglycemia, hypocapnia, hypomagnesemia, uremia, hepatic encephalopathy, and hyperammonemia states (26). 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 overt 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 psychotropic medications such as bupropion, tri-cyclic antidepressants, lithium, olanzapine, selective-serotonin reuptake inhibitors (SSRIs), venlafaxine, and clozapine; in addition to other drugs such as theophylline, isoniazid, lidocaine, phentoin, and ciprofloxacin. Furthermore, several commonly abused drugs can cause seizures, most notably cocaine, amphetamines, phencyclidine, and γ-hydroxybutyric acid (37,38).

**PATHOPHYSIOLOGY AND MECHANISMS**

The great majority of seizures stop spontaneously in less than 2 minutes (39). 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 status epilepticus 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 tried to shed some 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 status can be easily triggered in animal models using electrical stimulation (40). 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 (41). In contrast, once a self-sustaining state is established, it becomes more difficult to stop the seizure (42), and much higher dosages of inhibitory drugs are required, leading to significant toxicity, including cardiovascular depression (43). Another important feature of self-sustaining status is the progressive development of resistance to antiepileptic drugs. The anticonvulsant potency of benzodiazepines can decrease by 20 times within 30 minutes of self-sustaining status epilepticus (44). The same phenomenon was observed with other anticonvulsants, such as phenytoin; however, the decline in potency was slower (12).

Pathophysiologically, SE produces a number of changes, which can be divided into neurologic and systemic. Primary neurologic complications occur in both convulsive and nonconvulsive status, 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 (45,46), and cell death is thought to result from excessive neuronal firing through excitotoxic mechanisms (47). It is impossible to replicate these experiments in human beings; however, there is widespread belief—supported by some anecdotal evidence—that neuronal death occurs after prolonged seizures. For example, brain damage and decreased hippocampal neuronal density are often seen in patients who die from status epilepticus (48,49). Furthermore, cerebral edema and chronic brain atrophy seen on neuroimaging studies have been reported after status epilepticus (50–53).

Systemic complications of prolonged seizures are seen primarily in convulsive SE, 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 (46). 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 (4,45,54). Epinephrine levels are elevated and reach the arhythmogenic range; these may play a role in sudden death (54). With prolonged status—defined as lasting 30 minutes or more, systemic blood pressure and cerebral blood flow can drop significantly (45). Additionally, blood glucose is initially elevated in response to excessive adrenergic stimulation. However, after 30 minutes of SE, hypoglycemia may occur (45). Both hypoglycemia and decreased cerebral blood flow contribute to further neuronal injury (55). Excessive muscle contraction often causes severe metabolic acidosis, breakdown of muscle tissue, and hyperkalemia (4,45,46). Arterial pH has been reported to fall below 7.0 (56) and contribute, along with hyperkalemia, to cardiac arrhythmias. Rhabdomyolysis and myoglobinuria can also occur and may lead to acute renal failure (57).
Clinical Presentation

Obtaining a focused history and examination may be very helpful for diagnosis and management (Table 148.1). Convulsive and nonconvulsive SE have very different clinical presentations. 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 usually 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 nystagmoid jerking of the eyes (13,58). Sometimes the motor activity subsides completely, and patients remain stuporous or comatose. In this case, patients evolve from convulsive to nonconvulsive SE (20).

By the time patients arrive to the emergency room, 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 is approximately 5 minutes (59), and therefore, it is unlikely that a PNES could mimic convulsive status. However, patients with PNES may have repeated seizures and remain unresponsive between them, creating a diagnostic challenge. Although rare, one should always keep in mind the possibility of PNES in a patient presenting with SE. However, treatment should not be delayed, unless the diagnosis of PNES is certain.

Nonconvulsive SE has a different clinical presentation. 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. As mentioned earlier, NCSE may also occur in partially treated convulsive SE, when the convulsive activity is controlled (20). In either case, the common clinical presentation is that of decline in mental status that cannot be completely explained by other causes. Frequently, the underlying etiology may account in part for the impairment 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.

TABLE 148.1

<table>
<thead>
<tr>
<th>HISTORY AND PHYSICAL EXAMINATION</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of epilepsy</td>
<td>Current antiepileptic drugs, missed doses, compliance</td>
</tr>
<tr>
<td>List of current medications</td>
<td>Toxic ingestion of medications or other agents</td>
</tr>
<tr>
<td>History of psychiatric illness</td>
<td>Suicidal ideations or attempts</td>
</tr>
<tr>
<td>Trauma</td>
<td>Evidence of scalp laceration and bruises</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>May be difficult to assess; look for obvious signs</td>
</tr>
<tr>
<td>Signs of medical illness</td>
<td>Hispanic or renal disease, infection</td>
</tr>
<tr>
<td>Signs of substance abuse</td>
<td>Alcohol withdrawal, cocaine intoxication</td>
</tr>
</tbody>
</table>

Electroencephalogram

The EEG is the only diagnostic tool that can confirm or refute the diagnosis of SE. In convulsive status, an EEG may not be necessary initially, unless PNES needs to 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 3 hours 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% (22).

Several EEG patterns have been described during status epilepticus, reflecting probably different stages of brain activity (13). 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. 148.1) and breach rhythms after a craniotomy (Fig. 148.2). 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. Response to intravenous benzodiazepines has been suggested as a means to distinguish these rhythms from true epileptiform activity. Relying on changes in EEG activity alone in these cases can be dangerous, since intravenous benzodiazepines usually cause diffuse slowing of the EEG signal and may attenuate patterns of activity that are not necessarily epileptiform. On the other hand, if a clear clinical response is observed after the administration of intravenous benzodiazepines (i.e., improved level of consciousness), the diagnosis of seizure is therefore more evident, since patients with metabolic dysfunction are likely to become more drowsy if given sedatives. Newer techniques of quantitative EEG analysis, such as compressed spectral arrays, are now offered by many manufacturers and can be helpful in on-line monitoring. Experienced ICU nursing staff can be trained to recognize certain patterns that may indicate the occurrence of a nonconvulsive seizure. Review of the raw EEG data by
the electroencephalographer can then confirm the presence of seizure activity.

**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 subacute 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 148.2), including blood cell count, renal function, liver function, electrolytes, calcium, magnesium, and antiepileptic drug 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 subarachnoid hemorrhage, 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 (54). These abnormalities have been reported in up to 18% of patients with convulsive status, without any evidence of infection (54), and are thought to result from breakdown of the blood-brain barrier. Usually, the total white blood cell count in the cerebrospinal fluid (CSF) remains under 100 and glucose level remains normal. Treatment with antimicrobials should be initiated if there is clinical suspicion for a CNS infection.
Seizures and Epilepsy

Treatment with antiepileptic drugs (AEDs) is not recommended after a single unprovoked seizure (60); however, after a second unprovoked seizure, the likelihood of recurrent seizures is high, and treatment is recommended (60). Treatment with AEDs is successful and prevents the occurrence of seizures in about 70% of patients (61). Patients who continue to have breakthrough seizures despite adequate treatment with AEDs are believed to have medically refractory epilepsy. Other treatment options are then considered, including vagus nerve stimulation and epilepsy surgery (62). In addition, newer experimental approaches are currently under investigation. There are several antiepileptic drugs available. The choice of AED depends on several factors, including the type of epilepsy, side effect profile, comorbid conditions, drug interactions, previous treatment, cost, approved Food and Drug Administration (FDA) indications, and guidelines published by national and international societies (63–66). In the acute setting, treatment with intravenous benzodiazepine is indicated only if the seizure lasts more than 5 minutes, fulfilling the definition of impending status epilepticus.

Convulsive Status Epilepticus

Treatment Principles

Status epilepticus 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 (23,67). In addition, there is a time-dependent loss of efficacy of anticonvulsant medications (12,44). Therefore, early initiation of aggressive treatment is essential in the management of SE. It is highly recommended that every emergency department and intensive care unit have a well-defined and clear treatment protocol. This helps avoid many of the pitfalls leading to delayed and insufficient treatment of status (68).

Prehospital Management

In many cases, patients with convulsive SE are brought into the emergency room 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 (69,70) and intravenous diazepam and lorazepam (71) can be safely and effectively
Chapter 148: Seizures and Status Epilepticus

FIGURE 148.2. 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 rhythm, slowing is more random and intermittent.
and arterial pH falls below 7 (9). Results of laboratory abnormalities recommend treatment if the patient becomes hypotensive with intravenous bicarbonate remains controversial. Many exposure adequate cerebral blood flow (9). Correction of acidosis Systolic blood pressure should be maintained above 120 mm of intravenous medications. Hyperthermia is believed to continuous EEG monitoring should be performed. Large-bore seizure has stopped. If the use of a paralytic agent is necessary, possible, since it can result in the false impression that the intravenous benzodiazepines should be 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.

**Medical Management**

Medical management should focus on the prevention and reversal of medical complications (Table 148.3). 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 FiO\(_2\) of 1.0 should be given by nasal cannula or nonrebreather mask. Endotracheal intubation should be considered if there is evidence of respiratory failure, including hypoxemia and 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 (72,73). Systolic blood pressure should be maintained above 120 mm Hg if possible, but definitely not lower than 90 mm Hg, to ensure adequate cerebral blood flow (9). Correction of acidosis with intravenous bicarbonate remains controversial. Many experts recommend treatment if the patient becomes hypotensive and arterial pH falls below 7 (9). 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 (74). If hypoglycemia is present, or if the blood sugar level is not available, patients should receive 100 mg thiamine and 50 mL 50% glucose solution intravenously (75). 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 anticonvulsant medications should be started after 5 minutes of continuous seizure activity. Early initiation of treatment can potentially lead to a better response and prevent SE 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 (26,76). The choice of initial treatment largely depends on the institution, with different protocols being used by various institutions and specialists (68,77). 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 (78). 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 alone (11). The third study compared prehospital treatment with diazepam, lorazepam, and placebo, and found that both lorazepam and diazepam were efficacious (71).

Regardless of the choice of initial therapy, the rapid sequential use of several agents is strongly recommended until seizure activity is terminated (Table 148.4). The caveat of this approach is that the use of agents with long elimination half-life may lead to cumulative adverse effects, with high risk of inducing respiratory and cardiovascular depression. However, it is important to keep in mind that both respiratory and cardiovascular depression are usually easily treatable in the emergency room or intensive care unit settings, while prolonged SE may lead to irreversible neuronal injury. This formula should be kept in mind when making important therapeutic decisions. In the Veterans Affairs Cooperative Study (11), 60% of patients, on average, responded to the first drug; an additional 7.3% responded to the second drug; and only 2% responded to the third drug. Although these numbers seem discouraging, the number of drugs currently available has significantly increased, providing more options for treatment and potentially a better response rate. However, more clinical trials are needed to study the efficacy of newer agents.

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; phenytoin can cause hypotension and cardiac arrhythmias, which limits the rate of intravenous infusion. Benzodiazepines are the most commonly used first-line agents due to their potency and fast-acting effect. Pharmacologically, they enhance inhibitory \(\gamma\)-aminobutyric acid (GABA)

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**TABLE 148.2**

<table>
<thead>
<tr>
<th>LABORATORY EVALUATION</th>
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<tbody>
<tr>
<td>Complete blood count</td>
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<tr>
<td>Electrolytes, calcium, and magnesium</td>
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<tr>
<td>Liver function studies</td>
</tr>
<tr>
<td>Renal function studies</td>
</tr>
<tr>
<td>Toxicology</td>
</tr>
<tr>
<td>Serum antiepileptic drug levels</td>
</tr>
<tr>
<td>Brain imaging as soon as possible</td>
</tr>
<tr>
<td>Lumbar puncture if strong suspicion of meningitis</td>
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</tbody>
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**TABLE 148.3**

<table>
<thead>
<tr>
<th>INITIAL MANAGEMENT OF STATUS EPILEPTICUS</th>
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<tbody>
<tr>
<td>1. ABC</td>
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<tr>
<td>2. Blood glucose</td>
</tr>
<tr>
<td>3. Antiepileptic drugs</td>
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<tr>
<td>4. Evaluation</td>
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**TABLE 148.4**

<table>
<thead>
<tr>
<th>Step</th>
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<th>Dosage</th>
<th>Route</th>
<th>Maximum rate</th>
<th>Comment</th>
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<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></td>
<td>Phenytoin</td>
<td>20 mg/kg</td>
<td>IV bolus</td>
<td>50 mg/min</td>
<td>Consider valproate in patients with epilepsy on valproate, especially with subtherapeutic level.</td>
</tr>
<tr>
<td></td>
<td>Fosphenytoin</td>
<td>20 mg/kg PE</td>
<td>IV bolus</td>
<td>150 mg/min</td>
<td></td>
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<tr>
<td>2</td>
<td>Phenobarbital</td>
<td>20 mg/kg</td>
<td>IV bolus</td>
<td>50 mg/min</td>
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<td></td>
<td>Valproate</td>
<td>25 mg/kg</td>
<td>IV bolus</td>
<td>200 mg/min</td>
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<td>Pentobarbital</td>
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<td>IV bolus</td>
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<td></td>
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<tr>
<td></td>
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<td>1 mg/kg/h</td>
<td>IV infusion</td>
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<tr>
<td></td>
<td>Maintenance</td>
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</tr>
<tr>
<td>4</td>
<td>Midazolam</td>
<td>0.2 mg/kg</td>
<td>IV bolus</td>
<td>—</td>
<td>Repeat 0.2–0.4 mg/kg every 5 min until seizures stop, maximum 2 mg/kg.</td>
</tr>
<tr>
<td></td>
<td>Initial bolus</td>
<td>0.1 mg/kg/h</td>
<td>IV infusion</td>
<td>—</td>
<td>Titrate up to 2 mg/kg/h until desired EEG pattern attained.</td>
</tr>
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<td>Maintenance</td>
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<tr>
<td>5</td>
<td>Propofol</td>
<td>1 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.</td>
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<tr>
<td></td>
<td>Initial bolus</td>
<td>1 mg/kg/h</td>
<td>IV infusion</td>
<td>—</td>
<td>Titrate up to 1 mg/kg/h = 16 microgram/kg/min, until desired EEG pattern attained.</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
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<tr>
<td>6</td>
<td>Ketamine</td>
<td>Inhalation anesthetic</td>
<td>—</td>
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*Usually burst-suppression pattern. PE, phenytoin equivalent; EEG, electroencephalogram.*

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 cerebrospinal fluid 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 if 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 (11), 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 antiepileptic drugs 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 (12,44). This claim, however, remains to be proven in controlled clinical trials.

The recommended dose of intravenous phenytoin is 20 mg/kg. 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 (79). Phenytoin should be administered at a maximum infusion rate of 50 mg/minute. 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 (80). 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
Refractory Status Epilepticus

Status epilepticus is considered refractory if it does not respond to two or three first-line treatments (94). 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 Affairs Cooperative Study (11), failure of the first two agents was seen in 38% of patients presenting with convulsive SE and 82% of patients presenting with subtle SE. Patients with refractory SE are at higher risk of developing complications (93), including respiratory failure, fever, pneumonia, hypotension, sepsis, and requiring blood transfusion. In addition, the clinical outcome is worse than nonrefractory SE, with a mortality of 23% compared to 14% in nonrefractory cases (95).

In a survey conducted among neurologists (77), there was strong agreement for the use of benzodiazepines and phenytoin or fosphenytoin as first- and second-line therapies for SE. However, there was less consistency for the choice of third- and fourth-line therapies. 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 antiseizure medications—often termed “general anesthesia,” although this is a bit of a misnomer—is made, patients are committed to undergoing general anesthesia, especially given the safety profiles of intravenous valproate and levetiracetam.

Continuous intravenous infusions 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 disadvantages of each drug (94). 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, managing the placement of invasive monitoring devices to manage the significant negative inotropic state-induced inadequate 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 review of a number of articles reporting data about the use of propofol in refractory SE raised several concerns about the safety of propofol in this setting (96). In contrast, more recent emerging evidence suggests propofol to be superior and safer than pentobarbital (97), even in children (98).

Once continuous infusion of an anesthetic agent is initiated, a multidisciplinary approach, including an experienced neurologist and a critical care team, is crucial to ensure adequate 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% burst-suppression pattern on EEG—the infusion is maintained 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—and in this I agree—attaining electrocerebral silence in severely refractory cases. If infusion of one agent is not successful in stopping seizure activity despite high dosages, 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 isoflurane and desflurane have been reported to rapidly suppress all electrographic seizure activity in patients who failed treatment with propofol, midazolam, and pentobarbital (99). 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 (100). Ketamine offers the advantage of being neuroprotective and can increase blood pressure due to its sympathomimetic properties (67). The clinical experience with ketamine is very limited, and the potential for serious complications is unknown (101). Therefore, its use should be limited to severely refractory cases.

Nonconvulsive Status Epilepticus

There are two types of NCSE: absence and complex partial. The two subtypes can only be distinguished based upon the EEG pattern. Absence status is relatively rare and does not result in permanent neuronal injury. It usually occurs in patients with known primary generalized epilepsy due to low serum levels of AEDs. Most cases of absence status respond to intravenous benzodiazepines, with rapid return to baseline of the mental status. More recently, the use of intravenous valproate has been advocated, since valproate is in general an effective treatment for absence epilepsy.

Chapter 148: Seizures and Status Epilepticus

Status epilepticus is associated with significant morbidity and mortality. Several factors influence outcome, including etiology, age, and the duration of seizure activity (23,56). The overall mortality rate among adults is approximately 20% but rises significantly with age (23), reaching 38% in those older than 60 (14). 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 (23,24). Among survivors, the risk of developing chronic epilepsy and subsequent episodes of status is very high (76).

Patients with refractory SE and are identified as refractory SE, and aggressive management is recommended. NCSE that results from metabolic dysfunction will most likely subside once the metabolic disturbance is corrected, and therefore aggressive treatment may not be necessary. The difficult question involves patients with acute brain injury, such as intracranial hemorrhage, trauma, brain surgery, or stroke, who have impaired consciousness and continuous or intermittent seizure activity on EEG, without any evidence of motor activity. These patients have a poor prognosis regardless of the treatment, with a high mortality rate and high risk of permanent neurologic impairment. The exact contribution of seizure activity to permanent neuronal injury is not known. The controversy arises from the fact that the aggressive coma-inducing treatment of SE is associated with high morbidity and mortality (94). A large number of these patients die from ICU complications, especially infections (43,105). It is not yet known whether aggressive treatment will shorten or lengthen the stay in the ICU and the duration of intubation. Even more importantly, it is not yet known whether aggressive treatment will have any impact on prognosis. Our approach is to treat with multiple nonsedating AEDs, such as phenytoin, levetiracetam, and valproate at high dosages, and only resort to coma-inducing agents if seizure activity persists or progresses despite more conservative management. Aggressive approach in these cases is necessary, and decisions should be made on a case-by-case basis, taking into consideration several factors, such as the underlying etiology, age, and comorbidities.

PROGNOSIS

Status epilepticus is associated with significant morbidity and mortality. Several factors influence outcome, including etiology, age, and the duration of seizure activity (23,56). The overall mortality rate among adults is approximately 20% but rises significantly with age (23), reaching 38% in those older than 60 (14). 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 (23,24).

Among survivors, the risk of developing chronic epilepsy and subsequent episodes of status is very high (76).

Patients with refractory SE tend to have a worse outcome (67). 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 (95,106). Furthermore, patients with refractory SE are at significantly higher risk of developing chronic epilepsy than those with non-refractory SE (106).

Patients with acute neurologic disease, such as infection, stroke, intracranial hemorrhage, or trauma, and patients with concomitant systemic illnesses tend to have worse outcomes (107); patients with anoxic brain injury have a very poor outcome (108). However, in these patients, the etiology and
comorbid conditions are most likely the major determinants of outcome, with SE playing an additional complicating role. In contrast, patients with a history of chronic epilepsy who develop SE because of AED withdrawal, or patients with no history of epilepsy who develop SE because of alcohol withdrawal, tend to have a good outcome, often with return to their baseline level of functioning [106]. Mortality from NCSE seems to be higher overall, averaging 50% (25). Several factors can influence prognosis, including etiology and the level of consciousness at presentation. Patients presenting with minimal obtundation have a better outcome than those presenting with deep stupor or coma (105). Again, it is impossible to sort out which is the major determinant of prognosis—the severity of the status itself or the severity of the underlying condition.

**PEARLS**

- 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 antiepileptic drugs.
- Intracranial pathology and metabolic disturbances can cause status epilepticus.
- When possible, correction of the underlying etiology is the most effective treatment.
- Status epilepticus is a medical emergency requiring aggressive and immediate therapeutic intervention.
- Mortality and morbidity increase significantly if seizure activity persists longer than 60 minutes.
- Delayed treatment may cause the 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.
- Nonconvulsive status epilepticus is frequently underdiagnosed in comatose patients, especially those with acute neurologic injury.
- Continuous EEG monitoring is strongly recommended in most cases.

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